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REVIEW ARTICLE

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Preparing the soil: Adjusting the metabolic health of patients with chronic wounds and musculoskeletal diseases

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Abstract

In recent years, systemic inflammation has emerged as a pivotal player in the development and progression of various degenerative diseases. This complex, chronic inflammatory state, often undetected, can have far-reaching consequences for the body's physiology. At the molecular level, markers such as C-reactive protein, cytokines and other inflammatory mediators serve as indicators of systemic inflammation and often act as predictors of numerous musculoskeletal diseases and even certain forms of cancer. The concept of 'meta-inflammation', specifically referring to metabolically triggered inflammation, allows healthcare professionals to understand inflammatory responses in patients with metabolic syndrome. Driven by nutrient excess and the

List of Abbreviations: AGEs, advanced glycation end products; AMPs, antimicrobial peptides; AP, alkaline phosphatase; ATP, adenosine triphosphate; BMD, bone mineral density; BMP, bone morphogenetic protein (BMP-2, BMP-4); CRP, C-reactive protein; CXCR2, C-X-C motif chemokine receptor 2; DHEA, dehydroepiandrosterone; ERK, extracellular signal regulated kinase; GAGs, glycosaminoglycans; GH, growth hormone; GLUT-1, glucose transporter 1; Hb, haemoglobin; HbA1c, glycated haemoglobin; IGF-1, insulin-like growth factor-1; IL, interleukin (IL-6, IL-1β); LPS, lipopolysaccharide; MCP-1, monocyte chemotactic protein-1; MMP, matrix metalloproteinase (MMP-3, MMP-9, MMP-13); MS, metabolic syndrome; OA, osteoarthritis; p38, p38 mitogen-activated protein kinase; PGE-2, prostaglandin E2; PPARγ, peroxisome proliferator-activated receptor γ; RANKL, receptor activator of nuclear factor kappa-B ligand; rhIGF-I, recombinant human insulin-like growth factor I; ROS, reactive oxygen species; Runx2, runt-related transcription factor 2; SASP, senescence-associated secretory phenotype; SCF, stem cell factor; SCFAs, short-chain fatty acids; T2DM, type 2 diabetes mellitus; T3 and T4, triiodothyronine and thyroxine (thyroid hormones); Th, T helper cell; TIMP-3, tissue inhibitor of metalloproteinase-3; TNF-R2, tumour necrosis factor receptor 2; TNF-α, tumour necrosis factor-alpha; Treg, regulatory T cell; TR-α and TR-β, thyroid hormone receptors alpha and beta.

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expansion of adipose tissue, meta-inflammation is closely associated with insulin resistance, further propagating the metabolic dysfunction observed in many Western societies. Wound persistence, on the other hand, exacerbates the detrimental effects of prolonged inflammation at the local level. Acute inflammation is a beneficial and essential process for wound healing and infection control. However, when inflammation fails to resolve, it can impede the healing process, leading to chronic wounds, excessive scarring and even the activation of fibrotic pathways. This approach significantly reduces the efficacy of regenerative biological therapies. Our review focuses on the vital role of proteins, vitamins and minerals in collagen synthesis and cell proliferation for tissue healing. We also examine hormonal influences on regeneration, noting the negative effects of imbalances, and emphasize glucose regulation's importance in creating a stable environment for chronic wound healing.

KEYWORDS

chronic wounds, inflammation, metabolism, orthobiologics, regenerative medicine

Key Messages

- Systemic inflammation and meta-inflammation are pivotal in the development and progression of degenerative diseases, with implications for wound healing and regenerative therapies.
- Molecular markers of systemic inflammation serve as predictors of musculoskeletal diseases and cancer, highlighting their significance in clinical practice.
- Meta-inflammation, driven by nutrient excess and adipose tissue expansion, is closely associated with insulin resistance and metabolic dysfunction observed in Western societies.
- Prolonged inflammation impedes wound healing, leading to chronic wounds and reduced efficacy of regenerative biological therapies.
- Understanding and addressing systemic inflammation and meta-inflammation offer promising avenues for therapeutic interventions and preventive strategies in degenerative diseases and wound persistence.

1 | INTRODUCTION

Patients with similar pathological conditions can exhibit drastically different outcomes despite receiving identical treatments. In cancer, for example, two individuals might be diagnosed with the same cancer type at the same progression stage, but one might deteriorate rapidly while the other resists the disease for several years, seemingly unscathed by the disease.[1] A similar pattern emerges when considering candidates for regenerative therapy.[2] Numerous factors can affect the body's healing capacity. While some factors, such as age and genetics, are unchangeable, others, including diet, lifestyle, sleep quality and supplementation, can be adjusted.[3,4] In regenerative medicine, the effectiveness of treatment depends heavily on the body's response. A favourable cellular reaction hinges on several factors: the absence of persistent systemic inflammation, a well-functioning immune system and the availability of essential nutrients such as vitamins and minerals.[5]

In our review, we delve into the vital aspects of metabolic optimization. We use key clinical signs when assessing patients, recommend fundamental laboratory tests before regenerative treatments, and discuss potential treatment choices based on individual patient needs.

This manuscript aims to shed light on the metabolic pathways involved and the management of patients with chronic wounds who are potential candidates for regenerative medicine treatments. Systemic inflammation and degenerative diseases are strongly connected with meta-inflammation and wound persistence.[6,7] Therefore, we advocate for strategies that can minimize inflammation

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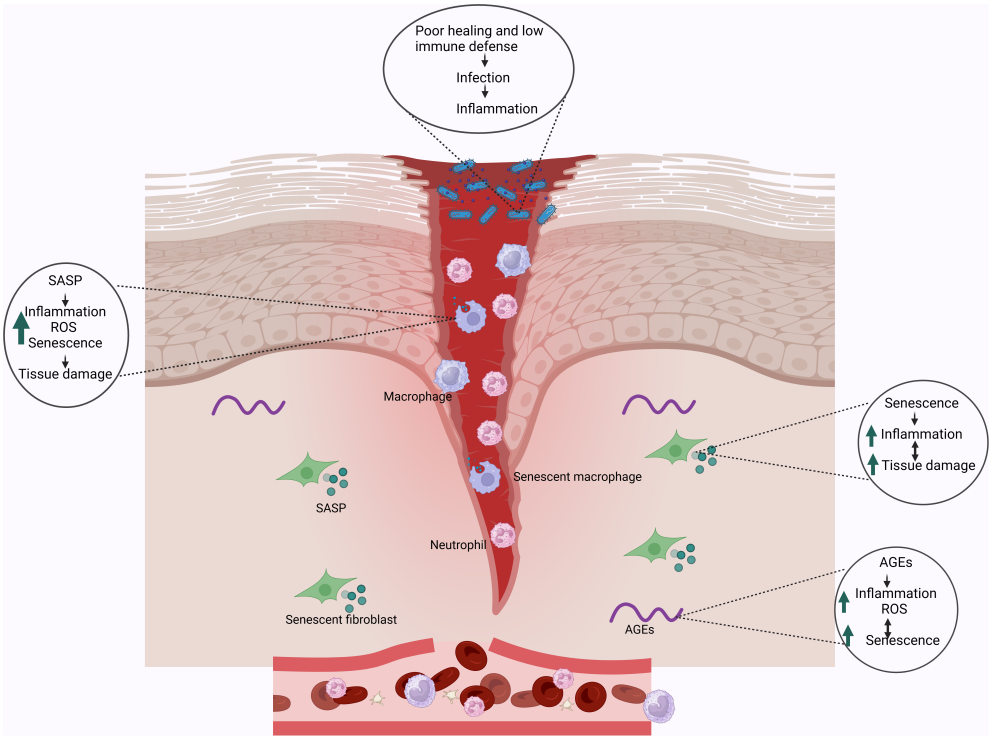


