THE IMPACT OF PATIENT HEALTH AND LIFESTYLE FACTORS ON WOUND HEALING, PART 2:

PHYSICAL ACTIVITY AND NUTRITION

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The impact of patient health and lifestyle factors on wound healing, Part 2:

Physical activity and nutrition

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This article should be referenced as: Gethin G, van Netten JJ, Probst S, Touriany T, Sobotka L; The impact of patient health and lifestyle factors on wound healing, Part 2: Physical activity and nutrition; J Wound Management, 2022; DOI: 10.35279/jowm2022.23.01.sup01.02

The document is supported by an unrestricted educational grant from BBraun, Nestlé Health Science and Urgo Medical.

Published by the European Wound Management Association, Nordre Fasanvej 113, 2, 2000 Frederiksberg, Denmark
Web: www.ewma.org. Email: ewma@ewma.org

Contents

1. Abbreviations

BCM: Body cell mass
DFU: Diabetic foot ulcer
LBM: Lean body mass
LMW: Low molecular weight
PU: Pressure ulcer
RCT: Randomised controlled trial
SR: Systematic review
TAT Complex: Human Thrombin-Antithrombin Complex
TCC: Total contact casting
VLU: Venous leg ulcer
WHO: World Health Organization

2. Introduction

Part two of the EWMA document 'The impact of patient health and lifestyle factors on wound healing' focuses on two factors: physical activity and nutrition. In this paper, the pathophysiological understanding of how physical activity and nutrition either increase the risk for wounding or impact the healing process will be presented. We review current evidence for the effectiveness of interventions in improving healing outcomes and offer some recommendations for practice and further research. This part of the document should be read in conjunction with Part 1[1], which discussed stress, sleep, smoking, illicit drug use and alcohol misuse and described how some commonly used medications impact the healing process.

3. Physical activity

Introduction

Physical activity concerns any bodily movement produced by skeletal muscles that requires energy expenditure.[2] This means walking, standing, household activities, exercise, sports and much more. Physical activity is what gets people from A to B and what gets things done. However, many tasks can increasingly be achieved while sedentary, which reduces the necessity to be active. This is problematic, as it reduces activity and increases sedentary behaviour. Physical activity confers many benefits, such as reduced mortality, reduced chronic disease incidence and improved mental health, cognitive health and sleep, while sedentary behaviour is associated with the inverse, such as increased mortality and chronic disease incidence.[2] It is for these reasons that the World Health Organization (WHO) recommends that all adults undertake regular physical activity.[2]

The WHO guidelines on physical activity and sedentary behaviour were updated in 2020 based on multiple systematic reviews and following a rigorous methodology. The recommendations on physical activity and sedentary behaviour are given for all adults but specifically for older adults and adults with a chronic disease. The last two demographic segments are more dominant in populations with chronic wounds, such as venous leg ulcers (VLUs), diabetic foot ulcers (DFUs), arterial ulcers or pressure ulcers (PUs). The WHO recommendations include undertaking regular physical activity and doing at least 150–300 minutes of moderate-intensity aerobic physical activity, at least 75–150 minutes of vigorous-intensity aerobic physical activity throughout the week or an equivalent combination of moderate and vigorous-intensity activity for substantial health benefits, with additional recommendations on muscle strengthening, functional balance and strength training.[2] At the same time, it is recommended to limit the amount of time spent being sedentary, as replacing this with any physical activity provides health benefits.[2] Adhering to the WHO recommendations is important but challenging for many people, including those with chronic wounds. Additionally, in those with lower limb oedema, sedentary lifestyle, particularly with legs down, may exacerbate oedema and it is recommended that where possible people should rest with legs elevated. Improving physical activity and reducing sedentary behaviour is important for any person, and we refer to the extensive WHO guidelines for those interested.

Physiology

In general, physical activity promotes many physiological responses that cause beneficial systemic short- and long-term autonomic and haemodynamic adaptations.[2] However, someone's general levels of physical activity and sedentary behaviour are a given when treatment for a chronic wound is initiated, and most systemic changes may only appear in the long-term if improving one's physical activity has not yet started. From a physiological perspective in relation to chronic wounds, local changes following physical activity are more important, and some can be linked to wound healing. This primarily concerns changes in lower-limb haemodynamics, both in the venous and arterial systems.[3-7] Key in these changes are the calf muscles, which have the capacity to improve blood circulation when exercised.[3-5] For this reason, they have been termed the 'body's second heart'.[8] Increased calf muscle function increases lower limb circulation in people with peripheral artery disease (as seen in some people with diabetes-related foot ulcers) and in people with venous insufficiency (as seen in people with VLUs).[5-7] In addition, exercise may facilitate

vasodilation and an increase in tissue blood flow.[5-7] This is especially important in people with diabetes, as it has been suggested that exercise increases nitric oxide synthesis and reduces oxidative stress.[9] Together, these are some of the key physiological processes underlying physical activity that may facilitate chronic wound healing.

However, there is one aspect of physical activity that may hinder chronic wound healing. This concerns weight-bearing physical activity that increases pressure on the location of a chronic wound, such as a diabetes-related foot ulcer on the plantar side of the foot. The locally increased pressure may debilitate the healing processes and cancel potential positive changes. Nevertheless, if such areas can be adequately offloaded, weight-bearing physical activity may still be feasible.

