Review

On the Merits of Targeted and Individualized Physical Exercise in Persons with Diabetic Foot Disease – from Controversies to Consensus

Edyta Sutkowska *, Anna Korzon-Burakowska, Karolina Biernat

Posted Date: 5 June 2025

doi: 10.20944/preprints202506.0367.v1

Keywords: diabetic foot disease; exercise; physical activity; diabetes; foot offloading

 doi:10.20944/preprints202506.0367.v1

Review

On the Merits of Targeted and Individualized Physical Exercise in Persons with Diabetic Foot Disease—From Controversies to Consensus

Subtitle: "Physical Activity in DFD"

Edyta Sutkowska [1,*], Anna Korzon-Burakowska [2] and Karolina Biernat [1]

[1] Department of Clinical Physiotherapy and Rehabilitation, Wroclaw Medical University, Wroclaw, Poland
[2] Department of Hypertension and Diabetology, Medical University of Gdansk, Gdańsk, Poland
* Correspondence: edyta.sutkowska@umw.edu.pl; Tel.: +4871-7343-220

Abstract: Exercise is a cornerstone of diabetes (DM) management, but the onset of diabetic foot disease (DFD) can significantly limit its implementation. Meanwhile, physical activity (PA) has been shown to reduce the risk of developing DFD through various mechanisms, and emerging evidence also supports the role of exercises in managing the active phase of the condition. Appropriately tailored PA offers both local and systemic benefits—even in clinical contexts where foot offloading is recommended. Research indicates that selected exercises can be safely incorporated into care plans, providing therapeutic effects without compromising wound healing. Drawing from current knowledge based on basic science, clinical research, and relatively general recommendations, this article summarizes the local and systemic effects of properly selected exercises in patients with DFD. It explains the underlying mechanisms and briefly discusses practical examples, integrating the most recently published findings.

Keywords: diabetic foot disease; exercise; physical activity; diabetes; foot offloading

1. Introduction

Exercise is the basis of diabetes (DM) treatment [1-3], as physical activity (PA) plays an important role in regulating glucose levels in the body [4-7]. Therefore undertaking activity by patients is recommended by all scientific societies dealing with the issue of carbohydrate metabolism disorders.

According to the definition of International Working Group on the Diabetic Foot (IWGD) [8], it is a condition when a patient with diabetes and neuropathy and/or arterial blood flow disorders in the lower limbs develops: ulceration, infection and/or destructive changes in the deep tissues below the ankle. There is ample evidence that targeted PA (exercise) reduces the risk of such a complication (prevention stage) [9]. Adequate exercise improves sole load distribution, skin sensitivity, peripheral nerve conduction, intraepidermal nerve fibre density or joint mobility of the foot which translates into proper gait [10,11] and reduces the risk of pathologies typical of diabetes occurring in that area [12-20]. As in patients without diabetes, walking has a beneficial effect on peripheral circulation, reducing the risk of clinically significant limb ischemia leading to ulcers and amputations [21-23]. At the prevention stage, patients are educated about the role of exercise and its safety. The condition of the peripheral nervous system (perception of injury) and blood supply to the limbs is assessed.

In some cases, due to overlapping diseases, patients are advised to discontinue or limit their current activities for the duration of treatment, which may have adverse effects not only on patients' glycemic control (increase in insulin resistance) and body weight but also on respiratory and cardiovascular systems as well as contribute to musculoskeletal disorders, which translates into delayed recovery and poorer functioning after recovery [24-31]. An example of such a situation in the life of a patient with DM is the occurrence of diabetic foot disease (DFD).

 doi:10.20944/preprints202506.0367.v1

In the case of the presence of an unhealed ulcer, current guidelines on the treatment of diabetes and its complications provide only the recommendation to eliminate weight-bearing activity [32,33] In the presence of Charcot deformity, the role of stretching and muscle-strengthening exercises is noted as potentially helpful [32]. In the Clinical Practice Guideline published in 2023 [34] the authors address this issue and explicitly raise the problem of "Various fitness/exercise routines with various intensities, including aerobic and resistance training" in the context of an expected outcome defined as: "Improved mobility in the context of wound healing." However, even in this document, the lack of precise recommendations regarding which exercises should be prescribed and what their potential benefits are is emphasized. Similarly, in the IWGDF guidelines [33] - the most authoritative document in this field- 29 recommendations are provided for managing DFD, but none of them refer to exercise. This situation results from the limited number of RCTs (Randomized Controlled Trials) dedicated to this topic that have included a sufficiently large number of patients in the intervention.

The aim of the article is to highlight the role that exercise, when performed with individualized precautions, can play in improving the condition of a patient with a wound and/or foot deformity due to diabetic foot disease.

