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Breaking the chronic wound inflammatory cycle by Copper Dressings enabling progression towards wound healing

Sergii Karpeniuk[1] and Gadi Borkow[2,3*]

[1]Department of Surgery No.1, Urology, Minimally Invasive Surgery, I. Horbachevsky Ternopil National Medical University, 46011 Ternopil, Ukraine
[2]The Skin Research Institute, The Dead-Sea & Arava Science Center, Masada 8693500, Israel; and [3]MedCu Technologies Ltd., Herzliya 4672200, Israel

*gadib@medcu.com

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ABSTRACT

Background: Hard-to-heal wounds pose a major challenge, as many fail to progress through the normal stages of healing and instead heal very slowly or remain persistently "stalled" despite standard interventions. An essential early step in chronic wound management is the removal of devitalized tissue, which is often associated with biofilm, in order to enable subsequent phases of wound healing. This is conventionally achieved through enzymatic, sharp, or surgical debridement. However, these approaches may damage viable tissue, cause pain, local irritation, or bleeding, and frequently do not result in sustained wound healing progression.

Aim: To evaluate the effectiveness of copper oxide–impregnated wound dressings (Copper Dressings) as an optimal autolytic debridement strategy for promoting healing of devitalized chronic wounds.

Methods: Venous leg ulcers (VLUs) and mixed leg ulcers associated with secondary lymphedema, post-thrombotic syndrome (PST), and peripheral arterial disease (PAD) were treated exclusively with Copper Dressings in combination with compression therapy. The patients presented with complex comorbidities, including cardiovascular disease, obesity, skin cancer, Raynaud syndrome, calf pump dysfunction, and prior unsuccessful debridement. All cases were followed until complete wound bed granulation or full wound closure.

Results: Across eight out patient representative cases, rapid and consistent removal of necrotic and devitalized tissue was observed, followed by robust granulation tissue formation and progressive wound closure. Effective autolytic debridement occurred without the use of adjunctive enzymatic agents, other nonsurgical techniques, or aggressive sharp debridement.

Conclusions: This retrospective case series suggests that Copper Dressings promote autolytic debridement by establishing an antimicrobial, moisture - balanced, and biologically active wound environment. Proposed mechanisms include broad-spectrum antimicrobial and anti-biofilm activity, optimization of wound moisture through high vapor permeability, modulation of inflammation and protease activity via copper-mediated macrophage polarization, and enhanced extracellular matrix stabilization through copper-dependent lysyl oxidase activity. Collectively, these effects may he lp disrupt the chronic inflammatory cycle characteristic of hard-to-heal wounds.

In summary, Copper Dressings represent an effective, optimal choice debridement technique, tissue-sparing strategy for stimulating autolytic debridement, enabling stalled wounds to progress toward healing.

Introduction

Hard-to-heal wounds represent a significant healthcare challenge, as millions of individuals suffer from them. For example, in the USA alone, ~2.5% of the population suffer from a chronic wound[1]. Inflammatory disorders, neurological, hematologic, and other metabolic diseases can cause chronicity of wounds and prevent healing. With the increase of worldwide aging population and diabetes, this problem is causing a huge burden on the healthcare systems[2]. The vast majority of the chronic wounds have biofilm, which further prevents wound healing[3]. The devitalised tissue in a wound delays wound healing, as it stops the generation of granulation tissue and serves as a source for bacterial growth[4]. A critical first step of chronic wound management is the removal of devitalized or necrotic tissue from the wound bed to allow the reconstruction of the extracellular matrix (ECM) and regeneration of new tissues[5].

Debridement is a key component of the TIME framework, directly affecting not only the wound bed but also the wound edges and periwound skin. By removing nonviable tissue and reducing inflammation, it promotes wound progression and ultimately contributes to improved patient quality of life[6]. Initial and repeated debridement—whether surgical or nonsurgical (autolytic, biological, enzymatic, or mechanical)—is a cornerstone of hard-to-heal wound management. Because biofilm formation, biochemical imbalances, and persistent cellular burden can impair healing, ongoing maintenance debridement is often required throughout the wound-healing process[7].

There are several methods to actively debride devitalized tissue, such as by sharp or surgical removal of the necrotic tissue[4]. The choice of technique depends on tissue type of the wound bed, level of its humidity and patient related factors[6]. However, these interventions require specific skills and in many cases result also in damage of the healthy tissue[4] or can not proceed due to wound localization, wound size or patient related factors. In contrast, autolytic debridement relies on the body's own enzymes, especially properly regulated matrix metalloproteinases (MMPs), activated phagocytes and moisture balance to break down necrotic tissue, without damaging healthy tissue[8,9]. Nevertheless, in chronic wounds, autolytic debridement does not occur, due to dysregulation of these systems[4,5,9].