Physical activity and venous leg ulcers

Among the 79 relevant publications identified on PubMed, there were 2 recent systematic reviews on the topic. Together, Smith et al.[10] and Jull et al[11] identified seven studies comparing physical exercise with another intervention or standard care, and Jull et al.[11] performed a meta-analysis on five of these studies. Since the search date of the systematic review, no new randomised controlled trials (RCTs) on the topic have been published, except for two protocols for ongoing trials for which no results have yet been published[12,13], making a total of seven studies on the topic. These studies will be described in the following paragraphs, starting with the newest and ending with the meta-analysis.

Klonizakis et al.[14] randomised 39 participants to either gym-based supervised exercise (progressive resistance, aerobic and flexibility exercise) in addition to compression (n = 18) or to compression alone (n = 21). The resistance exercises consisted of predominantly bodyweight training with and without dumbbells; the flexibility exercises focused on ankle joint function, and the aerobic training consisted of 30 minutes of treadmill walking and/or cycling, depending on preference. The participants had to exercise three times per week. The study was assessed as having a low risk of bias in 5/5 topics.[11] The primary outcome was that the median time to healing was significantly shorter in the exercise group than in the control group (13 vs. 34 weeks).

Mutlak et al.[15] randomised 40 participants to either home-based unsupervised exercise in addition to compression (n = 20) or to compression alone (n = 20). The exercise consisted of performing 10 dorsiflexions during every waking hour. The study was assessed as having a low risk of bias in 4/5 topics.[11] After 12 weeks, a statistically significant reduction of ulcer size of 1.67 cm^2 ($p < 0.001$) was seen in the intervention group, compared to no change in the control group (0.0 cm2; no p-value given).

O'Brien et al.[16] randomised 63 participants to either home-based unsupervised progressive resistance exercise and walking, in addition to compression (n = 31) or to compression alone (n = 32). The exercise consisted of seated heel raises performed daily, three times a day, starting with 3 sets of 10, then 15, then 20, then 25, and subsequently progressing to standing heel raises and 1-legged heel raises. Progression was done when one level was successfully completed for three days. In addition, the participants were asked to walk for 30 minutes 3 times per week. The study was assessed as having a low risk of bias in 4/5 topics.[11] Healing rates at 12 weeks were 77% in the intervention group and 53% in the control group, although this 24% difference was statistically not significant. A per-protocol analysis that only included those who adhered to the exercise protocol for 75% or more found a statistically significant difference (95% vs. 53% healed at 12 weeks).

In a feasibility RCT from the same research group preceding the above-described RCT, O'Brien et al.[17] randomised 13 participants to a similar home-based unsupervised routine of progressive resistance exercise in addition to compression, yet without the prescribed walking (n = 6), or to compression alone (n = 7). The study was assessed

as having a low risk of bias in 4/5 topics.[11] Clinical, but not statistical, significance was observed in the intervention group, with a 32% greater decrease in ulcer size compared to usual care and a 10% improvement in the number of participants healed.

Heinen et al.[18] randomised 184 participants to the Lively Legs programme (n = 92) or to usual care (n = 92). Lively Legs is a nurse-led self-management counselling programme that combines counselling sessions on physical activity and on adherence to compression therapy. The study was assessed as having a low risk of bias in 4/7 topics.[10] Although the intervention group performed significantly better on conducting leg exercises and 10-minute walks five days a week, there was no difference in reaching 30 minutes of walking on five days a week. At 18 months, ulcer healing was 55% in the intervention group and 45% in the control group.

Meagher et al.[19] randomised 35 participants to home-based unsupervised exercise in addition to usual care (n = 18) or to usual care (n = 17). The study was assessed as having a low risk of bias in 3/5 topics.[11] Only 33% of the exercise group achieved an average of 10,000 steps per day. The risk difference for prescribed walking was a non-significant 7 additional cases healed per 100 patients. Comparing all participants who increased their daily steps with those who did not, healing rates at week 8 were 67% and 35%, respectively. Jull et al.[20] randomised 40 participants to home-based unsupervised exercise in addition to compression (n = 20) or to compression alone (n = 20). The progressive training routine consisted of three sets of heel raises at 80% of each participant's maximum tolerance level. These were re-prescribed by a nurse at 3, 6, and 9 weeks after randomisation and were to be done on alternate days for a period of 12 weeks. The study was assessed as having a low risk of bias in 4/5 topics.[11] Although the ejection fraction of the calf muscle increased significantly in the exercise group, there were no significant differences in ulcer healing parameters, with more healed ulcers in the control group.

In their meta-analysis, Jull et al.[11] pooled the outcomes of five studies. Overall, they found that healing rates were 61% for the combined physical activity intervention groups (57 out of 94 participants) compared to 46% in the combined control groups (44 out of 96 participants). This resulted in a risk difference of 0.14, or an additional 14 cases healed per 100 patients (p = 0.04). The effect was mainly driven by two studies that combined progressive resistance exercise with prescribed physical activity[14,16], resulting in a risk difference of 0.27, or an additional 27 cases healed per 100 patients (p = 0.004). Progressive resistance exercise alone or a prescription of walking 10,000 steps per day alone were not more beneficial than usual care.