2. Methodology

The foundation of our narrative review article is a comprehensive systematic review published in 2023 [35], which summarized the limited but growing body of clinical research focused on exercise interventions initiated after a diagnosis of DFD. This review highlighted the potential benefits of various exercise modalities based on the available studies. Following its publication, a new randomized clinical trial was released [36], further supporting the inclusion of exercise in the management of patients with DFD—although it has not yet influenced clinical guidelines [32,33].

In addition to the available clinical studies discussed in the mentioned systematic review and new data from 2024, we incorporated findings from basic research, including preclinical experiments (on animals and humans), which provide mechanistic insights into how even simple physical exercises may contribute to both local and systemic improvements in individuals with DFD.

Until more large-scale, high-quality trials become available, clinicians may consider relying on the current evidence from both basic and clinical research to guide individualized therapeutic decisions.

The authors of the publication have medical (diabetology: ES, AK-B, vascular: ES diseases) and physiotherapeutic (ES, KB) backgrounds, as well as many years of experience in treating patients with diabetic foot disease.

3. Results

3.1. The Role of Exercise in Patients with Active Diabetic Foot Disease

In the event of a complication such as diabetic foot, the primary goal achieved through appropriate pharmacotherapy is: control of glycemia, correction of other risk factors (cholesterol level and blood pressure values), use of antiplatelet drugs, sometimes low doses of anticoagulants (applies to treatment of limb ischemia) and, in justified cases, administration of antibiotics and painkillers.

Treatment includes revascularisation (for vascular lesions), removal of dead tissue, orthopaedic procedures to correct foot deformity or, supportively, physical therapy procedures [8-23,37].

Regardless of the above, however, the essential recommended management of ulceration, deformation and deep tissue inflammation in DFD is the offloading of the affected area [38-40]. The purpose is not to expose damaged tissues to further injury and to create conditions for healing by, e.g., eliminating the pressure forces in the tissues of the foot, arising in the situation of loading. The recommendation to offload is often associated with immobilisation of the patient or significant restriction of their activity (to essential activities) [38,39], which is also determined by the way in which offloading is achieved: wheelchair, elbow crutches, special footwear or total contact cast (TCC).

 doi:10.20944/preprints202506.0367.v1

Thus, in the described case, a conflict of recommendations arises. On the one hand, local changes require offloading, which means avoiding walking and standing [41], on the other hand, local changes, such as inflammation, generate an increase in glycemia per se and activity restriction promotes that increase and hinders healing. In addition, lack of exercise reduces muscle mass and deteriorates blood supply to the wound area and its bottom. This is a significant issue as proper blood supply is fundamental to wound healing [21,22].

Lack of muscle contraction and joint flexion (natural activities when walking) can cause swelling, which further impedes microcirculatory flow and stiffens joints reducing their range of motion (ROM). Prolonged inflammation can lead to bone resorption due to local vasodilation [42]. Chronic immobilisation also promotes the development of osteoporosis. Each of those disorders has an adverse local impact but also worsens many of the patient's functions [26-31].

Meanwhile, the benefits of exercise are local and general [43-45]. Studies confirm that PA in diabetes has beneficial effects on the cardiovascular system [46,47], microcirculation [48,49] or kidneys [50], which is not without significance taking into account the fact that the correlation between chronic complications and cardiovascular risk has been known for years. Improvements in insulin sensitivity, the patient's functional and psychological state and quality of life are also the effects of targeted activity, i.e. exercise [51]. Therefore, exercise is necessary for the patient not only in the phase of preventing complications but also when they have already appeared. The essence of the appropriate approach is to implement exercises in a planned manner.

Last year, an expert position was published [52], summarising recommended actions for DFD. They include an assessment of the usefulness of exercises that the patient may undertake during the treatment of the condition in question. While emphasising the lack of sufficient evidence that exercise directly accelerates wound healing, the authors recommend performing some of them due to the potential benefits demonstrated in animals [53,54] and humans [55].The rather modest work on the subject of exercise by patients with diabetic foot to date is supplemented by the recent report [36], released after the publication of the above-mentioned document. The condition for undertaking exercises is to adhere to the principle of relieving the local change and its surrounding area.

3.2. The Effect of Exercise on the Local Condition in Diabetic Foot Disease

Long-term offloading can provoke local osteoporosis and also generate it in other areas of the relieved limb [56]. Local inflammation may also contribute to that, due to increased flow in the microcirculation.