Copper is an essential trace element involved in numerous physiological processes across body tissues, including the skin[10]. Many tightly regulated wound-healing mechanisms depend on copper[11]. It supports platelet-derived growth factor (PDGF) activity during hemostasis and promotes angiogenesis through key mediators such as vascular endothelial growth factor (VEGF) and angiogenin during the proliferative phase. Copper also stimulates dermal fibroblasts to produce collagen (types I, III, and V), elastin, fibrillins, and HSP-47, contributing to ECM formation and remodeling[12].

In addition, copper serves as a cofactor for lysyl oxidase (LOX), enabling effective cross-linking of collagen and elastin and stabilizing the newly formed ECM. Copper modulates keratinocyte integrins during remodeling and influences protease activity, including MMPs and neutrophil elastase, which are critical for controlled tissue turnover[13]. Copper has also been shown to directly stimulate the secretion of MMP-1 at the protein, mRNA, and promoter levels, indicating transcriptional regulation[14].

Dressings containing copper oxide microparticles (hereafter referred as Copper Dressings) are in clinical use since 2019[15]. These dressings possess potent antimicrobial properties[16] and kill microorganisms even when they are protected by biofilm[17]. Importantly, the copper ions, which are constantly and stably released from the Copper Dressings at ppm levels, stimulate wound healing processes. This was demonstrated in animal models[18], human explant studies[19,20], and in non-infected chronic diabetic wounds[21,22], venous ulcers[23], and other hard-to-heal wounds[24-26]. In the current study we analyzed the capacity of the Copper Dressings combined with compression therapy as a standart of care to stimulate autolytic debridement in hard-to heal wounds that did not respond to previous standard of care (SOC) treatments, "stagnated" in a non-responsive condition, with significant slough and necrotic tissue. We describe clinical cases in which the capacity of the Copper Dressings to highly and efficiently stimulate autolytic debridement releases the wounds from their "stuck" condition allowing

them to heal. We also have showed the evolution of wound bed, inflammation and infection control, moisture balance and the quality of wound edges and periwound skin in patients using Copper Dressings and compression therapy. We discuss the potential mechanisms of autolytic debridement stimulation by the Copper Dressings.

Methods

Ambolutary patients, with chronic wounds (present between 2 months to 15 years) that did not respond favourably to previous standard to care treatments that were stuck at the inflammatory wound healing stage with necrotic tissue, were included in the study after signing informed consent. Following Copper Dressings wound management, the patients were observed until complete debridement and wound bed granulation or complete healing. No pharmacological agents, other medical products, nutritional supplements or any other auxiliary procedures (oxygen therapy, lymphatic drainage, VAC-therapy, etc.) were performed. Cardiological, endocrinological, nephrological or any other support was carried out by a related specialist according to the indications. The ulcers condition and size were evaluated according to the TIME-concept[9] at all visits. Toe Brachial Pressure Index (TBPI) was determined for all patients. All patients were treated exclusively with Copper Dressings combining with a multi-component (rest and active) elastic bandage from the distal parts of the foot to the knee. The layering, application technique, quantitative and qualitative composition of the bandage components and the level of compression were determined according to the configuration of the limb, its circumference, the patient's movement mode and were selected in each case individually. During follow-up visits, dressings were changed three times per week during the initial phase of treatment, decreasing to twice weekly in the later stages, except in one case involving a severely necrotic wound bed that required more frequent changes. The frequency of dressing changes was determined by the level of exudate and the type of tissue present in the wound bed.

Patient-related factors such as daily activity (walking and rest), nutritional status, smoking habits, and other variables that might positively or negatively influence wound healing were not systematically monitored due to the ambulatory nature of care. Wound bed evolution and condition was monitored by using WoundDoc software (Dalian Orientech Co.) in a 2D mode on each dressing change.

Results

Across eight outpatients (ages 27–82) with complex, long-standing lower-extremity wounds, Copper Dressings were associated with rapid and consistent clinical improvement. The cohort included individuals with VLUs and mixed leg ulcers due to secondary lymphedema, PTS, PAD with complex comorbidities such as obesity, skin cancer, Reynolds syndrome, calf pump disfunction, prior failed autodermoplasty, and significant cardiovascular comorbidities. Wound duration prior to copper treatment ranged from 2 months to 15 years, and many wounds were characterized by extensive necrotic or devitalized tissue and had failed previous therapies.