As also concluded by Jull et al.[11] in their recent meta-analysis, the evidence described above can now be considered sufficiently suggestive for clinicians to recommend simple progressive resistance exercise in combination with prescribing physical activity to people with a VLU who are capable of performing the exercise and physical activity to promote healing of the VLU. Being based on a meta-analysis of RCTs with a low risk of bias, the quality of the evidence is considered high. Further, the benefits of doing such exercises outweigh the potential harms. While some patients may not prefer exercise, the flexibility of either prescribing home-based unsupervised exercise or gym-based supervised exercise provides clinicians with opportunities to match the exercise therapy with individual preferences. This makes the prescribed exercise feasible to perform. Resource use is limited, especially with home-based unsupervised exercise. Taken together, this is a strong recommendation.

Diabetes-related foot ulcer

Of the 127 publications identified on PubMed, we found 2 recent systematic reviews on the effect of non-weight-bearing exercise for people with a diabetes-related foot ulcer and multiple systematic reviews on the topic of physical activity and its association with the (non-)healing of diabetes-related foot ulcers. Given the important distinction

between non-weight-bearing and weight-bearing exercise in this population, these two forms of training will be discussed separately.

Non-weight-bearing exercise for people with diabetes-related foot ulcers

In a systematic review that focused on the effect of exercise on wound healing in people with diabetes-related foot ulcers, Tran and Haley[21] found three RCTs on the topic. In a systematic review that focused on the benefits of exercise on health-related quality of life (HRQoL) and on potential harms (e.g. musculoskeletal problems, increased wound size, amputation) in people with diabetes-related foot ulcers, Aagaard et al.[22] found the same three RCTs, an additional five cohort or feasibility studies and two unpublished studies. In addition, we identified one study protocol for an ongoing RCT.[23] Details of these RCTs will be described in the following paragraphs, starting with the newest. Findings from the cohort, feasibility and unpublished studies will be summarised.

Eraydin and Aysar (2018) randomised 60 participants to either home-based unsupervised non-weight bearing foot exercises to be completed seated in addition to usual care (n = 30) or to usual care alone (n = 30).[24] The training consisted of a total of 18 different exercises to be repeated 10 times twice daily for 12 weeks. The self-reported adherence to the exercise was low (< 50%). The study was assessed as having a low risk of bias in 4/10 topics[21] or 0/5 topics.[22] Both the intervention and control group showed a significant reduction in wound area, while only the intervention group showed a reduction in wound depth. However, no comparison between intervention and control was made, and the intervention group had significantly smaller ulcer sizes at baseline, a finding that agrees with previous studies.[24,25] HRQoL and adverse events were not reported.

Joseph et al.[26] randomised 61 participants to either clinic-based supervised bicycle ergometer exercise in addition to usual care (n = 30) or to usual care alone (n = 31). During the ergometry exercise, the participants rode with the foot interaction with a standard gym pedal kept constant and using specialised offloading insole padding to relieve pressure on the ulcer. The exercise was performed 3 times per week for 12 weeks, during which the participants were encouraged to increase their exercise time in order to reach 50 minutes of exercise. Adherence to the exercise was not reported. The study was assessed as having a low risk of bias in 6/10 topics[21] or 1/5 topics.[22] The intervention group showed a significantly greater percentage reduction in ulcer size at 12 weeks (94% vs. 55%; $p < 0.05$). HRQoL and adverse events were not reported.

In a pilot RCT, Flahr[27] randomised 18 participants to either home-based unsupervised non-weight bearing exercises in addition to usual care (n = 10) or to usual care alone (n = 8). The training routine consisted of a total of 4 different exercises to be repeated 10 times twice daily for 12 weeks. The frequency of adhering to the exercise was mixed, although generally low. The study was assessed as having a low risk of bias in 4/10 topics[21] or 1/5 topics.[22] The percentage reduction in ulcer size did not differ between the intervention and control group ($p = 0.70$), although no participants in the intervention group showed an increase in ulcer size, while three participants in the control group did. One complication was observed in the intervention group: a participant withdrew because of developing osteomyelitis. HRQoL was not reported.

Seven observational studies collectively included 136 participants with a diabetes-related foot ulcer.[22] Exercise programmes varied and included Buerger's exercises[28-30], a clinic-based exercise programme comprising a combination of aerobic, resistance training exercises and active dorsal–plantar ankle flexion exercises[31], a clinic-based individualised exercise programme consisting of aerobic and resistance exercises with specific safety precautions[32], a seated exercise programme[33] and a passive movement exercise programme.[34] One unpublished study suggested improvements in HRQoL aspects, fatigue and physical function following exercise, yet without

providing details that could be adequately assessed.[22] A variety of adverse events were reported, including musculoskeletal problems, increased wound size and amputations.[22] At the same time, some positive outcomes on wound size and wound healing were also reported.[22] Adherence and satisfaction with most exercise programmes were high; as this is contrary to the findings in the controlled studies, it cannot be ruled out that this effect could be the result of increased attention from health-care professionals or social desirability in answering.

Therefore, as also concluded by Tran and Haley[21] and Aagaard et al.[22], there is insufficient evidence to claim that non-weight-bearing exercise is beneficial in ulcer healing. It is unclear whether the potential benefits of this type of training outweigh the harms, and the effect on HRQoL or other patient-reported outcomes is unknown.

Weight-bearing physical activity for people with diabetes-related foot ulcers

On the topic of weight-bearing physical activity for people with diabetes-related foot ulcers, no intervention studies were found, which was not surprising given the debate around this topic. However, we identified multiple systematic reviews summarising the outcomes of observational studies on the association between weight-bearing activity and ulcer healing.