FIGURE 1 Factors that contribute to the healing of chronic wounds. Chronic wounds may become infected with bacteria that worsen inflammation. Keratinocytes from chronic wounds exhibit aberrant activation, causing hyperproliferation and impaired migration. A large proportion of chronic wound cells (e.g., macrophages and fibroblasts) becomes senescent, producing a senescence-associated secretory phenotype (SASP) that perpetuates senescence, triggers the release of reactive oxygen species (ROS) and exacerbates inflammation. Large amounts of advanced glycation end products (AGEs) also contribute to inflammation and cellular senescence in the wound environment. These characteristics cause tissue rupture and impair cellular functions, which leads to re-epithelialization.

and prepare a patient's body for biological treatments to optimize regenerative outcomes. The significance of sleep, the gut microbiota and hormonal equilibrium will also be included, underscoring the potential of these conditions in achieving a balanced state optimal for regenerative procedures.

2 | CONCEPTS OF SYSTEMIC INFLAMMATION AND META-INFLAMMATION

Disturbances in cellular processes associated with wound healing, often observed in conditions such as diabetes and ageing, can result in impaired healing and the development of chronic wounds resistant to closure. Extensive research has pinpointed obesity, dyslipidaemia, insulin resistance and hypertension as key metabolic risk factors, collectively referred to as the 'deadly quartet'.[1] These factors contribute to the dysregulation of physiological processes, leading to detrimental alterations in the subchondral bone, cartilage damage, changes in the joint microenvironment and compromised skin integrity.[2,3]

The inflammatory state linked to metabolic syndrome does not align precisely with the criteria for either acute or chronic inflammation.[4] Oftentimes, there is no apparent tissue damage, and the magnitude of inflammatory activation is relatively limited. Hence, chronic inflammation is frequently referred to as 'low-grade' chronic inflammation or 'meta-inflammation', denoting inflammation triggered by metabolic factors. Consequently, meta-inflammation is marked by elevated serum levels of pro-inflammatory cytokines like TNF-α, IL-6 and IL-1β.[5] Other systemic markers, such as ferritin, uric acid, fibrinogen, phospholipase A2 and homocysteine, may or may not be elevated. Furthermore, hyperglycaemia and hyperlipidaemia maintain active meta-inflammation.[6]

Metabolic syndrome (MS) and type 2 diabetes (T2DM) are recognized contributors to the diminished multipotency of mesenchymal stem cells. As depicted in Figure 1, his phenomenon arises from the generation of advanced glycation end products (AGEs), oxidative stress and inflammation, which collectively suppress proliferation, induce apoptosis and elevate the production of intracellular reactive oxygen species (ROS). The elevated rate of apoptosis and ROS accumulation may, in part,

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account for the observed decrease in differentiation potential among cells within the framework of MS.[7]

As a whole, excess glucose changes the metabolism and shape of cells, as well as the structure of the extracellular matrix, by slowing the production of collagen and degrading proteoglycans.[8]

In various tissues, the glucose receptor GLUT-1 exhibits overexpression, possibly exacerbating glucotoxicity, particularly under hyperglycaemic conditions. Moreover, elevated glucose levels have been demonstrated to attenuate the differentiation capacity of mesenchymal stem cells originating from adipose tissue, muscle or bone marrow in vitro.[8]

In meta-inflammation, the inflammatory response differs from that observed in conditions like rheumatoid arthritis and other autoimmune disorders. It manifests as a chronic, relatively low-grade inflammation primarily mediated by the innate immune system. Adipokines, a class of inflammatory mediators produced and secreted by adipose tissue, represent another systemic source of inflammation in individuals affected by obesity. The participation of pro-inflammatory adipokines released from white adipose tissue in obese adults is also associated with processes such as cartilage degradation, synovial inflammation and the development of joint osteophytes.[9] Additionally, research has shown that stem cell factor (SCF), which is produced by keratinocytes, is important for wound healing because it brings together a special group of skin and immune system cells more quickly after injury. This chemokine has reduced expression in the setting of meta-inflammation, hindering cell migration and proliferation in the wound bed.[10,11]

In meta-inflammation, the roles of key adipokines such as leptin, adiponectin, visfatin and resistin have been extensively investigated. Notably, in meta-inflammation, the expression of leptin and its receptors in various tissues has been observed to elevate, leading to cellular apoptosis and the secretion of metalloproteinases.[12] Conversely, adiponectin levels in synovial fluid obtained from individuals with knee osteoarthritis (OA) displayed a positive correlation with aggrecan degradation. Furthermore, plasma adiponectin levels were linked to joint pain in female patients and were found to induce the expression of various catabolic and pro-inflammatory factors such as MMP-3, MMP-9, MMP-13, PGE-2, nitric oxide synthase-2, IL-6 and monocyte chemotactic protein-1 (MCP-1) in chondrocytes.[13] This process can potentially occur on the skin of patients with chronic wounds.[14]

Adipokines can also alter cell fate, inducing cellular senescence. Studying the response of these cells to stimulation by different adipokines, whether in the joint environment or the skin, can establish new guidelines for the treatment of degenerative diseases and chronic wounds.[5] Significantly, during ageing and obesity, adipocytes accumulate within the bone marrow. These adipokines possess the capability to function as senescence-associated secretory phenotypes (SASP), thereby contributing to cellular senescence and influencing energy metabolism, consequently affecting tissue remodelling processes.[15] Senolytic drugs such as quercetin target senescent cells and have already shown promise in reducing the senescent cell burden and improving diabetes symptoms, including inflammation and hyperglycaemia.[16] Furthermore, blocking the senescence-linked receptor CXCR2 directly accelerates diabetic wound repair in vivo.[17] Repurposing these existing treatments (several senolytic drugs and CXCR2 antagonists) is an attractive approach for wound management. Therefore, adipokines and their by-products are closely related to metabolic syndrome and degenerative pathological changes in cartilage, bone and skin.