Following initiation of copper dressings, a rapid reduction in necrotic and devitalized tissue was typically observed within the first few days. This was consistently followed by the development of healthy granulation tissue and progressive improvement of the wound bed. In several cases, marked wound reduction occurred within weeks, including near-complete closure (96.7% reduction by day 56) and full healing by day 47 in one patient. Even among patients with impaired perfusion (e.g., low TBPI) or significant systemic comorbidities, the dressings were associated with effective clearance of necrotic tissue, stimulation of granulation, and steady progression toward healing, including improvement of the wound edges and periwound skin.

A clear reduction in local inflammation and improved moisture balance was observed. Until complete and effective debridement was achieved, dressing changes were simple and rapid, requiring no additional manipulation of the wound bed beyond routine replacement. No adverse events occurred, even under high-level compression therapy. There were no cases of maceration or skin irritation, and pain levels decreased as wound healing progressed.

A detailed description of each case is hereby provided:

CASE #1:

A 43-years old female patient, suffering from Post-Thrombotic Syndrome (PST) and secondary lymphedema, had a 30.59 cm^2 "stuck" venous ulcer for 6 months, with plenty of devitalised tissue (Figure 1A) when the Copper Dressings wound management started. Shortly after the devitalised tissue was replaced by granulation tissue (Figure 1C) and after 56 days of Copper Dressings wound management, the wound size was reduced by 96.7% (Figure 1K) as measured by WoundDoc software (Dalian Orientech Co.).

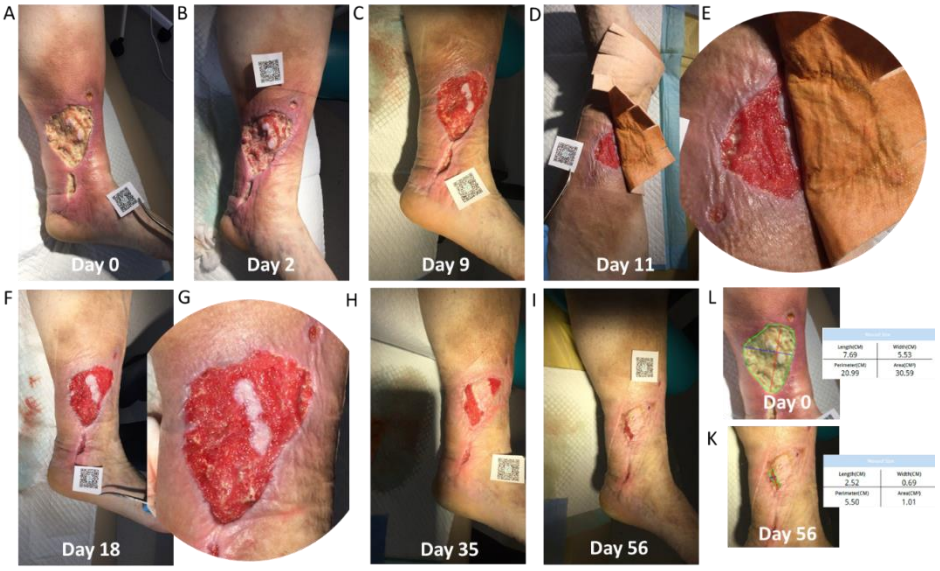

Figure 1. A. Wound condition after 6 months of treatment, when the application of the Copper Dressings was initiated. The wound condition after 2 (B), 9 (C), 11 (D & E), 18 (F & G), 35 (H), and 56 (I) days of Copper Dressings management. The wound was almost completely closed at Day 56, with 96.7% wound size reduction as compared to Day 0 (L and K).

CASE #2

An 82-years old female patient, suffering from secondary lymphedema and skin cancer, had a large wound spread from below the right knee throughout her lower leg and top of the foot (Figure 2A) for 9 months. After 9 days of Copper Dressings wound management, the devitalised tissue was replaced by granulation tissue (Figure 2B). The wound continued to improve as can seen after 27 days (Figure 2C). Skin cancer area was revealed after debridement.