In two recent systematic reviews, Jarl et al.[35] and Hulshof et al.[36] reported on the outcomes of, in total, six unique studies on the connection between weight-bearing physical activity and ulcer healing. Two studies assessed the association directly, while another four indirectly.

In an RCT, Najafi et al.[37] recruited 49 participants with non-ischemic plantar neuropathic ulcers. The participants were randomised to two groups, which were assigned a non-removable or a removable knee-high offloading device. Adherence to wearing was not assessed for the removable device. The study was evaluated as having a low risk of bias in 1/6 topics.[36] A proportion of 51% of the participants with a healed ulcer at 12 weeks had more daily steps at baseline compared to those with an ulcer that did not heal (5,304 vs. 4,312); however, this was the opposite at the last visit before healing (2,595 vs. 5,586). Neither of the associations was statistically significant. In a secondary analysis of this RCT, the authors found that 1,000 daily steps reduced ulcer healing rates by approximately 5% and suggested that up to 3,000 daily steps would not negatively impact ulcer healing.[38]

In an RCT, Van Netten et al.[39] recruited 31 participants with a neuropathic plantar ulcer. The participants were randomised to wear a knee-high or ankle-high removable offloading device. Adherence to wearing was assessed subjectively, based on self-reports. The study was assessed as having a low risk of bias in 3/6 topics.[36] A proportion of 68% of the participants whose ulcer healed within 12 weeks had non-significantly lower daily steps compared to those whose ulcer did not heal (7,222 vs. 9,706). However, the number of average daily steps in those whose ulcer healed (over 7,000) is higher than the global average[40] and indicates that relatively normal levels of weight-bearing activity might still be feasible while also reaching ulcer healing within 12 weeks.

In a prospective study, Crews et al.[41] followed 79 participants with a neuropathic or neuroischemic ulcer in a pressure-bearing area. They found that this population spent an average of 6.7 hours daily performing a physical activity. Ulcer healing at 6 weeks was 24%. In a secondary analysis, higher numbers of daily step counts were associated with smaller ulcer size at 6 weeks, suggesting the potential benefit of physical activity.[42] However, this association was not statistically significant in multivariate analyses, and no further details were provided.

Three studies assessed the association between weight-bearing activity and ulcer healing indirectly. Armstrong et al. (2001) and Lavery et al. (2015) recruited a total of 196 participants in two RCTs, comparing one non-removable Total Contact

Cast (TCC) with two removable offloading devices (walkers and sandals).[43,44] The devices with the lowest daily step counts, the TCC, had the highest healing rates. However, the group assigned walkers had similarly low step counts and much poorer healing rates, while the group assigned to wear sandals had much higher step counts but healing rates similar to the first group. As such, these studies do not provide evidence for an association either way, as adherence to wearing the devices and the biomechanical functionalities of the devices may also explain the differences in healing outcomes. In the last study, Saltzman et al. (2004) investigated the effects of the daily number of steps on the time to ulcer healing in an observational study on a cohort of patients treated with a TCC for up to 13 weeks.[45] Their analyses suggest that patients taking an average of 2083 daily steps would heal in 6.7 weeks, while patients taking double that number of steps would heal in 8.9 weeks. The difference was not statistically significant.

Overall, in line with both systematic reviews[35,36], it can be concluded from these studies that there is no statistically significant association between weight-bearing activity (most frequently reported as the number of daily steps) and ulcer healing; however, a direction was seen in most studies towards a negative association, with a higher number of steps in those patients whose ulcers did not heal at the time of primary outcome assessment (generally 12 weeks).

Physical activity recommendations for people with a diabetes-related foot ulcer

Findings from studies on non-weight-bearing and weight-bearing physical activity and their associations with ulcer healing paint a mixed picture. There is no straightforward evidence to suggest that weight-bearing activity negatively impacts ulcer healing, as up to 3,000 daily steps may not affect healing at all, while even 7,000 daily steps may be possible while still achieving plantar neuropathic forefoot ulcer healing within 12 weeks. However, the direction seen in most studies seems to suggest that it is clinically wise to be cautious with weight-bearing activity during the course of ulcer healing and that non-weight-bearing activities are preferred to achieve physical activity targets.

Concerning non-weight-bearing activities, however, these require structured exercise, which is difficult to perform regularly, with low adherence rates observed in the three RCTs on this topic[21] and with limited clinical effects on ulcer healing.[21] Therefore, there is no evidence to recommend such non-weight-bearing physical activity with the aim of improving ulcer healing outcomes. The requirements concerning adherence to these exercise regimens are different from weight-bearing activities, as the latter primarily includes steps that are needed to simply go from A to B and, as such, are part of daily life. This means weight-bearing physical activity can be considered easier to engage with. Additionally, the more physically active people are while their ulcers heal, the quicker and easier their transitioning to pre-ulcer mobility[46,47], concerning weight-bearing physical activity in particular.

While it is obvious that more studies are needed to better investigate this association, contemporary evidence offers suggestions that at least some daily weight-bearing activity is not detrimental to ulcer healing—especially when adequate offloading is provided.[48] This means that patients with a plantar diabetes-related foot ulcer can maintain at least some general fitness and lower-extremity muscle strength without having to participate in structured exercise programmes.