3 | SLEEP AND HOMEOSTASIS

Another crucial aspect to consider inpatient evaluation is their sleep quality. Controlled experimental studies investigating the effects of acute sleep deprivation in humans have revealed alterations in inflammatory mediators due to sleep loss.[4] Increases in these mediators have been detected in healthy individuals subjected to experimental wakefulness lasting more than 24 h, as well as in response to varying degrees of sleep restriction, ranging from 25% to 50% of the usual 8-h sleep duration.[18] Recent investigations have shown that delayed wound healing in obese diabetic mice caused by sleep fragmentation is homologous to delayed wound healing in some patients with type 2 diabetes.[19] The authors suggest that altered leptinergic signalling and inflammatory proteins contribute to the delay in wound healing. Interestingly, elevated levels of TNF-α were evident in the wounds of sleep-deprived rats. Similarly, the literature suggests a greater incidence of sleep apnoea in patients with chronic wounds than in the general population.[20]

The circadian rhythm regulates numerous cellular functions, including cell division, cell migration, metabolism and various intracellular biological processes. It is thought that physiological changes occurring during sleep create an optimal microenvironment for the proliferation, migration and differentiation of stem cells.[18] Circadian clock genes directly or indirectly mediate these effects through the release of hormones and cytokines during sleep phases. Hormones such as melatonin and cortisol are released in response to neural and optical signals, working in an orchestrated fashion to regulate a multitude of biological functions.[21]

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Recent findings have shown that melatonin promotes osteogenesis and chondrogenesis while inhibiting adipogenesis. Additionally, melatonin has a protective effect against mesenchymal stem cell apoptosis triggered by oxidative stress.[22] Melatonin attenuates the intracellular generation of ROS to improve cell viability and increase the differentiation of progenitor cells into other lineages. Melatonin also plays an important role in regulating the proliferation and differentiation of embryonic stem cells.[22]

Several studies have reported the stimulatory effects of melatonin on bone formation and its inhibitory effects on bone catabolism. The reinforcing effect of melatonin on osteoblasts has also been suggested to be mediated by its direct action on the differentiation and proliferation of bone-forming cells.[23] Similarly, the role of melatonin in protecting the dermis has been demonstrated because there are melatonin receptors in the skin, and this organ can produce melatonin.[21] Among the good effects of melatonin on bone are increasing alkaline phosphatase levels and mineralization, encouraging type I and type III collagen synthesis, increasing bone mass and facilitating the growth and fusion of new bones with existing bones. These findings indicate that melatonin is a promising candidate for tissue regeneration.[23]

In both laboratory experiments and studies involving living organisms, researchers have investigated how melatonin could impact bone healing. Notably, melatonin has been shown to enhance wound healing and stimulate the production of osteogenic markers like BMP-2 and -4, osteocalcin, and runt-related transcription factor 2 (Runx2), with its effects varying depending on the dosage used.[23] Melatonin effectively reverses the decline in cell proliferation caused by iron overload in bone marrow-derived stem cells by reversing the increase in the protein expression of p53, ERK and p38.[24] New studies have also shown the influence of sleep on the composition of the intestinal microbiome, for example, an increase in strains considered 'bad' was associated with a poor-quality diet, obesity and cardiovascular risk in other studies.[25]

4 | THE ROLE OF PHYSICAL ACTIVITY IN THE MANAGEMENT OF PATIENTS WITH CHRONIC WOUNDS

Effective management of chronic wounds and associated conditions like sarcopenic obesity necessitates a comprehensive understanding of the roles of physical exercise, nutritional supplementation and metabolic control.

The blood circulation in the calf muscles improved when exercise was used. Resistance training increases calf muscle pump function, lower limb circulation and walking ability in individuals with limited ambulation due to peripheral arterial disease or venous insufficiency.[26] Exercise improved acute wound healing in diabetic mice and healthy elderly humans, but the evidence is still insufficient on the effectiveness of exercise in healing ischaemic ulcers, venous leg ulcers and diabetic foot ulcers.[27] In addition to the potential direct benefits on chronic wounds, physical activity results in a series of important metabolic changes in the management of these patients.

From a strategic point of view, the type of physical exercise is fundamental as improving glycaemic patterns is the key point of the initial approach. In recent work, strength training was shown to be superior to aerobic training alone, while no significant difference was observed between strength training and combined training (aerobic + resistance training) for reducing glycated haemoglobin (HbA1c) levels. This result emphasizes the need for muscle activation and contraction to reduce glycaemic levels.[28] Muscle tissue is known to capture glucose independently of insulin, and increasing lean mass is an important factor in the fight against diabetes (Figure 2).

Sarcopenia is a multifactorial condition associated with poor glucose control, insulin resistance, and, subsequently, type 2 diabetes. The pathophysiological connection between sarcopenia and T2DM involves glycaemic control, inflammation, oxidative stress and adiposity.[29] The approach to treating sarcopenia in this context should not change, and it is important to prioritize the gain of lean mass as a way of increasing basal metabolic expenditure through resistance exercises and adequate supplementation, such as whey protein, creatine, vitamin D and omega 3.[9,10]

In cases requiring the management of sarcopenic obesity, combined strategies such as intermittent fasting and guided resistance exercise are recommended. Compared with moderate-to-vigorous physical activity alone, intermittent fasting combined with moderate-to-vigorous physical activity had a more significant effect on improving body mass, glycaemic indices and lipid profiles.[30]

As patients with chronic wounds tend to be more sedentary, the question of how much is enough for weekly exercise is common in the initial approach. Studies suggest that up to 60 min of strength training per week may be sufficient to mitigate age-related chronic diseases and a decrease in muscle function.[31] However, it is important to remember during the consultation that the guidelines from the American College of Sports Medicine for patients with osteometabolic disorders involve 150 min per week of aerobic exercise and 2 or 3 days of strength training, which should be ideal for functional improvement.[32]

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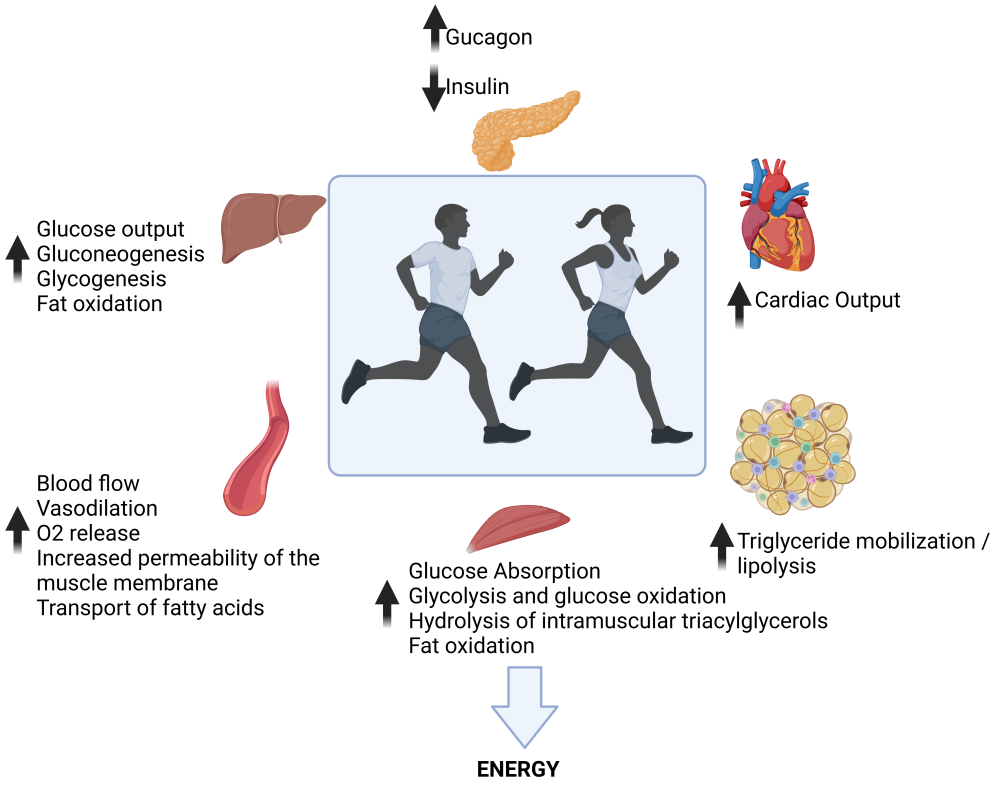