The implementation of properly selected exercises can be helpful and have measurable benefits [57,58], preventing further reduction in bone mineral density (BMD), having a beneficial effect on glycemic control and the patient's well-being [31]. Even local inflammation [59] causes oxidative stress, which disrupts the repair processes in the wound and has an adverse effect on the entire body, which translates into, e.g., increased insulin resistance and, consequently, increased glycemia. That triggers a vicious cycle mechanism as normalisation of glycemia is necessary for wound healing. The changes taking place during local infection and their consequences are comprehensively described by Huang H. et al [60]. There is data supporting the impact of exercise on the reduction of the severity of local inflammation, regardless of other standard actions taken in this regard [61-65]. This is due to mechanisms activated during exercise, which limit the production of pro-inflammatory cytokines and increase the secretion of anti-inflammatory myokines. The latter also enhances local angiogenesis [66,67]. Exercise is an important part of improving glycemia, playing an important role in making the local condition better [23]. In a hyperglycemic environment, the activity of antioxidant enzymes is reduced, the number of advanced glycation end products (AGEs) increases, which enhances the hypoxia of local tissues, which is further intensified by oxygen-consuming pathogens (in the case of infection) and inflammatory cells [60]. High glycemia inhibits the proliferation and differentiation of fibroblasts, impairs the secretion of transforming growth factor-β (TGFβ) and reduces collagen synthesis [67]. Additionally, in such an environment, the activity of endothelial nitric oxide synthase

 doi:10.20944/preprints202506.0367.v1

(eNOS) is inhibited, which leads to vascular damage [68]. Hyperglycemia and vascular damage are thus closely related.

Various forms of planned activity such as Buerger exercises [69-71], exercises improving ROM or stretching [19,37] contribute to improving local circulation, which creates better conditions for the healing of changes in the foot. Additionally, improving the ROM is important for the patient's future [72,73] as its limitation again causes abnormal load on the plantar surface of the foot, callus formation and an incorrect operation of the muscle pump. However, some of the forms of offloading, such as TCC, may be an obstacle to performing exercises [35]. The necessity of conducting research on an offloading device that does not hinder the involvement of the affected limb in simple exercises was emphasized by the authors of one of the last articles [74].

There is a lot of controversy when it comes to exercises during the active phase (open wound or inflammation) [16,75]. This is understandable considering the fact that most clinical trials are quite old, involve a relatively small number of patients and are not uniform in their design [40]. This makes them difficult to interpret in terms of patient benefits. Based on the available studies, the existing knowledge is sufficient to consider properly conducted rehabilitation as necessary even in the acute phase, with the principle of relieving the affected area of the foot and the absence of signs of general infection [76].Consistent with the above are the aforementioned recently published research results [36], which showed significant improvement in the healing of foot ulceration in patients with diabetes.

3.3. Impact of Exercises on the General Condition of a Patient with Diabetic Foot Disease

Immobilisation of the foot, unless there are general signs of inflammation, does not have to result in complete immobilisation of the patient in bed or a chair.

To perform a large part of daily activities, people involve the lower limbs. When this is limited by a disease, it should be considered whether lower limb muscle activity can be replaced with exercises that exclude the affected area of the foot or with work of the upper limbs or trunk. This is supported by the results of studies that emphasise the role of aerobic exercise in wound healing in animals [77-80] and humans [81], most likely through benefits for the respiratory and cardiovascular systems and improved glucose burning [35,82] resulting from tissue sensitisation to insulin. Strength training in preventing atrophy is also helpful in keeping the patient's muscles in better shape and building muscle mass, which translates into better glucose utilisation and improves muscle tone and coordination of movements [52]. Strengthening the muscles and the patient's general condition is of tremendous importance also if the treatment of the diabetic foot fails. If amputation and subsequent prosthetics are necessary, the patient's energy expenditure (EE) when moving is much higher than in able-bodied persons [83]. People whose condition indicates a high risk of amputation should be adequately prepared physically so that they can fully use the prosthesis in the future.

3.4. Benefits of Different Types of Exercises Performed by a Patient with Diabetic Foot Disease

Patients can exercise while sitting or lying down, depending on their overall health and the location of the ulcer. Ankle mobility exercises, such as plantar and dorsal flexion (including toes, separately), pronation and inversion or foot circles are safe and easy to perform, even for elderly people. Their role is to maintain or improve blood flow and joint mobility, they have an antithrombotic and anti-swelling effect. There are also no contraindications to performing simple exercises involving the larger joints of the lower limb (such as alternating flexion/extension at the knee or hip joint or the so-called bicycle exercise while lying on the back). In patients with heel ulcers, a prerequisite during such exercises is the ability to lift the heel during movement, e.g., when bending at the knee joint, so that the patient does not rub the affected area on the ground.

Patients with an ischemic foot may also (if they tolerate pain or take pain medication) raise their lower limb and perform the exercises in that position. This is an element of the Buerger [69-71] exercises recommended for leg ischemia.

 doi:10.20944/preprints202506.0367.v1

In the absence of contraindications to loading (e.g. when the wound involves the dorsum of the foot) a standing or at least sitting position is recommended. Energy expenditure is approximately 10% higher in the standing position compared to when a person is sitting or lying [84], therefore the change in the patient's position should be considered beneficial, e.g. for the degree of glucose utilisation.