We therefore recommend that people with a diabetes-related foot ulcer not change their physical activity routine compared to the period before their ulcer developed, provided the ulcer is adequately offloaded. This can be maintained as long as the ulcer shows signs of being on a healing trajectory. However, reducing the levels of physical activity needs to be considered when adequate offloading cannot be provided, when ulcer healing stalls or when the ulcer has still not healed after 12 weeks of multidisciplinary treatment. The benefits

of maintaining weight-bearing physical activity can be expected to outweigh the harms, provided the conditions outlined above are followed. We expect patients to value their independence and mobility over being restricted in their physical activity while it is both feasible and does not involve resource use. However, given the low quality of evidence, this is a weak recommendation.

We do not recommend structured non-weight-bearing exercises with the aim of improving ulcer healing, as there is no evidence that this is beneficial—in fact, it involves potential harm. Given the low quality of evidence, this is also a weak recommendation.

Other chronic wounds

For other chronic wounds, we found 344 publications using the general term 'chronic wounds', 47 addressing arterial ulcers and 85 examining PUs. However, none of these publications studied the effects of exercise on the healing of arterial ulcers, PUs or other chronic wounds. As such, we cannot provide recommendations on physical activity to improve the healing of these chronic wounds.

Concluding remarks

Given the high quality of evidence and beneficial effects on ulcer healing, we strongly recommend prescribing exercise for people with a VLU with the aim of improving healing. For people with diabetes-related foot ulcers, some weak recommendations could be made; however, the debate will continue on this topic, as more studies are needed. For other chronic wounds, unfortunately, we cannot provide any recommendations.

For all people with chronic wounds, it is generally advised to adhere to the WHO recommendations on physical activity. This involves undertaking general physical activity and limiting sedentary behaviour with the aim of maximising health benefits. However, it is important that patients and clinicians together ensure that this physical activity can be performed in a safe environment that does not harm the patient and their chronic wound.

4. Nutrition

Introduction

Nutritional status and wound healing capacity are closely associated. From an evolutionary point of view, the period of inflammation following the injury and the subsequent wound healing were associated with decreased food intake. In the wild, an animal usually hides after an injury and does not eat until the inflammatory phase connected with the injury has disappeared, the healing process has moved (at least partially) towards the anabolic phase and the catabolic reaction has terminated.[49] Immediately after injury and during the early stages of wound healing, the wild animal loses appetite, and during the anorexia phase, the energy substrates and substrates necessary for inflammation and regeneration are released from their own tissues. Physical activity also decreases significantly during the early stages of wound healing. The combination of inactivity and inflammation during the early phase supports the mobilisation of substrates needed for survival and wound healing.[50]

The metabolic and nutritional consequences are important for all phases of the wound healing process (see Table 1)[49,51] For reference purpose we provide a table of normal nutritional values for healthy adults in Appendix 2 (Available at https://ewma.org/what-we-do/projects/lifestyle-factors).

When the tissue stores of energy and other substrates (proteins, lipids, electrolytes and micronutrients) are sufficient, the catabolic reaction associated with wound healing will provide all the metabolites necessary for a successful healing process. This reaction ensures the healing of the wound and the survival of the organism; in this situation, no special nutritional support is required. However, there are certain problematic situations in which the wound healing process cannot take place successfully due to a lack of nutritional substrates:

- The body stores of necessary energy and metabolic substrates are depleted before injury and wound formation.

Table 1: The metabolic and nutritional consequences of the wound healing process

1. Haemostasis: Blood clotting prevents blood loss; during this phase, both pro-inflammatory and fibroblast proliferation stimulating agents are released.
2. Inflammation: In addition to protecting against infectious invasion at the wound side, the inflammatory response also supports the mobilisation of substrates necessary for wound healing and substrates important for the resolution of the inflammatory process.
3. Proliferation: The substrates released form peripheral tissues that are utilised in the formation of granulation tissue and the epithelisation of the wound.
4. Remodelling: This phase is important for improving the function of injured and healed tissue. It takes several weeks to months. During this time, the granulation tissue is rebuilt, the scar is transformed and the collagen is maturated. The intake of appropriate nutrition substrates together with rehabilitation and specific physiotherapy are important for this phase

References:[49,51]

- The healing process is complicated and prolonged, and due to chronic inflammation, the body stores are exhausted before the wound healing process is finished.

- Both situations mentioned above are combined.

Depleted body stores impair wound healing

Malnutrition (inadequate nutritional status) negatively influences wound healing.[52] In particular, an adequate amount of lean body mass (LBM) or body cell mass (BCM) is important in this context. This was confirmed by numerous studies on patients who underwent surgical procedures when malnourished.[53] It was repeatedly demonstrated that a depletion of LBM is related to the poor healing of surgical wounds.[54,55] In Western countries, malnutrition is usually a consequence of an ongoing subacute or chronic disease. However, recent studies from Africa, where undernutrition is still a big problem, also showed that poor nutritional status is one of the risk factors for the poor healing of surgical wounds.[56,57]

Nutrition support was shown to improve post-operation healing in preoperatively malnourished patients.[58-60] However, in patients with chronic wounds, a loss of LBM was demonstrated despite adequate nutrition, with subsequent fat accumulation and obesity. This is probably because long-term inflammation, pain and immobility cause the loss of body cell (especially muscle) mass[61] and excessive energy intake leads to fat accumulation. Nevertheless, increased body fat stores do not seem to be protective for wound development or supportive for wound healing.[62] This is a probable explanation for why obesity that is combined with loss of LBM is rather frequent in patients with chronic wounds (e.g. VLUs, DFUs and PUs).[63,64] This type of malnutrition is termed sarcopenic obesity. The connection between sarcopenic obesity and chronic non-healing wounds can be explained by different substrate cycles (see below).