FIGURE 2 Mechanisms of physical activity in soil preparation and tissue homeostasis.

Integrating appropriate physical exercise regimens and nutritional strategies into patient care can significantly enhance outcomes in chronic wound healing and related metabolic disorders, emphasizing the importance of individualized and evidence-based approaches.

5 | THE IMPORTANCE OF DIET FROM A REGENERATIVE PERSPECTIVE

In recent literature, there has been an increasing awareness of the impact of diet on bone and cartilage health, particularly in the context of comparing fat and carbohydrate diets.[33] A high-sugar diet has been associated with the expansion of bone marrow adipose tissue, alongside the promotion of a pro-inflammatory environment. These factors could collectively exert a detrimental effect on bone and skin metabolism.[34] Additionally, research has demonstrated that fructose-induced MS reduces the ex vivo osteogenic capacity of marrow stromal cells while simultaneously augmenting their ex vivo adipogenic potential.[35] This phenomenon is associated with a decrease in the expression of the Runt-related transcription factor (Runx2) and an increase in peroxisome proliferator-activated receptor γ (PPARγ) under basal conditions. These results showed that fructose-induced MS caused severe changes in the microarchitecture and re-ossification of bone lesions. These changes may be related to how mesenchymal cells differentiate and commit to becoming fat cells or bone cells by changing the relationship between Runx2 and PPARγ. These findings show that diets with a high inflammatory content hinder the regenerative potential of progenitor cells.[36] Increased dietary inflammatory levels also correlate with a higher prevalence of symptomatic radiographic osteoarthritis of the knee and elevated serum levels of interleukin (IL)-6 and tumour necrosis factor (TNF)-R2. This suggests a robust connection between diet, inflammatory markers and the advancement of osteoarthritis.[37]

The Mediterranean diet has demonstrated a notable impact on alleviating symptoms in individuals with osteoarthritis, making it a compelling option among anti-inflammatory dietary approaches.[33] Individuals with higher adherence to the Mediterranean diet exhibited a notably reduced occurrence of knee osteoarthritis compared with those with lower adherence. The Mediterranean-style diet, recognized as a healthful dietary regimen, consistently demonstrates favourable impacts on various conditions including musculoskeletal, cardiovascular, metabolic and cognitive health. This dietary pattern is associated with decreased markers of oxidative stress, elevated levels of type II collagen and aggrecan, and suppression of proteins linked to apoptosis.[7,33] Moreover, a hyperglycaemic environment prevents satellite cells from differentiating into myocytes.[7] The Mediterranean diet, when combined with adequate hydration (over 1 litre daily), can enhance the healing of

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arterial ulcers, indicating that dietary assessments and interventions may improve wound healing and overall health in patients with chronic leg ulcers.[11]

Specifically, in patients with chronic wounds, glycaemic control is imperative; therefore, low-carbohydrate diets are the best option for initial management, combined with intermittent fasting.[38] An adequate protein intake, as well as its fractionation throughout the day, should be prioritized. In general, these patients ingest 1.6–2.5 g of protein per kilogram of body weight every day, which increases satiety, basal metabolism and healing potential.[39] Concerning dietary carbohydrates, a range of approximately 1.0–2.0 g of complex carbohydrates per kilogram of body weight per day should be used, and prioritizing vegetables, legumes and sources of fibre should also be an efficient way of controlling the glycaemic index.[40] Healthy fats such as olive oil, nuts, coconut oil and yellow cheeses might be recommended. A vegan diet is an option because it is considered an anti-inflammatory diet or a lifestyle. The survey focused on healthy fats (olive oil, nuts, almonds, avocado, fish), nutrient-rich foods (fruits, vegetables, and legumes), carbohydrates with a low glycaemic load (whole grains), and fresh herbs and spices. The aim is to reduce the consumption of processed and ultra-processed foods.[41]

6 | NUTRITIONAL SUPPLEMENTATION IN THE MANAGEMENT OF CHRONIC WOUNDS

Wound healing is a complex process that demands a large amount of tissue energy. The relationship between nutrition and wound healing has been recognized for many centuries. Evidence indicates that nutritional deficiencies are more prevalent in patients with chronic wounds. Malnutrition can alter the inflammatory response, collagen synthesis and tensile strength of wounds, which are crucial factors for healing.[42] It is necessary to identify and correct nutritional imbalances to avoid any potential deterioration of the healing process.

Achieving adequate energy intake through macronutrient delivery is of utmost importance. Traditionally, the dietary distribution of macronutrients is 40%–60% carbohydrate, 25%–30% fat, and 15%–20% protein, but protein requirements increase during all phases of healing by up to 250%.[43] This proportion can change depending on the comorbidities and the initial objective in preparing the patient. Protein deficiency impairs the proliferative phase by preventing angiogenesis, fibroblast proliferation and collagen production, reducing the overall formation of connective tissue. Carbohydrate deficiency impairs the synthesis of adenosine triphosphate (ATP), further compromising protein synthesis and angiogenesis. Fatty acids and cholesterol play important roles in cellular functions, such as the formation of cell membranes and nerve axons.[43]

In a recent clinical trial, compared with those of the control group, the effects of supplementing for 12 weeks with daily omega-3 fatty acids (1 g twice daily) resulted in a significant reduction in ulcer measurements and an increase in insulin sensitivity and total antioxidant capacity. In another study, omega-3 supplementation increased the levels of inflammatory cytokines, such as interleukin-1 beta (IL-1-β), in the wound bed, which is involved in inflammatory phases.[44,45]

The antioxidant properties of micronutrients also play a key role in the wound healing process. Amino acids such as arginine and glutamine are considered essential amino acids. Arginine, a precursor to nitric oxide, is necessary in the inflammatory phase and plays a role in collagen synthesis through the hydroxylation of proline. Glutamine is widely abundant in the human body and is also an essential amino acid that functions in metabolic, enzymatic, immunological and antioxidant processes.[42]