Exercises can also be performed with the involvement of the upper limbs. Strengthening the muscles of the rim and the free upper limb, apart from its overall impact on the patient's well-being, respiratory and circulatory systems, is useful due to the patient's potential need to move in a wheelchair or on crutches if the treatment fails and amputation is necessary [85]. The work of the arms seems to be as burdensome for the body as the work performed using the lower limbs [86], with even better synchronisation of breathing with the movements of the upper limbs (vs lower limbs) during submaximal exercises [87]. However, whenever possible, patients should be encouraged to perform dynamic exercises using both the upper and lower limbs (e.g. non-weight bearing combined arm + leg cycling), if only due to the accompanying higher energy expenditure and effect on aerobic conditioning, necessary with limited other types of activities [88].

Isometric exercises (alternate tensing and relaxing of muscle parts, without changing the distance of their attachments) are also a frequently used form of rehabilitation when one is unable to move or as a supplement to dynamic exercises. Due to the lack of need for additional movements, they can be performed by people with low physical fitness and poor physical condition, thus easily improving muscle strength and blood flow. Tensing muscles should be avoided in the area where sutures are placed (e.g., to bring the edges of a wound closer or minor amputation) or in the area of fractures (Charcot's foot) so as not to cause the bones to shift relative to each other due to the tensing of the muscles. The undoubted advantage of the exercises is that they can also be performed in situations of permanent immobilisation, with dressings often used for the purpose of offloading.

Learning to walk using crutches remains an element of rehabilitation, both in terms of utility (a way to move around without burdening the affected foot) and EE. Walking on crutches on flat ground or up the stairs is an effort of about 4.5 and 5.0 metabolic equivalent (MET), respectively [89]. Therefore, patients should not be persuaded to use electric wheelchairs for no reason, especially to cover short distances.

Calisthenics strengthens muscles and leads to an additional EE and good heart rate (HR) response [90]. Simple muscle-strengthening exercises like bedside squats (only when the wound is on the upper part of the foot) [91], sit-ups or other forms of muscle strengthening using simple instruments, e.g. stretching rubber bands, squeezing rubber balls, upper limb exercises with weights, are useful in working with patients. Their role often seems small and is underestimated but, e.g., the intensity of chair-assisted exercises could be at least moderate and these exercises can give about 61% of VO2max, 67% HRmax and about 3.9 METs loading [91].

In addition to the above-mentioned exercises, patients with foot deformity without ulceration can perform low-intensity aerobic exercises in standing or walking position after fitting an orthotic, if necessary, or with the use of made-to-measure shoes or individual orthotics. If such exercises are performed on a bicycle, the orthosis must be adapted to the foot deformity and the need to redistribute the pressure of the sole on the pedals should also be taken into account [52] . A good exercise environment for people with deformities without ulceration is water [52].

Table 1 presents examples of simple exercises that can be performed by patients with diabetic foot disease.

 doi:10.20944/preprints202506.0367.v1

Table 1. Type and examples of exercises that may benefit patients with diabetic foot disease.

Type of Exercise	Benefits	Example of Exercise
range of motion	↓ local inflammation ↑ local circulation ↓ swelling ↑ muscle pump antithrombotic effect ↑ joints mobility improvement of plantar load ↓ callus formation ↑ flexibility	-plantar/dorsal flexion -pronation/inversion of the foot -foot circles -alternating flexion/extension of the knee joint -alternating flexion/extension of the hip joint
stretching	↑ local circulation ↓ swelling ↑ flexibility	-attempt to touch the toes of an extended leg with your hand (Hamstring Stretch) -attempt to touch the toes of an extended leg with your hand while sitting with legs spread apart (Inner Thigh Stretch) -brifly sitting on the heels (Shin Stretch)
aerobic	improve respiratory endurance improve circulatory endurance ↓ glucose ↑ energy expenditure	-exercises in standing or walking position after fitting an orthotic if not contraindicated - non-weight bearing combined arm + leg cycling - non-weight bearing arm ergometer
strength	↓ risk of osteoporosis ↑ energy expenditure ↑ muscle tone ↑ muscle strength ↓ glucose (in the long-term context) ↑ blood flow ↑ flexibility improvement of coordination	- weight bearing combined arm and leg (if not contraindicated) cycling -upper and lower limbs exercises with weights - stretching rubber bands (exercise for the upper and lower extremity)
isometric	↑ muscle strength ↑ blood flow ↓ swelling antithrombotic effect	alternating tensing and relaxing the muscle of then calf, thigh, buttock
other specific exercise	↑ muscle strength ↑ energy expenditure ↑ local circulation ↑ blood flow improve respiratory endurance	calisthenics (using natural body movements) Buerger exercises calisthenics Buerger exercises Respiratory exercises: - diaphragmatic breathing - pursed-lip breathing - resisted breathing