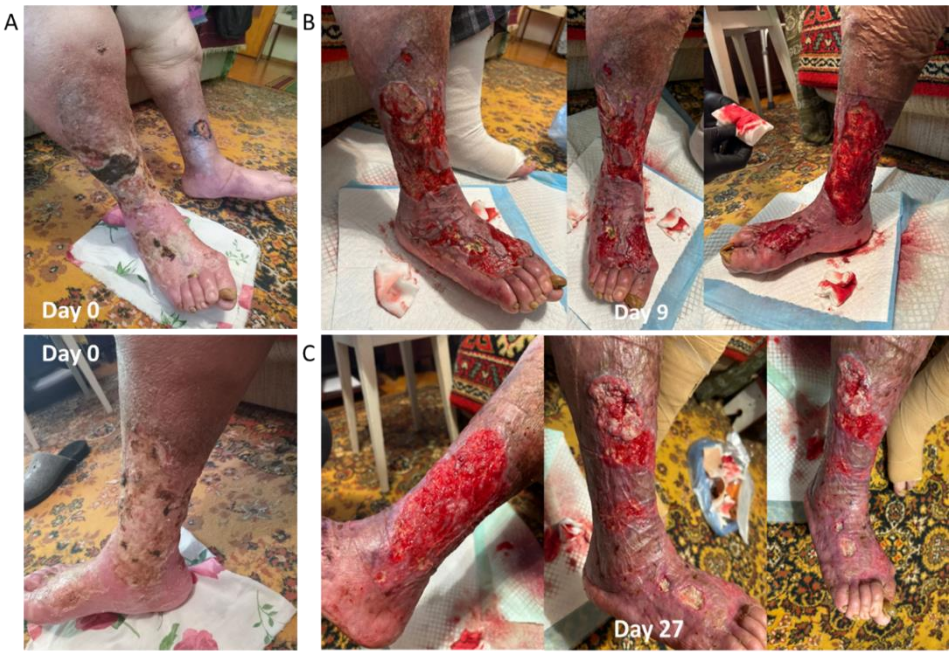

Figure 2. A. Wound condition after 9 months of treatment, when the application of the Copper Dressings was initiated. B. Wound condition after 9 days of Copper Dressings management. All devitalized tissue disappeared and the wound was filled with granulation tissue. C. The wound condition after 27 days of Copper Dressings management.

CASE #3

A 49-years old female patient, suffering from secondary lymphedema, obesity and several unsuccessful autodermoplasty, had a large venous leg ulcer in each leg (Figures 3A) for 5 years, despite positive pedis pulse palpation, when Copper Dressings wound management was initiated. Shortly after, the devitalised tissue was replaced by granulation tissue in both wounds (Figure 3B) and after 14 days the wound bed was filled with healthy granulation tissue (Figure 3C).

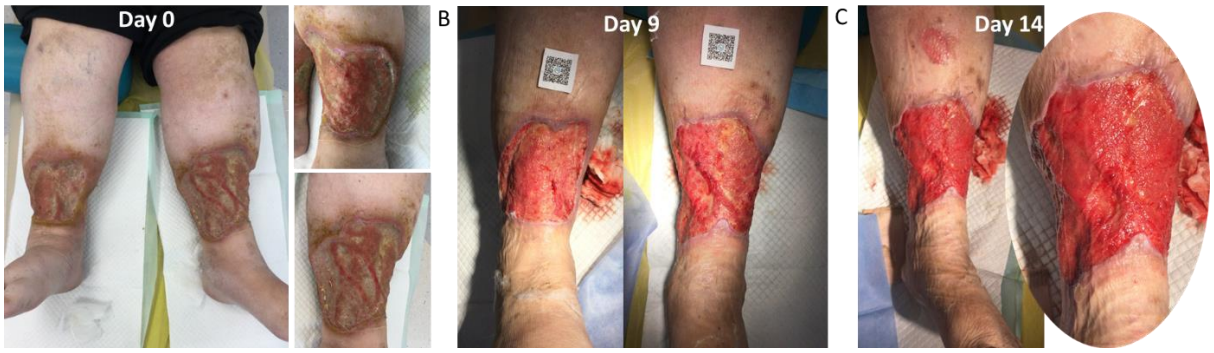

Figure 3. A. Wounds condition after 5 years of previous unsuccessful treatment, when the application of the Copper Dressings was initiated. B. Wounds condition after 9 days of Copper Dressings management. Devitalized tissue disappeared and the wound started to be filled with granulation tissue. C. The wound condition after 14 days of Copper Dressings management – the wound beds were full with healthy granulation tissue.

CASE #4

A 72-years old female patient, suffering from secondary lymphedema and calf pump dysfunction, with reported PTS 6 years earlier, had a large venous leg ulcer for 3 months (Figures 4A) prior to the Copper Dressings wound management initiation. Two days (Figure 4B) following the Copper Dressings application, already devitalised tissue started to disappear. This process continued (Figures 4C-4G) as the wound healing progressed, achieving full wound healing at 47 days (Figure 4H) of Copper Dressings wound management. The comparison of the initial wound condition and after 47 days of Copper Dressings wound management can be seen in the enlargements of the wounds in Figures 4A and 4H.