The role of vitamins as enzymatic co-factors in wound healing processes is crucial. Deficiencies in essential vitamins, such as vitamin A (retinoic acid), vitamin C (ascorbic acid) and vitamin D, have been implicated in prolonging the wound healing process. For example, vitamin A plays a role in the function of B and T cells and is essential, especially during the inflammatory phase of wound healing, while vitamin C assists in collagen synthesis, affecting the proliferative and remodelling phases.[46] A randomized, double-blind, placebo-controlled clinical trial showed that after 12 weeks of vitamin D supplementation, there was a significant reduction in wound size parameters.[47]

Minerals such as zinc, selenium and iron have been identified as basic entities necessary for optimal wound healing by affecting enzyme function.[48] Zinc plays a role in all phases of wound healing, affecting immunity and assisting in fibroblast proliferation, collagen synthesis, epithelialization and cell division, and may also have antibacterial effects.[48] Iron is necessary for the hydroxylation of lysine and proline during collagen synthesis, and iron deficiency leads to anaemia, which can contribute to wound hypoxia.[49] The summary of the roles of macro- and micronutrients during the inflammatory and proliferative phases of wound healing are tabulated in Table 1.

7 | COMPLEMENTARY EXAMINATIONS BEFORE REGENERATIVE TREATMENT

A very important aspect of pre-treatment evaluation is complementary examinations. Some of the tests

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TABLE 1 Summary of the roles of macro- and micronutrients during the inflammatory and proliferative phases of wound healing.

Macro and micronutrients	Inflammatory phase	Proliferative phase
Protein and energy[12–14]	Increased need for acute-phase proteins and proliferation of neutrophils, lymphocytes and macrophages	Increased need for a synthesis of collagen and extracellular matrix proteins, angiogenesis, myofibroblast formation and epithelial proliferation
Arginine[12–14]	Nitric oxide synthase: Permeability, vasodilation and cytotoxicity	Arginase I and II: Collagen formation and cell growth
Glutamine[12–14]	Synthesis of acute-phase proteins, immune cells, energy source, DNA replication, phagocytosis, formation of superoxide and glutathione, and antigen presentation	Preferred source of energy for fibroblasts
Vitamin C[12–14]	Antioxidant, chemotaxis	Prolyl and lysyl hydroxylases
Zinc and Copper[12–14]	Proliferation of B and T lymphocytes and neutrophils, protein synthesis and superoxide dismutase	Epithelialization and tissue granulation
Iron[12–14]	Immune response, catalase	Prolyl and lysyl hydroxylases
Vitamin E[12–14]	Reduction in free radicals and increase in glutathione peroxidase levels	Accelerated wound closure
Magnesium[12–14]	Interacts with ATP in collagen processing and involvement in protein formation	Reduces the risk of recurrence of diabetic ulcers

considered extremely important for the doctor to have a good characterization of the patient's metabolic state will be discussed.

7.1 | C-reactive protein

C-reactive protein (CRP) is a key acute-phase reactant that undergoes a significant increase, up to 1000-fold, in response to inflammation or infection. Its synthesis primarily occurs in hepatic hepatocytes but is also observed in smooth muscle cells, endothelial cells, macrophages, adipocytes and lymphocytes. Utilizing ultrasensitive CRP as a marker for inflammation is crucial, and a reduction in its plasma concentration signifies a favourable outcome in regenerative therapies.[50]

7.2 | Blood count

This test is both simple and cost-effective, providing essential data on haemoglobin, leukocytes and platelets. Haemoglobin levels directly impact the body's regenerative capabilities, as they are critical for oxygen transport to areas experiencing heightened inflammatory activity, often associated with local tissue hypoxia. Correcting low haemoglobin levels is imperative for optimal regeneration. Additionally, leukocytes and platelets play pivotal roles in various regenerative treatments, including platelet-rich plasma and bone marrow aspirate procedures.[51] Therefore, quantifying these parameters is crucial for determining an effective therapeutic approach.

7.3 | Homocysteine

Elevated levels of homocysteine can induce mitochondrial oxidative damage, thereby reducing tissue regenerative capacity. Furthermore, heightened homocysteine levels detrimentally impact wound healing and serve as a significant marker of inflammation.[52] Homocysteine disrupts the synthesis of insoluble collagen fibrils by interfering with their normal cross-linking process. In terms of cartilage homeostasis, these alterations in matrix organization impede chondrocyte-mediated mineralization, thereby potentially affecting the function and characteristics of calcified cartilage.[53] It is crucial to replenish co-factors such as vitamins B12, B6 and B9 for the conversion of homocysteine into methionine.

7.4 | Serum protein electrophoresis

Serum protein electrophoresis is a straightforward technique aimed at the fractionation of human plasma proteins.[54] The interpretation of serum protein electrophoresis provides valuable insights for regenerative physicians, aiding in the investigation and diagnosis

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of various diseases. Key fractions including albumin, alpha-1-globulin, alpha-2-globulin, beta-globulin and gamma globulin offer significant diagnostic information. Serum albumin concentration serves as a biomarker of overall health, with decreased levels indicating reduced healing capacity. Elevated alpha-globulin levels are indicative of inflammatory, infectious or immunological processes. Beta-globulin elevation is associated with lipid metabolism disorders or iron deficiency anaemia. Decreased or absent gamma fraction signals congenital or acquired immunodeficiencies, while its increase suggests a polyclonal elevation in immunoglobulins linked to inflammatory, neoplastic (such as multiple myeloma and lymphoproliferative diseases) or infectious conditions.[54] Comprehending these patterns assists physicians in evaluating the general condition of patients.

7.5 | Osteocalcin

Osteocalcin, being produced by osteoblasts, is often utilized as an indicator of the bone formation process. Researchers have shown that higher levels of osteocalcin in the blood are closely linked to greater bone mineral density in people who are taking anabolic osteoporosis drugs such as teriparatide. Osteocalcin frequently serves as an initial biomarker in studies assessing the efficacy of a particular drug on bone formation.[55] When in its carboxylated state, which is dependent on vitamin K2, osteocalcin binds directly to calcium, leading to its accumulation in bone. However, recent research has unveiled its significance beyond bone mineralization. In its uncarboxylated form, osteocalcin serves as a hormone, communicating with various organs such as the pancreas, brain, adipose tissues, muscles and testicles to enhance metabolic functions.[56]

7.6 | Alkaline phosphatase

The majority of alkaline phosphatase (AP) isoenzymes originate from bone and the liver. Elevated AP levels are commonly detected during routine blood tests in elderly individuals. Osteoporosis can lead to a significant increase in serum AP levels, often reaching three to five times the normal range. Conditions associated with elevated AP of bone origin include Paget's disease, hyperparathyroidism, osteomalacia, metastatic bone disorders and recent bone fractures.[57] Hence, it is crucial to assess bone remodelling thoroughly, particularly when contemplating the application of cellular therapies for regenerative purposes.