Chronic and complicated healing processes lead to the loss of body cell mass

The presence of malnutrition (especially decreased BCM) is a common consequence of a chronic inflammatory process. This is because inflammation stimulates catabolic processes and simultaneously decreases protein synthesis in skeletal muscle.[65,66] Net protein loss of muscle tissue with subsequent decreased amount of skeletal muscle and inadequate muscle function are additional consequences. Moreover, chronic inflammation leads to loss of appetite, which prevents normal food intake.[67,68] Increased satiety can also change the normal ratio between carbohydrates and fat intake. This can lead to a relatively higher intake of fat energy, which is then stored in adipose tissue and can also negatively influence the inflammatory process and wound healing.[69] Moreover, the presence of the wound is usually connected with pain and loss of function of the wounded part of the body; the wound-related inflammation, pain and impaired function lead to decreased physical activity. As physical activity is an essential condition for muscle regeneration (see section 'The effect of physical activity') and net muscle protein synthesis, the loss of muscle mass and muscle function is a logical consequence.[70,71] Therefore, the inflammatory process itself, disease-related malnutrition and decreased physical activity induce the development of sarcopenia, which is often hidden by the accumulation of fat tissue. This leads to malnutrition and is called sarcopenic obesity.[61]

Combination of both situations

The shortage of endogenous substrates for effective wound healing is evident in people who were undernourished prior to injury. In this situation, the endogenous substrates necessary for effective wound healing are deficient and thus postpone the healing process immediately after injury and wound formation.[72] The shortage of endogenous substrates necessary for complete wound healing also leads to abnormal systemic reactions. In this case, the inflammatory processes are not modulated by anti-inflammatory pathways as under normal conditions.[73]

Inflammation–malnutrition cycling

It is necessary to draw attention to the possibility of a problematic looping of the conditions. A non-healing wound becomes a source of inflammatory reaction. This reaction results in chronic inflammatory irritation, which has catabolic consequences for the whole body. The reduced ability to synthesise muscle proteins[74] is one of these consequences. At the same time, appetite and food preferences change due to chronic pain and inflammation, which leads to either loss of appetite or increased intake of high-fat food.[75] Ingestion of high-fat food together with low intake of protein and micronutrients increases inflammation and produces the subsequent loss of muscle mass—which can be combined with obesity.[67] A lack of exercise then closes the vicious circle of inflammation and malnutrition immobility because without exercise, the synthesis of structural proteins in skeletal muscle cannot continue.[76] In developed countries, problematic wound healing does not usually lead directly to death (as in animals) due to advanced health care. However, it frequently results in the transition to the chronic stage. Thus, the patients do not die directly from the injury and the wound but due to the long-lasting presence of the non-healing wound. Their condition may gradually deteriorate, and they may eventually die of the consequences of chronic inflammation and complicating disability. This scenario is particularly common in older patients.

Nutritional support

It is evident from the above information that control of both nutritional status and food intake must always be part of the complex treatment of the patient. However, the treatment should also be holistic; without appropriate local and focused systemic treatment, the influence of nutritional support is uncertain. On the contrary, the patient who has already suffered from severe malnutrition before the onset of the wound cannot achieve the desired wound healing without nutritional support. Therefore, nutritional screening must always be part of the treatment of a patient with a wound. There are several screening tools described in the literature. In Europe, the most frequent is still NRS 2003, according to which malnutrition is anticipated if:

1 – BMI = (weight in kg) / (height^2 in m^2) < 20.5 kg/m^2

2 – The patient lost weight within the last 3 months.

3 – The patient had a reduced dietary intake in the last week.

4 – The patient is severely ill (e.g. in intensive therapy).

In conjunction with these criteria, in older people, malnutrition may also be due to:

A – Mobility problems (bed-/chair-bound, able to get out of bed/chair or able to go out)

B – Psychological stress or acute disease in the last 3 months

C – Neuropsychological problems, such as mild/severe dementia or depression

For further reading, see the provided references.[77,78]

The practice of nutritional support is different according to the following situations:

- Acute wound in a well-nourished individual
- Acute wound in a patient with malnutrition
- Chronic wound in a patient without malnutrition
- Chronic wound in a malnourished patient.

Acute wound in a well-nourished patient

In this situation, special nutritional support is usually not mandatory. An acute wound usually

heals well, and the metabolic consequences of its presence are not long-lasting. Even the temporary loss of appetite, which is usually associated with pain, does not persist for a long time; within one week, food intake usually returns to normal. In these patients, it is only necessary to monitor food intake and control the overall nutritional status. If the reduced food intake is longer than seven days, the possible risks should be identified and nutritional support should be considered.[77]

Acute wound in a patient with malnutrition

If the patient was malnourished before wounding (loss of skeletal muscle mass and subcutaneous fat and unable to eat), the wound healing would probably be complicated. This is apparent from studies on acutely operated patients with different states of nutritional status.[53-55] In acutely operated undernourished patients, both wound healing and postoperative complications are negatively affected.[56,57] Due to malnutrition, the risk of ineffective wound healing and delay of the healing process can lead to the prolongation of the healing process and wound chronicity. This may also be partially associated with microcirculatory disorder, which occurs in patients with low plasma protein levels.[79]