 doi:10.20944/preprints202506.0367.v1

Analysing recent reports, it is worth mentioning the possibilities offered by virtual therapy. The impact of some forms of virtual training on aerobic capacity, functional lower-limb strength, reaction time and pain reduction have been documented [92]. This new and still experimental form of rehabilitation takes advantage of the well-known physiological phenomenon of activating the neural networks of the cerebral cortex and cerebral subcortex, which contain the so-called mirror neurons. After watching an exercise being performed (the element of virtual therapy), its performance is simpler and more correct due to the enhancing adaptive neuroplasticity mechanisms [93]. Although there are no studies for patients with limited mobility due to the diabetic foot, various research using mirror neuron-based therapy have proved its effectiveness on several motor functions in populations with neurological diseases [94-97] and it seems reasonable to preliminarily extrapolate the obtained results also to patients with DM and foot problems until that population is studied. The introduction of virtual reality-based therapy can be an additional tool in the effective use of rehabilitation time in the aforementioned group of people, without the risk of tissue damage or other side-effect.

4. Conclusions

In the absence of data on the harmful effects of properly performed exercises in patients with diabetic foot disease and taking into account the documented benefits of exercises on the general condition of the patient, and in some cases the local condition, it should be recommended that their performance should be part of the DFD therapy. Exercises can be dynamic, aerobic or anaerobic and may include isometric exercises or other: calisthenics, stretching and joint mobility improving exercises. Their choice depends on the location and nature of the foot change, the need for and offloading type, the presence of pain and the patient's condition. One should remember not only to exercise the affected limb but also, and often especially, other parts of the body. If possible, virtual therapy should be considered. Staff emphasising the advisability of incorporating exercises into the therapy plan and their safety is probably one of the most important factors determining the patient's involvement. The exercise plan should be prepared at the beginning of treatment and modified according to changes in the patient's general condition and local changes, as well as the implemented therapies and their effect.

Author Contributions: E.S: Conceptualization; Funding acquisition (publication fee); Supervision; Writing - original draft; Writing - review & editing. A.K-B: Funding acquisition (publication fee); Writing - review & editing. K.B.: Writing - original draft.

Funding: Wroclaw Medical University and Medical University of Gdansk covered the publication fee.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflicts of interest. The funders had no role in the design of the article and its preparation.

References

1. Chen L, Pei JH, Kuang J, Chen H-M, Chen Z, Li Z-W et al. Effect of lifestyle intervention in patients with type 2 diabetes: a meta-analysis. *Metabolism* **2015**;*64*(2):338-347. https://doi.org/10.1016/j.metabol.2014.10.018.
2. Thomas DE, Elliott EJ, Naughton GA. Exercise for type 2 diabetes mellitus. *Cochrane Database Syst Rev 2006*; **2006**(3). https://doi.org/10.1002/14651858.CD002968.pub2.
3. American Diabetes Association: Standards of medical care in diabetes-2021. *Diabetes Care* **2021**; *44*(Suppl 1):1-232. https://doi.org/10.2337/dc21-S002.