7.7 | Ferritin

Besides homocysteine, ferritin, the iron storage protein, is also a recognized inflammatory marker. It is associated with indicators of cellular damage and oxidative stress, as well as the presence and severity of various diseases. Significantly, 95% of individuals with elevated ferritin levels exhibit heightened inflammatory activity, whereas only 5% of cases result from excess iron accumulation.[58] To separate these two categories, assessing transferrin saturation (a protein facilitating iron transport in the bloodstream) is feasible. Confirmation of a systemic inflammatory condition occurs when transferrin saturation falls below 45% in a patient exhibiting elevated ferritin levels.[58]

7.8 | Hormone screening

Establishing hormonal balance is imperative for optimal results.[59] Numerous studies have illustrated the advantageous impacts of thyroid hormones on augmenting the biochemical content of cells. Specifically, there is evidence suggesting that thyroid hormones increase collagen production in cultured chondrocytes.[60] Other studies evaluating the potential of thyroid hormones to improve the functional properties of articular chondrocytes are being conducted, but these hormones have not been extensively studied.[61] The same applies to the skin.

The anabolic effects of testosterone on cartilage and bone have been thoroughly described in the literature.[62] However, this effect is not solely accredited to a single action of testosterone on tissues. Testosterone stimulates osteoprotegerin mRNA expression, thereby inhibiting osteoclastogenesis, similar to dehydroepiandrosterone (DHEA) and transforming growth factor-beta.[63] Testosterone, IGF-1 and estradiol appear to have combined effects on bone and skin.

Testosterone also plays a crucial role in preserving or reinstating muscle mass and significantly impacts the outcomes of various therapies. Decreased testosterone levels in both men and women promote heightened muscle breakdown and elevated levels of body fat.[64] Testosterone stimulation enhances the proliferation and self-renewal capabilities of mesenchymal stem cells and endothelial progenitor cells. This suggests that, alongside other contributing factors, this hormone has the potential to augment the therapeutic efficacy of cells.[65] In sarcopenic patients and patients with sarcopenic obesity, hormone replacement is an important tool. Recent work has shown its safety when indicated correctly, as it is an ally in metabolic control and improving the healing potential of wounds.[66]

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DHEA, a 19-carbon steroid hormone, is categorized as an adrenal androgen. DHEA can antagonize cartilage and skin catabolic mediators, including matrix metalloproteinases (MMPs) that degrade the extracellular matrix.[67] Recent studies indicate that DHEA exerts favourable effects on osteoarthritis by modulating the equilibrium between aggrecanases and tissue inhibitors of metalloproteinase-3 (TIMP-3) within cartilage tissues. This suggests that DHEA could potentially safeguard articular cartilage from degeneration at a molecular level.[68]

Consistent data in the literature have shown the homeostatic role of oestrogens. When the Hb level decreases, there is an increase in bone resorption in both men and women. The same is true for its role in tendons.[69] Estradiol also demonstrates the capability to defend chondrocytes against oxidative harm.[70] Postmenopausal women exhibit a higher prevalence of dysregulated cartilage turnover compared with the general population. Animal studies have shown that estradiol reduces radiation-induced inflammation in the skin and significantly inhibits fibrotic changes and accumulated DNA damage in dermal microvascular endothelial cells.[71]

Maintaining hormonal balance, particularly involving thyroid hormones, testosterone, DHEA and oestrogens, is essential for optimizing regenerative therapies and musculoskeletal health, as these hormones significantly influence cellular processes, tissue healing and metabolic regulation.

8 | GUT–BONE AND GUT–SKIN AXIS REGULATION USING PROBIOTICS

The gut microbiome significantly regulates bone health, with alterations in microbiota composition influencing pathological bone loss, while prebiotic and probiotic supplements show potential in preventing or reversing bone loss, as supported by associations between microbiome diversity and osteoporosis in human studies.[15–17] In contrast, the literature on the microbiome's impact on skin health is more limited. As shown in Figure 3, skin commensals are essential for maintaining epithelial barrier function, regulating the host immune system, and protecting against invading pathogenic microorganisms.[72] Oral and topical probiotics appear to be effective in treating certain inflammatory skin diseases (atopic dermatitis, acne vulgaris, psoriasis and seborrheic dermatitis) and play promising roles in wound healing and skin cancer treatment.[18–21]

Short-chain fatty acids (SCFAs), produced through the fermentation of complex carbohydrates and dietary fibre in the gut by beneficial bacteria, are recognized as crucial regulatory metabolites within the intestinal microbiota. As shown in Figure 4, SCFAs inhibit the recruitment and activation of macrophages and neutrophils by reducing the production of pro-inflammatory cytokines.[73] SCFAs indirectly induce regulatory T lymphocytes (Tregs), which have been shown to control immune responses through Th1 and Th2 balance. In this sense, greater fibre intake would increase the production of butyrate, an anti-inflammatory SCFA used as an energy substrate source by colonocytes.[74]

The current average fibre intake among adults in the United States is estimated to be merely half the recommended amount of 30 grams per day, which is advised for consumption as part of a healthy diet.[75] To address this deficiency, supplementation with prebiotics and probiotics has emerged as a viable alternative. Probiotics are live microorganisms that, when consumed in adequate amounts, confer health benefits. Prebiotics, on the other hand, are non-digestible fermentable food components that foster the growth of beneficial microbes or induce favourable changes in microbiome activity.[76]

Mounting evidence suggests that probiotics have a beneficial impact on skeletal health in humans. Initial trials demonstrated that consuming fermented kefir milk for 6 months led to increased bone mineral density (BMD) in men. Additionally, treatment with Lactobacillus casei Shirota improved the healing of distal radius fractures in elderly individuals of both sexes.[77] A clinical trial conducted in women has provided evidence of beneficial alterations in bone mass following probiotic supplementation. In a study involving Japanese women, supplementation with the probiotic Bacillus subtilis C-3102 resulted in increased total hip BMD and decreased bone resorption.[78] In humans, prebiotic supplementation has been associated with increased BMD in adolescents and decreased bone turnover in postmenopausal women. The mechanism by which prebiotics exert their effects on bone is multifaceted, but recent findings suggest that bacterial metabolic pathways, particularly those involved in SCFA production, play a role.[79] The same could apply to skin homeostasis. Oral supplementation with Lactobacillus casei was found to be effective at healing episiotomy wounds in a recent study, with the authors suggesting the possible topical use of Lactobacillus casei 431 (1.5 billion/capsule) for repairing these wounds.[80]

An intriguing area of study involves gut-derived lipopolysaccharide (LPS), a key constituent of the outer membranes of Gram-negative bacteria. LPS can induce pro-inflammatory reactions by modulating the polarization of alternatively activated M2 macrophages towards the pro-inflammatory M1 phenotype.[81] Additionally,