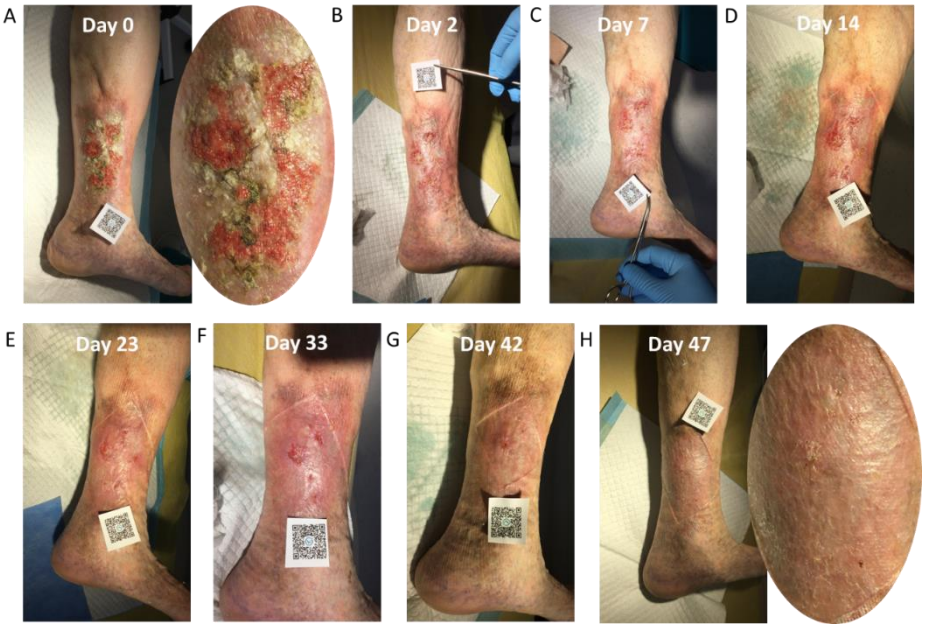

Figure 4. A. Start of the Copper Dressings wound management. B. Devitalised tissue started to disappear already after 2 days of treatment. Wound condition continued to improve until full wound healing was achieved at Day 47.

CASE #5

A 27-years old male patient, suffering from secondary lymphedema, Raynaud syndrome and several unsuccessful autodermoplasty, calf pump dysfunction, and despite positive pedis pulse palpation, had a large venous leg ulcer for 8 years (Figures 5A) prior to the Copper Dressings wound management initiation. The necrotic and devitalised tissue was then after replaced with granulation tissue as seen after 16 (Figure 5B), 32 (Figure 5C) and 51 (Figure 5D) days of the Copper Dressings application.

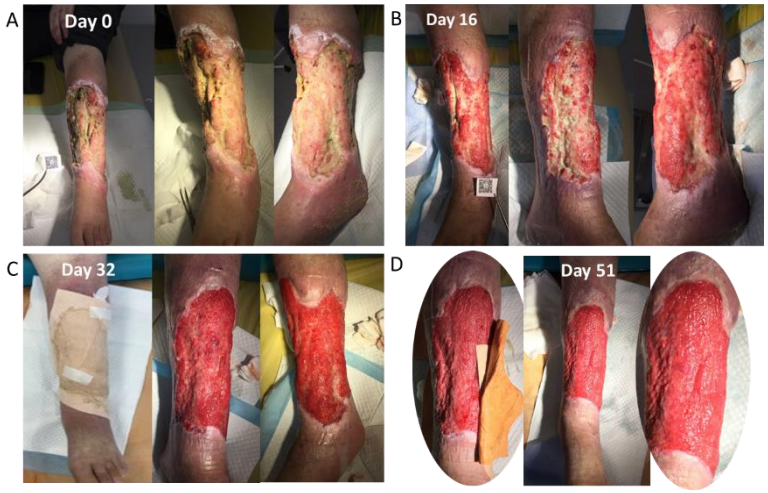

Figure 5. A. Copper Dressings wound management initiation. Pictures taken from two different angles. The necrotic and devitalised tissue was replaced with granulation tissue as seen after 16 (B), 32 (C) and 51 (D) days of the Copper Dressings application.

CASE #6

A 59-years old female patient, suffering from PTS, with positive pedis pulse palpation, had a venous leg ulcer for 1 year (Figures 6A) prior to the Copper Dressings wound management initiation. The necrotic and devitalised tissue, especially in the periwound, disappeared and was replaced with granulation tissue as seen after 14 days (Figure 6B) and 29 days (Figure 6C) of Copper Dressings application.

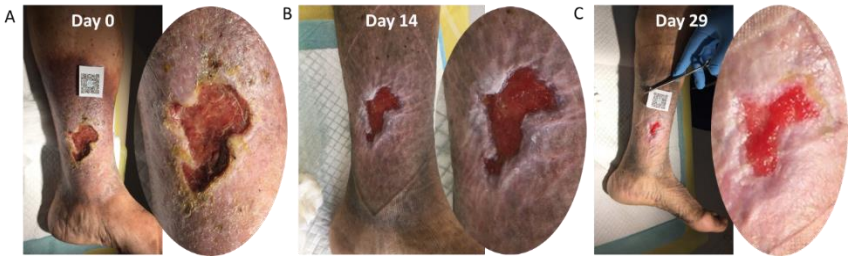

Figure 6. A. Commencement of the Copper Dressings treatment of the venous leg ulcer, present for 1 year. B. Wound condition after 14 days. The surrounding necrotic tissue disappeared and the wound bed was filled with granulation tissue. C. The wound bed was filled with healthy looking granulation tissue and the wound size was significantly reduced at Day 29 of the Copper Dressing wound management.