 doi:10.20944/preprints202506.0367.v1

4. Hu FB. Globalization of Diabetes. *Diabetes Care* **2011**;*34*(6):1249-1257. https://doi.org/10.2337/dc11-0442.
5. Little JP, Francois ME. High-intensity interval training for improving postprandial hyperglycemia. *Res Q Exerc Sport* **2014**;*85*(4):451-456. https://doi.org/10.1080/02701367.2014.963474.
6. Mann S, Beedie C, Balducci S, Zanuso S, Allgrove J, Bertiato F et al. Changes in insulin sensitivity in response to different modalities of exercise: a review of the evidence. *Diabetes Metab Res Rev* **2014**;*30*(4):257–268. https://doi.org/10.1002/dmrr.2488.
7. Shaban N, Kenno KA, Milne KJ. The effects of a 2 week modified high intensity interval training program on the homeostatic model of insulin resistance (HOMA-IR) in adults with type 2 diabetes. *J Sport Med Phys Fitness* **2014**;*54*(2):203–209.
8. van Netten JJ, Bus SA, Apelqvist J, Lipsky BA, Hinchliffe RJ, Game F et al. Definitions and criteria for diabetic foot disease . IWGDF guidelines, https://iwgdfguidelines.org/wp-content/uploads/2019/05/definitions-and-criteria-final.pdf. [Accessed 28 May 2025].
9. Matos M, Mendes R, Silva AB, Sousa N. Physical activity and exercise on diabetic foot related outcomes: A systematic review. *Diabetes Research and Clinical Practice* **2018**;*139*:81-90. https://doi.org/10.1016/j.diabres.2018.02.020.
10. Mueller MJ, Tuttle LJ, Lemaster JW, Strube MJ, McGill JB, Hastings MK et al. Weight-bearing versus nonweight-bearing exercise for persons with diabetes and peripheral neuropathy: a randomized controlled trial. *Arch Phys Med Rehabil* **2013**;*94*:829-838. https://doi.org/10.1016/j.apmr.2012.12.015.
11. Sartor CD, Hasue RH, Cacciari LP, Butugan MK, Watari R, Passaro AC et al. Effects of strengthening, stretching and functional training on foot function in patients with diabetic neuropathy: results of a randomized controlled trial. *BMC Musculoskelet Disord* **2014**;*15*:137. https://doi.org/10.1186/1471-2474-15-137.
12. Lemaster JW, Mueller MJ, Reiber GE, Mehr DR, Madsen RW, Conn VS. Effect of weight-bearing activity on foot ulcer incidence in people with diabetic peripheral neuropathy: feet first randomized controlled trial. *Phys Ther* **2008**;*88*:1385-1398. https://doi.org/10.2522/ptj.20080019.
13. Balducci S, Iacobellis G, Parisi L, Di Biase N, Calandriello E, Leonetti F et al. Exercise training can modify the natural history of diabetic peripheral neuropathy. *J Diabetes Complicat* **2006**;*20*:216-223. https://doi.org/10.1016/j.jdiacomp.2005.07.005.
14. Dixit SM, Maiya AG, Shastry BA. Effect of aerobic exercise on peripheral nerve functions of population with diabetic peripheral neuropathy in type 2 diabetes: a single blind, parallel group randomized controlled trial. *J Diabetes Complicat* **2014**;*28*:332-339. https://doi.org/10.1016/j.jdiacomp.2013.12.006.
15. Francia P, Anichini R, De Bellis A, Seghieri G, Lazzeri R, Paternostro F et al. Diabetic foot prevention: the role of exercise therapy in the treatment of limited joint mobility, muscle weakness and reduced gait speed. *Ital J Anat Embryol* **2015**;*120*(1):21-32.
16. Keylock KT, Young H. Delayed wound healing: can exercise accelerate it? *Int J Exerc Sci* **2010**;*3*(3):70-78. https://doi.org/10.70252/PTMT9509.
17. Tran MM, Haley MN. Does exercise improve healing of diabetic foot ulcers? A systematic review. *J Foot Ankle Res* **2021**;*14*(1):19.https://doi.org/10.1186/s13047-021-00456-w.
18. Eraydin S, Avşar G. The effect of foot exercises on wound healing in type 2 diabetic patients with a foot ulcer: a randomized control study. *J Wound Ostomy Continence Nurs* **2018**;*45*(2):123-130. https://doi.org/10.1097/WON.0000000000000405.
19. Flahr D. The effect of nonweight-bearing exercise and protocol adherence on diabetic foot ulcer healing: a pilot study. *Ostomy Wound Manage* **2010**;*56*(10):40-50.
20. Nwankwo MJ, Okoye GC, Victor EA. Effect of twelve weeks supervised aerobic exercise on ulcer healing and changes in selected biochemical profiles of diabetic foot ulcer subjects. *Int J Diabetes Res* **2014**;*3*(3):41-48. https://doi.org/10.5923/j.diabetes.20140303.03.
21. Lyu X, Li S, Peng S, Cai H, Liu G, Ran X. Intensive walking exercise for lower extremity peripheral arterial disease: a systematic review and meta-analysis. *J Diabetes* **2016**;*8*(3):363-377. https://doi.org/10.1111/1753-0407.12304.