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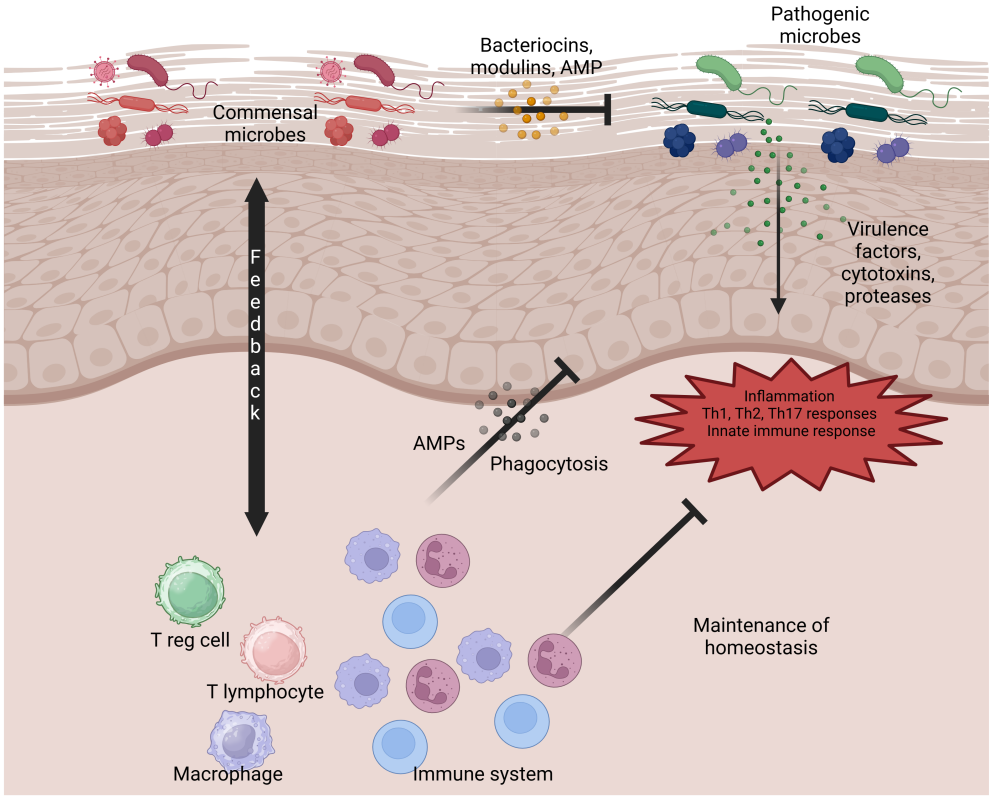


FIGURE 3 Mechanisms of disease inhibition by commensal bacteria. Commensal bacteria occupy an ecological niche similar to that of pathogenic microbes, directly preventing colonization. Commensal strains can also directly secrete antimicrobial factors such as bacteriocins, modulins, propionic acid and antimicrobial peptides (AMPs), or indirectly prime the immune system to attack disease-causing microbes. Commensal bacteria can also promote immune tolerance, reducing inflammation and disease severity. Th, T helper cell; Treg, regulatory T cell.

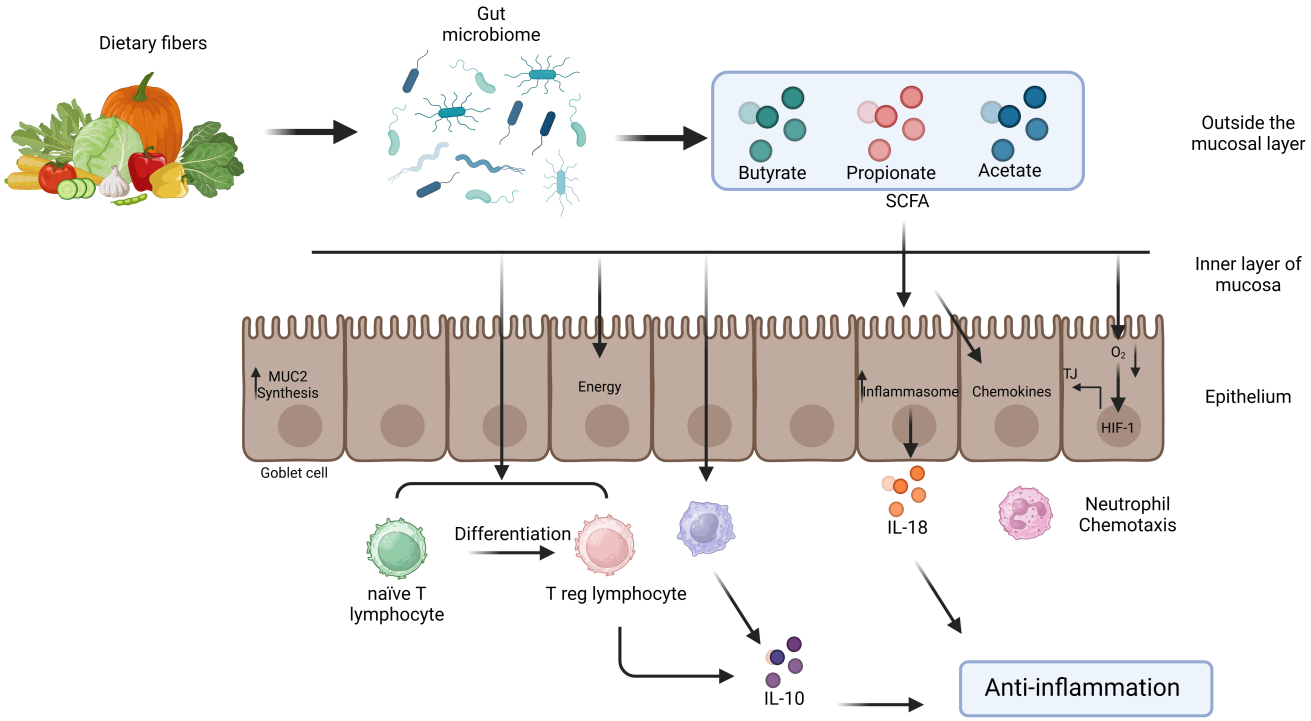


FIGURE 4 Mechanism of action of prebiotics on intestinal homeostasis. Short-chain fatty acids (SCFAs) are produced by healthy microbiota through the digestion and fermentation of fibre. These products are ultimately food for enterocytes and co-factors involved in the production of anti-inflammatory interleukins.

research indicates that physical exercise can influence the composition of the gut microbiome, enhancing the abundance of beneficial bacteria such as Lactobacillus and Bifidobacterium. Exercise also bolsters the immunity of the intestinal mucosa by attenuating the effects of LPS through suppression of Toll-like receptor signalling.