CASE #7

A 59-years old female patient, suffering from secondary lymphedema, obesity, moderate Peripheral Artery Disease (PAD), had a mix leg ulcer for 15 years (Figures 7A). The TBPI was 0.5 with atherosclerosis process in the arteries, based on duplex examination of the lower extremities. Following the application of Copper Dressings, the necrotic tissue disappeared as seen 7 days later (Figure 7B) and was replaced with granulation tissue (Figure 7C) as seen 18 days after the commencement of the Copper Dressings wound management.

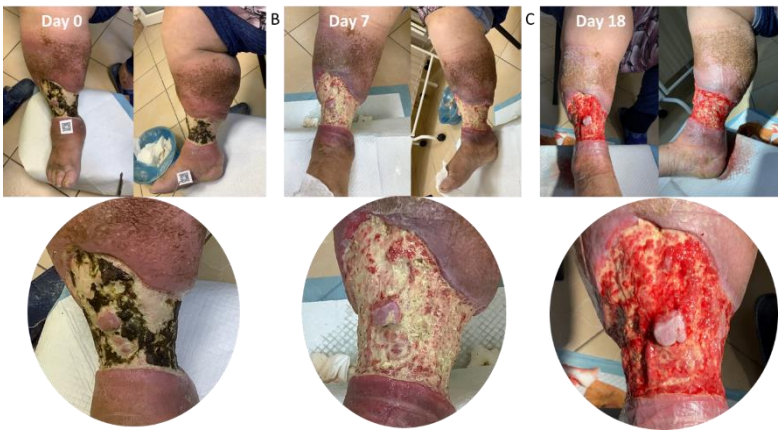

Figure 7. A. Wound condition at the start of treatment. B. Wound condition after 7 days of Copper Dressings wound management. The necrotic tissue disappeared. C. Day 18 - the devitalized tissue in the wound bed was almost completely replaced with granulation tissue. Enlargements of the wounds are shown in Figures 7A-C.

CASE #8

A 62-years old male patient, suffering from secondary lymphedema, 2 prior heart attacks, two cardio stents, arrhythmia, dilated cardiomyopathy, a Left Ventricular Ejection Fraction of 30%, a TBPI of 0.75, and a pulse wave of 90 mmHg, suffered from skin necrosis and a wound in the posterior part of the leg for 2 months (Figure 8A). Prior to the initiation of the Copper Dressings treatment, the necrotic tissue was removed surgically (Figure 8B). However, the necrotic tissue at the edges of the wound were not removed, in order not to potentially damage healthy tissue (Figure 8B). The Copper Dressings were then applied (Figure 8C). After 2 days, the devitalised tissue was significantly reduced (Figure 8D). The reduction of devitalised tissue and appearance of granulation tissue continued as documented on Days 6 (Figure 8E), 13 (Figure 8F), 22 (Figure 8G), 34 (Figure 8H), and 40 (Figure 8I) with the disappearance of the surrounding necrotic tissue.