 doi:10.20944/preprints202506.0367.v1

22. Singh S, Young A, McNaught CE. The physiology of wound healing. *Surgery (Oxford)* **2017**;*35*(9):473-477. https://doi.org/10.1016/j.mpsur.2017.06.004.
23. Cañedo-Dorantes L, Cañedo-Ayala M. Skin acute wound healing: a comprehensive review. *Int J Inflamm* **2019**;*2019*:1-15. https://doi.org/10.1155/2019/3706315.
24. Aagaard TV, Moeini S, Skou ST, Madsen UR, Brorson S. Benefits and harms of exercise therapy for patients with diabetic foot ulcers: a systematic review. *Int J Low Extrem Wounds* **2020**;*21*(3):219-233. https://doi.org/10.1177/1534734620954066.
25. Otranto M, Nascimento AP, Monte-Alto-Costa A. Insulin resistance impairs cutaneous wound healing in mice. *Wound Repair Regen* **2013**;*21*(3):464–472. https://doi.org/10.1111/wrr.12042.
26. Winget CM, Deroshia CW . Psychosocial and Chronophysiological Effects Of Inactivity and Immobilization. In : Sandler H., Vernikos J, editors. *Inactivity*: Physiological Effects; 1986, p. 123–147.
27. Garber CE, Blissmer B, Deschenes M R, Franklin BA, Lamonte MJ, Lee I-M et al. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. *Med Sci Sports Exerc* **2011**;*43*:1334–1359. https://doi.org/10.1249/MSS.0b013e318213fefb.
28. Bull FC, AL-Ansari S S, Biddle S, Borodulin K, Buman MP, Cardon G et al. World Health Organization 2020 guidelines on physical activity and sedentary behaviour. *Br. J. Sports Med* **2020**;*54*:1451–1462. https://doi.org/10.1136/bjsports-2020-102955.
29. Greenleaf J E, Kozlowski S. Physiological consequences of reduced physical activity during bed rest. *Exerc. Sport Sci. Rev* **1982**;*10*:84–119.
30. Zhang S, Huang X, Zhao X, Li B, Cai Y, Liang X et al. Effect of exercise on bone mineral density among patients with osteoporosis and osteopenia: a systematic review and network meta-analysis. *J Clin Nurs* **2022**;*31*(15–16):2100–2111. https://doi.org/10.1111/jocn.16101.
31. Nejatian MM, Sobhi S, Sanchez BN, Linn K, Manning L, Soh S-C et al. Reduction in femoral neck and total hip bone mineral density following hospitalisation for diabetes-related foot ulceration. *Sci Rep* **2021**;*11*(1):22742. https://doi.org/10.1038/s41598-021-02233-y.
32. Colberg SR, Sigal RJ, Yardley JE, Riddell MC, Dunstan DW, Dempsey PC et al. Physical Activity/Exercise and Diabetes: A Position Statement of the American Diabetes Association. *Diabetes Care* **2016**; *39*(11): 2065–2079.
33. Wound healing interventions guideline (2023 update); https://iwgdfguidelines.org/wound-healing-2023/. [accessed 28 May 2025].
34. Wendland DM, Altenburger EA, Swen SB, Haan JD. Diabetic Foot Ulcer Beyond Wound Closure: Clinical Practice Guideline. *Phys Ther* **2025**;*105*(1):pzae171. doi: 10.1093/ptj/pzae171. PMID: 39574416; PMCID: PMC11962593.
35. Wendland DM, Kline PW, Simmons L, Sinacore DR. The effect of exercise, physical activity, stepping characteristics, and loading on diabetic foot ulcer healing: a systematic review. *Wounds* **2023**;*35*(1):9-17. https://doi.org/10.25270/wnds/22007
36. Nayak D, Ray R, Anand C, Baruah TD, Goyal A. Protocolized Foot Exercises Help in Improvement of Diabetic Foot Ulcers and Quality of Life When Added to Standard Therapy–A Randomized Clinical Trial. *Int J Low Extrem Wounds* **2024**; 15347346241262591. https://doi.org/10.1177/15347346241262591.
37. Turan Y, Ertugrul BM, Lipsky BA, Bayraktar K. Does physical therapy and rehabilitation improve outcomes for diabetic foot ulcers? *World J Exp Med* **2015**;*5*(2):130-139. https://doi.org/10.5493/wjem.v5.i2.130.
38. Ibrahim A, Jude E, Langton K, Martinez-De Jesus FR, Harkless LB, Gawish H et al. IDF Clinical Practice Recommendations on the Diabetic Foot – 2017. A guide for healthcare professionals, https://idf.org/media/uploads/2023/05/attachments-61.pdf. [accessed 2 August 2024].
39. Faglia E, Caravaggi C, Clerici G, Sganzaroli A, Curci V, Vailati W et al. Effectiveness of removable walker cast versus nonremovable fiberglass off-bearing cast in the healing of diabetic plantar foot ulcer: a randomized controlled trial. *Diabetes Care* **2010**;*33*(7):1419-1423. https://doi.org/10.2337/dc09-1708.