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Moreover, exercise has been associated with alterations in the Bacteroidetes-Firmicutes ratio, adjustments in the bile acid profile and enhanced production of SCFAs.[81]

Research into novel strategies for restoring healthy microbiota, augmenting commensal microbes that counteract pro-inflammatory species and fortifying the intestinal barrier holds significance for addressing skin lesions and degenerative diseases. Interventions involving prebiotic and probiotic supplementation, which enhance SCFA production, could offer a promising and safe avenue for managing metabolic disorders.[82] Skin wounds can alter the gut microbiome, reducing the abundance of *Akkermansia muciniphila*, *Lactobacillus gasseri* and *Bacteroides thetaiotaomicron*, contributing to gut dysbiosis and inflammation.[22] Probiotics such as *Lactobacillus* species promote wound healing by modulating immune cells and cytokine levels in the skin, enhancing the innate immune response, and producing antimicrobial molecules.[23] In diabetic foot ulcers, *Lactobacillus plantarum* solution and oral probiotics like *Lactobacillus paracasei LPC-37*, *Bifidobacterium lactis HN0019*, *Lactobacillus rhamnosus HN001* and *Lactobacillus acidophilus NCFM* improved wound healing in Wistar rats, demonstrating probiotics' potential in modulating the gut–skin axis for better wound management in diabetic patients.[24] Additionally, *Lactobacillus reuteri* enhanced wound healing in mice by up-regulating oxytocin, promoting wound contraction and fast epithelialization, while *Lactobacillus acidophilus* increased breaking strength in sutured wounds, granuloma dry weight and collagen content, showing significant improvement in wound healing through gut-skin axis modulation.[25]

9 | HORMONAL HOMEOSTASIS IN SOIL PREPARATION

Much of what is known about hormonal homeostasis for musculoskeletal health applies to the preparation of patients in general. Ensuring adequate levels of insulin is paramount, alongside monitoring fasting blood glucose and HbA1c levels. Diabetic patients often exhibit elevated levels of IL-1β and advanced glycation end products in their tendons, underscoring the importance of vigilant monitoring and management of these markers.[83] Diabetes exacerbates chronic inflammation, leading to elevated levels of pro-inflammatory cytokines such as TNF-α, IL-1β and advanced glycation end products within tendons, thereby increasing the risk of rupture. This inflammatory milieu similarly impacts the skin. Moreover, heightened glucose levels upregulate the expression of MMP-9 and MMP-13 in tenocytes, further contributing to tendon degeneration and susceptibility to injury.[84]

Sex hormones exert a significant influence on tissue healing processes. Protein analysis has revealed that oestrogen and progesterone intricately regulate the expression of key proteoglycans, including aggrecan, biglycan, decorin and versican within skin and tendons.[69] Furthermore, oestrogen deficiency negatively affects metabolism and tissue healing in women and men, reducing the rate of proliferation, increasing apoptosis and altering the tendon composition in terms of collagen I, aggrecan and elastin. This is because tendons express the oestrogen receptors α and β.[85]

Administration of androgens has been shown to decrease the expression of matrix MMPs in tendons, thereby exerting a positive influence on tissue remodelling throughout various training programmes.[69] In laboratory settings, the gradual elevation of testosterone levels demonstrates direct effects on human male tenocytes, leading to an increase in cell numbers after 48 and 72 h of treatment.[86] Excessive administration of testosterone can induce alterations in the biomechanical characteristics of tendons, including decreased elasticity, tendon dysfunction and fibrosis, consequently raising the likelihood of spontaneous tendon ruptures.[86,87] Although it is not clear whether the same applies to dermal physiology, it is believed that such concepts can be extrapolated when preparing patients with wounds.[69] Indeed, preserving the equilibrium of physiological levels of oestrogen and testosterone seems crucial for the health of tendons and skin. Extremely low or high concentrations of endogenous or exogenous sex hormones can elevate the risk of injury and impede proper adaptation to biomechanical stresses.[88]

The growth hormone (GH)/insulin-like growth factor-1 (IGF-1) system is intricately connected to collagen synthesis and the maturation of connective tissue.[89] Researchers have examined the deep flexor tendon in rabbits and cultured it for a short time. Recombinant human insulin-like growth factor (rhIGF-I) helps tenocytes repair and grow the extracellular matrix. In humans, heightened availability of GH stimulates collagen synthesis within skeletal muscle and tendons, potentially leading to an augmentation in the cross-sectional area of tendons. However, it does not appear to influence myofibrillar protein synthesis, a point of contention within the literature.[90] GH is the main determinant of progenitor cell stimulation and interacts with adipose and cartilage tissue progenitor cells, and IGF-1 stimulates subsequent clonal expansion. Osteoblasts and chondrocytes possess receptors for GH, and administering GH at physiological levels directly impacts osteoblasts by stimulating their proliferation and differentiation. Additionally, IGF-1 decreases osteoblastic apoptosis and fosters osteoblastogenesis.[91]

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Lastly, the effects of thyroid hormones on tendons are mediated by the ubiquitous thyroid hormone receptors (TR)-α and TR-β.[92] In particular, the thyroid hormones T3 and T4 play antiapoptotic roles in tenocyte proliferation. They are also capable of influencing the secretion of extracellular matrix proteins in vitro from tenocytes, increasing collagen production.[93] T3 promotes the production and posttranslational alteration of type I collagen, triggers AP expression and governs the synthesis and release of bone matrix proteins like osteopontin and osteocalcin.[60,94] T3 also facilitates bone matrix restructuring by encouraging the expression of matrix metalloproteinases-9 and -13. Additionally, thyroid hormones oversee pivotal pathways related to osteoblast proliferation and differentiation, impeding osteoclast formation through the control of osteoprotegerin, a decoy receptor that effectively hinders receptor activator of nuclear factor-kB ligand (RANKL).[95] Clinically, hypothyroidism may manifest with complaints related to tendinopathy, as well as skin and nail alterations. This condition can lead to an accumulation of GAGs in the extracellular matrix and a reduction in cellular turnover.[59] In terms of bone health, hypothyroidism prolongs the period of secondary mineralization. Conversely, thyrotoxicosis accelerates bone turnover, leading to high bone turnover osteoporosis due to a shortened remodelling cycle, resulting in a loss of about 10% of mineralized bone per cycle.[92] Epidemiological studies have revealed that hypothyroidism is linked to a two- to threefold rise in fracture risk, whereas thyrotoxicosis is a recognized contributor to osteoporosis and fragility fractures.[96]

10 | CONCLUSION

In this manuscript, we focus on the crucial elements that make up 'metabolic soil' for effective chronic wound healing. Just as nutrient-rich soil promotes exuberant growth in plants, a balanced diet is essential for sustaining tissue growth in humans. We review the importance of specific nutrients, including proteins, vitamins and minerals involved in collagen synthesis and cell proliferation, highlighting their role in tissue healing. Furthermore, we explored the influence of hormones on regenerative processes, emphasizing how hormonal imbalances can adversely affect the body's response. Additionally, we discuss metabolic control, focusing especially on glucose regulation, a key factor in promoting a stabilized microenvironment that facilitates tissue repair. We consider nutritional, hormonal and metabolic aspects to be the foundation upon which chronic wound healing flourishes.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

No new data were generated.

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