For the reasons described above, it follows that the appropriate assessment of food intake is required in malnourished wounded (or operated) persons.[60,77] If the nutrition intake is insufficient, it is necessary to start nutritional support without delay. Nutritional support should provide not only the energy and nutrients for the basic energy requirement of a person (measured, for example, by indirect calorimetry) but also the substrates that are necessary for the wound healing process. This applies predominantly to the supply of protein (at least 1.5 $g \cdot kg^{-1} \cdot day^{-1}$); however, the need for carbohydrates, essential fatty acids, vitamins and trace elements must also be considered. These are particularly important for people who are already malnourished before undergoing a surgical procedure.[50,60,80] The problem is that there are no randomised controlled nutritional studies in malnourished patients, as such studies are difficult and unethical to perform in already malnourished people, who almost certainly need nutrition support.[81]

Chronic wound in a patient without problematic food intake

When a wound progresses to the chronic stage, it becomes a permanent source of inflammatory irritation for the whole body.[50,82] Although this inflammatory response is of low or moderate intensity, it changes the metabolism in numerous organs. The typical organs that are affected are the skeletal muscles, in which low-grade inflammation reduces the synthesis of structural proteins.[65] In the liver, inflammation influences the synthesis of plasma proteins and increases the production of glucose.[83] In this way, the inflammation caused by the wound changes the fluxes of nutritional substrates in the body.[84] The anabolism in skeletal muscles is reduced, while the muscle protein breakdown is increased.[74] At the same time, insulin resistance escalates and gluconeogenesis and glucose turnover increase.[83] This frequently leads to elevated plasma glucose levels. In diabetic patients, the compensation gets worse, and this may lead to severe hyperglycaemia with all the metabolic consequences.[85] Inflammation also leads to the increased turnover of free fatty acids due to increased lipolysis in adipose tissue. The elevated free fatty acid turnover changes the fat distribution, and fatty acids are subsequently stored, not only in subcutaneous adipose tissue but also in other organs, especially in the skeletal muscles, liver and intraabdominal area.[86-88]

The presence of a chronic wound often reduces physical activity. This leads to the loss of muscle mass (see section 'Physical activity and wound healing').[76] Furthermore, the immobilisation and absence of physical activity increases insulin resistance, which negatively influences wound healing. Especially in the legs, muscle function is important for microcirculation (both blood and lymphatic); therefore, it is negatively influenced by inactivity.[3] In this way, inactivity has adverse effects on the interstitial fluid circulation, which is important for the negative interstitial fluid pressure

that is naturally present in subcutaneous tissue.[89] Consequently, impaired microcirculation and the ensuing oedema compromise the delivery of substrates important for wound healing.[90]

The patient goals may be:

- To increase the mass of muscle tissue (LBM) to improve physical activity
- To prevent the unwanted accumulation of adipose tissue (especially in already obese individuals) and sarcopenic obesity
- To provide energy for the physical activity needed for rehabilitation.

These nutritional goals are very often mutually combined. For example, in an obese patient with muscle loss and a skin ulcer, the nutritional goals are:

- To improve wound healing
- To reduce body fat mass
- To improve physical activity and mobility
- To increase growth and the strength of skeletal muscles.

Chronic wounds in malnourished patients

The situation is especially problematic when the chronic wound is complicated by pre-existing malnutrition. This is either due to the presence of a complicated wound in an already malnourished subject or due to the negative effects of the chronic wound on nutritional status (see above).

This is a difficult situation, because malnutrition negatively influences wound healing, and the presence of a wound and chronic inflammation is unfavourable for improving nutritional status, especially for the restoration of BCM.[91] Moreover, the repair of muscle tissue requires physical activity, which is usually negatively influenced in patients with chronic wounds. Therefore, the patient is in a vicious cycle, and only a complex approach can improve both the nutritional status and the wound healing process. In this situation, local wound treatment must always be combined with proper nutrition and other treatment plans, especially physiotherapy and appropriate physical activity.[92]

In malnourished patients with non-healing wounds, the special nutritional mixtures seem to be effective[93] (these substrates will be discussed in the next part). Supplements enriched with arginine, proteins and antioxidants increased the rate of PU healing in non-malnourished people. However, the effect was more pronounced in malnourished patients who required nutritional support.[94-96]

Special substrates

The seeking of special substrates for medical purposes has been popular among both patients and caregivers, and wound healing is no exception in this aspect.[97] Unfortunately, belief in miraculous substrates diminishes the emphasis on a holistic approach and the lifestyle changes that are important for many patients with non-healing wounds. Several special substrates have been suggested to improve wound healing. They can be divided into:

- Proteins and amino acids
- Fatty acids
- Vitamins
- Trace elements.