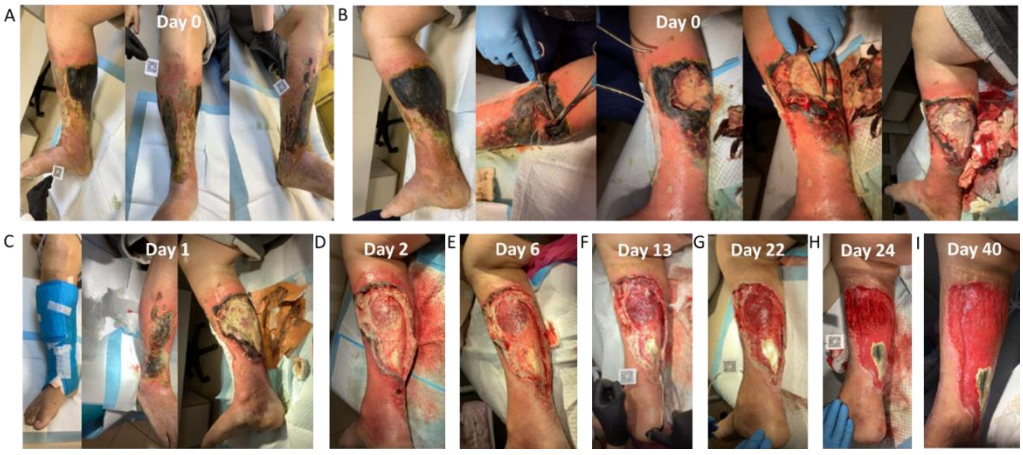

Figure 8. A. Wound condition at the start of treatment. B. Necrotic tissue was removed surgically without reaching the edges of the wound. C. The Copper Dressings wound management was then commenced. The remaining necrotic tissue at the wound edges gradually disappeared in parallel to the appearance of granulation tissue throughout the wound bed, which replaced the devitalized tissues (D-I).

Discussion

Chronic wounds may persist for years, imposing substantial physical and psychological burdens on patients and generating significant healthcare costs[2]. They are typically characterized by persistent inflammation and the presence of devitalized and necrotic tissue. Standard management therefore begins with tissue removal, most commonly through surgical or enzymatic debridement[4,5]. However, these approaches do not always succeed in resolving the chronic inflammatory state and may inadvertently damage viable tissue, thereby impeding healing progression[27,28].

In the present case series, we aimed to evaluate whether Copper Dressings can enhance healing of chronic wounds by stimulating autolytic debridement, without the need for direct debridement techniques. Given that the goal is to reduce the wound area as quickly as possible, high-quality debridement must be performed as promptly as possible. Debridement and wound healing are continuous, dynamic processes that evolve constantly. Therefore, the most effective, patient-friendly, and cost-efficient debridement techniques should be employed throughout the entire course—from initial treatment to complete wound closure.

As we have shown in the 8 cases presented in this article, the application of Copper Dressings in hard-to-heal devitalized chronic wounds resulted in the "release" of the wound healing "stalled" condition and allowed the wounds to progress towards healing. All the wounds treated were stalled in the inflammatory phase, in which the presence of devitalized and necrotic tissues, and most probably biofilm, prevented the wounds to progress towards the proliferative wound healing stage. Based on previous observations, including a case in which the application of Copper Dressings healed an anterior ankle full thickness skin necrosis wound without any other debridement[29], we decided to manage these wounds with Copper Dressings. Taken together, it is clear that the Copper Dressings stimulate debridement in hard-to-heal wounds, even in patients with significant comorbidities. Similar report is also currently in press (Melamed E. and Cheyne I. personal communication).

Since the Copper Dressings do not have a direct enzymatic activity (e.g. collagenase activity), it is therefore clear that the Copper Dressings stimulate the autolytic debridement natural physiological process in these chronic wounds, allowing them to "exit" the "stuck" state in which they are found and allowing for the wound healing processes to advance.

The enhancement of the autolytic debridement process by Copper Dressings probably occurs through several parallel mechanisms (Figure 9). Firstly, the dressings have potent biocidal properties including against biofilm[16,17]. The broad-spectrum antimicrobial activity and anti-biofilm property of the dressings support autolysis by reducing the microbial and biofilm burden, known to impaire protease activity in chronic wounds[30]. These activities continue throughout the wound management with the Copper Dressings, preventing repeated wound colonization and biofilm formation, allowing the wound to continue the healing process.