Proteins and amino acids

An adequate supply of protein is important for cell division and reliable wound healing because it is a source of essential amino acids, which cannot be synthetised in the human body. Since collagen is the principle protein that is produced in the healing wound, a lack of essential amino acids decreases the synthesis of collagen and the production of fibroblasts. Although all proteinogenic amino acids are important for the healing process, some amino

acids can be crucial. For example, methionine and cysteine are involved in the synthesis of connective tissue and collagen. However, the most frequent amino acid supplement in mixtures designed for wound healing is arginine.[98] Arginine can improve cell proliferation, collagen accretion, immune reaction and growth hormone secretion.[99-101] However, the effect of arginine is dependent on its metabolic pathway.[102] Arginine metabolism to polyamides is important for cell division and tissue regeneration.[103] On the other hand, the positive effect of arginine can be switched to negative in the presence of severe inflammation. This is probably due to decreased arginase activity[104], which shifts the arginine metabolism to metabolites that are pro-inflammatory and antiproliferative.[105] Therefore, the effect of arginine is dependent on the general state of the patient, as well as on the type of wound and phase of wound healing. Probably due to this, there is no convincing evidence that arginine supplementation alone can improve wound healing.[106]

Omega-3 fatty acids

Fatty acids are important components of cell membranes and are a substrate for eicosanoid synthesis, which promotes the inflammatory process. Local and systemic application of omega-3 fatty acids was found to improve the healing of experimental wounds in healthy volunteers.[107] Surprisingly, supplementation with these fatty acids was found to increase local inflammation.[107] Recently, conjugated linoleic acid (CLA) was shown to improve wound closure in experimental animals.[108] However, animals supplemented with omega-3 fatty acids exhibited worse responses during E. coli sepsis and had significantly worse outcomes during Staphylococcus aureus skin infection.[109] Due to the lack of appropriate studies, the clinical relevance of fatty acids on wound healing remains to be determined.[110,111]

Vitamin C

Ascorbic acid is an essential co-factor for collagen synthesis and the stabilisation of its triple helix structure. It is also required for monocyte migration into the wounded tissue, optimal immune response and cell division during the inflammatory phase of wound healing. However, convincing data in patients with chronic wounds are missing.[109,110]

Zinc

Zinc is a co-factor for many enzymatic reactions that are involved in the biosynthesis of RNA, DNA and proteins. Hence, zinc is essential for all proliferating cells, and a low zinc status decreases closure of the wound and suppresses the inflammatory process.[112] The efficacy and risk of zinc supplementation for wound management is a subject of much discussion in the literature; the general belief is that zinc supplementation is beneficial when a patient is deficient in zinc but not in the absence of deficiency.[113] Nevertheless, convincing data on chronic wounds are missing.[110,111]

Iron

Iron is a co-factor of the prolyl and lysyl hydrolysis enzymes, which are essential for the synthesis of collagen. In consequence, severe iron deficiency and anaemia can interfere with the wound healing process.[114,115] However, prospective studies are scarce.

Other micronutrients

The specific roles of many other micronutrients, such as vitamins A, B and E and trace elements (selenium, copper, and manganese), have been defined in the wound healing process.[114] The deficiency of these nutrients is specifically associated with skin lesions. Due to the complexity related to the mutual effects of various nutrients, it is difficult and probably impossible to highlight one or more nutrients that are the most important in this process. Therefore, the prevention of deficiencies is probably important for the treatment of all large or non-healing wounds. However, partly due to the logistic and ethical problems mentioned above[81], there are no data based on meta-analyses of prospective randomised studies.

Concluding remarks

The holistic approach for the patient with a chronic

and difficult to heal wound is essential. Nutrition intake should be carefully monitored. For this purpose, it is appropriate to use a method in which the food intake is evaluated by monitoring the consumed part of the portion (quarter-waste method). If the actual food consumption does not match the planned intake, then nutritional supplements should be used. When needed, supplements should be used as soon as possible and primarily via the oral route. However, the patient's intake must be calculated to fulfil not only the energy expenditure but also the substrates for wound healing, body (muscle) regeneration and physical activity.

In undernourished and depleted patients, it seems to be advantageous to use a special nutritional supplement designed for wound healing. The combination of antioxidants, vitamins, trace elements and inflammatory modifiers, together with an increased dose of protein, improved the healing of PUs in prospective double-blind and randomised studies.[93] In cases of malnourished subjects, when special nutrients or nutritional support are suggested, supervision by a dietician is therefore required.

5. Recommendations

Table 2: Recommendations for research and practice

Section	Recommendations
Physical activity	• We recommend simple progressive resistance exercise in combination with prescribing physical activity to people with a venous leg ulcer who are capable of performing the exercise and physical activity to promote healing of the ulcer • For people with a diabetes-related foot ulcer we recommend not to change their physical activity compared to the period before their ulcer developed, provided the ulcer is adequately offloaded. • For people with a diabetes-related foot ulcer we recommend reducing the levels of physical activity when adequate offloading of the ulcer cannot be provided, when ulcer healing stalls or when the ulcer has still not healed after 12 weeks of multidisciplinary treatment. • Structured non-weight-bearing exercises with the aim of improving ulcer healing are not recommended for people with a diabetes-related foot ulcer, as there is no evidence that this is beneficial, while it does involve potential harm. • More research is needed on the association between weight-bearing physical activity and diabetes-related foot ulcer healing and patient-related outcomes. • Research is needed on the effect of physical activity and other chronic wounds.

Section	Recommendations
Nutrition	• Nutrition screening and the treatment of potential malnutrition should be included in the wound healing plan. • The treatment of systemic inflammation together with nutritional care and support is important for malnourished patients with chronic wounds. • Nutrition support should always be accompanied by rehabilitation and exercise to prevent muscle loss and fat accumulation. • Referral to a dietician is recommended for people with a chronic wound where nutritional supplementation is required. • Further research on fat accumulation, obesity development, sarcopenia and inflammation related to nutrition support is needed.

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