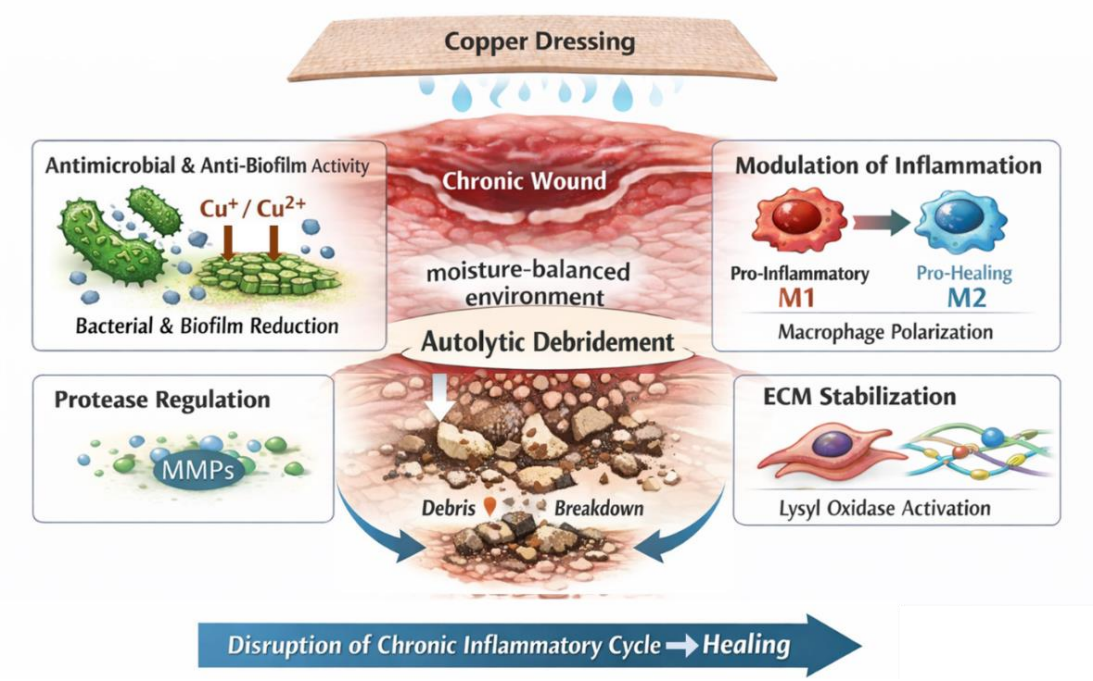

Figure 9. Proposed mechanisms of disruption of the chronic inflammatory cycle of chronic wounds by the Copper Dressings.

Secondly, the Copper Dressings create an optimal moisture environment in the wound bed. Moisture balance is a well-established requirement for autolysis[31,32]. This is achieved by the high-permeability of the Copper Dressings, determined by their high Moisture Vapor Transmission Rate (MVTR) of 4000–5000 g/m²/24 h (≈ 4–5.8 × 10^{-2} L/m²/s; unpublished data). High MVTR maintains optimal moisture[31,32]. In addition, the Copper Dressings absorption is vertical[23]. Thus, as long as the dressing is not completely full with wound exudate, the wound exudate and moisture is removed from the wound bed without causing maceration, which is ideal for autolytic conditions.

Thirdly, the copper ions released from the Copper Dressings stimulate key physiological processes that enhance autolytic debridement. Copper ions promote the transition of macrophages from a pro-inflammatory M1 phenotype to a pro-healing M2 phenotype[33]. M2 macrophages secrete tissue inhibitors of metalloproteinases (TIMPs) and reduce expression of inflammatory cytokines (e.g., TNF-α, IL-1β) that drive excessive MMP-2 and MMP-9 production in chronic wounds[34]. MMPs are central regulators of the inflammatory phase of wound healing[35]. For example, elevated levels of MMP-9 are strongly associated with venous leg ulcers chronicity[36]. Notably, copper has been shown to selectively enhance MMP-1 activity without increasing MMP-2 and MMP-9 levels[14]. MMP-1, the most widely expressed interstitial collagenase, initiates ECM remodeling by cleaving collagen and other substrates[37,38]. By rebalancing the MMP/TIMP ratio, copper helps prevent destructive proteolysis while preserving early-phase enzymatic activity required for autolysis[39]. Thus, a central effect of the copper ions is the modulation of chronic inflammation, creating a microenvironment conducive to wound progression.

Copper is also essential for ECM rebuilding through its role as a mandatory cofactor for lysyl oxidase (LOX)[40], the enzyme responsible for crosslinking collagen and elastin. LOX-mediated crosslinking strengthens newly formed ECM and shifts the wound from a degradation-dominated state toward structural stability[41]. Copper deficiency reduces LOX activity and collagen deposition[42], while Copper Dressings increase collagen synthesis and deposition[19,20]. Enhanced ECM integrity indirectly downregulates excessive MMP activity, as unstable ECM typically upregulates protease release in chronic non-healing wounds[43]. Copper also stabilizes HIF-1α and increases VEGF expression[18,44], supporting angiogenesis and enhancing oxygen and nutrient delivery—conditions that normalize protease function[45,46].

An additional important advantage of the Copper Dressings through their ability to 'kick-start' the wound-healing process by promoting autolytic debridement, is that they can eliminate the need for alternative debridement methods that may adversely affect healthy tissue or damage regenerating structures, as may occur with more aggressive approaches such as surgical, enzymatic or sharp debridement. The findings of this case series are in agreement with previous reports[15,23,26,47] showing fast production of granulation tissue and wound closure in hard to heal wounds.

Conclusions

Copper Dressings contribute to "un-stalling" the wound chronicity by creating an antimicrobial, moist, pro-healing environment that helps break the chronic inflammatory cycle, enabling subsequent progression towards tissue repair. Copper Dressings represent an effective, tissue-sparing strategy for stimulating autolytic debridement, enabling stalled chronic wounds to progress toward healing while potentially reducing the need for aggressive debridement techniques.

Conflict of Interest Statement:

G.B. is the Chief Scientist of MedCu, the manufacturer of the Copper Dressings.

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