 doi:10.20944/preprints202506.0367.v1

40. Jones K, Backhouse MR, Bruce J. Rehabilitation for people wearing offloading devices for diabetes-related foot ulcers: a systematic review and meta-analyses. *J Foot Ankle Res* **2023**;*16*(1):16. https://doi.org/10.1186/s13047-023-00614-2.
41. Najafi B, Grewal GS, Bharara M, Menzies R, Talal TK, Armstrong DG. Can't Stand the Pressure: The Association Between Unprotected Standing, Walking, and Wound Healing in People With Diabetes. *J Diabetes Sci Technol* **2017**;*11*(4):657-667. https://doi.org/10.1177/1932296816662959.
42. Rogers LC, Frykberg RG, Armstrong DG, Boulton AJM, Edmonds M, Ha Van G et al. The Charcot foot in diabetes. *Diabetes Care* **2011**;*34*(9):2123-2129. https://doi.org/10.2337/dc11-0844.
43. Fiuza-Luces C, Garatachea N, Berger NA, Lucia A. Exercise is the real polypill. *Physiology* **2013**;*28*:330–358. https://doi.org/10.1152/physiol.00019.2013.
44. Lee I M, Shiroma E J, Lobelo F, Puska P, Blair SN, Katzmarzyk PT et al. Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy. *Lancet* **2012**;*380*:219–229. https://doi.org/10.1016/S0140-6736(12)61031-9.
45. Pedersen BK, Saltin B. Exercise as medicine - evidence for prescribing exercise as therapy in 26 different chronic diseases. Scand. *J Med Sci Sports* **2015**;*25*:1–72. https://doi.org/10.1111/sms.12581.
46. Lin X, Zhang X, Guo J, Roberts CK, McKenzie S, Wu W-C et al. Effects of exercise training on cardiorespiratory fitness and biomarkers of cardiometabolic health: a systematic review and meta-analysis of randomized controlled trials. *J Am Heart Assoc* **2015**;*4*(7): e002014. https://doi.org/10.1161/JAHA.115.002014.
47. Hafstad AD, Lund J, Handler-Olsen E, Höper AC, Larsen TS, Aasum E. High- and moderate-intensity training normalizes ventricular function and mechanoenergetics in mice with diet-induced obesity. *Diabetes* **2013**;*62*(7):2287–2294. https://doi.org/10.2337/db12-1580.
48. Laughlin MH. Physical activity-induced remodeling of vasculature in skeletal muscle: role in treatment of type 2 diabetes. *J Appl Physiol (1985)* **2016**;*120*:1–16. https://doi.org/10.1152/japplphysiol.00789.2015.
49. Olver TD, Laughlin MH. Endurance, interval sprint, and resistance exercise training: impact on microvascular dysfunction in type 2 diabetes. *Am J Physiol Heart Circ Physiol* **2016**;*310(3)*:H337–350.
50. Nataraj M, Maiya GA, Nagaraju SP, Shastry BA, Shivashankara KN, Shetty S et al. Effect of exercise-based rehabilitation on functional capacity and renal function in type 2 diabetes mellitus with nephropathy: a randomized controlled trial. *Int Urol Nephrol* **2024**;*56*(8):2671-2682. https://doi.org/10.1007/s11255-024-03987-w.
51. Amaravadi SK, Maiya GA, Vaishali K, Shastry BA. Effectiveness of structured exercise program on insulin resistance and quality of life in type 2 diabetes mellitus- A randomized controlled trial. *PLoS One* **2024**;*19*(5):e0302831. https://doi.org/10.1371/journal.pone.0302831.
52. Gracia-Sanchez A ,Lopez-Pineda A, Lazaro-Martínez JL, Perez A, Pomares-Gomez FJ, Fernandez-Seguin LM et al. Consensus-based recommendations on physical activity and exercise in patients with diabetes at risk of foot ulcerations: a Delphi study. *Brazilian Journal of Physical Therapy* **2023**;*27*(2):100500. https://doi.org/10.1016/j.bjpt.2023.100500.
53. Pence BD, Woods JA. Exercise, obesity, and cutaneous wound healing: evidence from rodent and human studies. *Adv Wound Care (New Rochelle)* **2014**;*3*(1):71–79. https://doi.org/10.1089/wound.2012.0377
54. Keylock T, Meserve L, Wolfe A. Low-intensity Exercise Accelerates Wound Healing in Diabetic Mice. *Wounds* **2018**;*30*(3):68–71.
55. Eraydin Ş, Avşar G. The effect of foot exercises on wound healing in type 2 diabetic patients with a foot ulcer: a randomized control study. *J Wound Ostomy Continence Nurs* **2018**;*45*(2):123–130. https://doi.org/10.1097/WON.0000000000000405.
56. Nejatian MM, Sobhi S, Sanchez BN, Linn K, Manning L, Soh S-C et al. Reduction in femoral neck and total hip bone mineral density following hospitalisation for diabetes-related foot ulceration. *Sci Rep 2021;11*(1):2274210. https://doi.org/10.1038/s41598-021-02233-y.

 doi:10.20944/preprints202506.0367.v1

57. Aitken E, Hiew J, Hamilton EJ, Manning L, Ritter JC, Raby E et al. Exercise in adults admitted to hospital with diabetes-related foot ulcers: a pilot study of feasibility and safety. *J Foot Ankle Res* **2023**;*16*(1):18.
58. Kanade RV, van Deursen RW, Harding K, Price P. Walking performance in people with diabetic neuropathy: benefits and threats. *Diabetologia* **2006**;*49*(8):1747-1754. https://doi.org/10.1007/s00125-006-0309-1.
59. Mathur N, Pedersen BK. Exercise as a means to control low-grade systemic inflammation. *Mediators Inflamm* **2008**;*2008*:109502. https://doi.org/10.1155/2008/109502.
60. Huang H, Xin R, Li X, Zhang X, Chen Z, Zhu Q et al. Physical therapy in diabetic foot ulcer: Research progress and clinical application. *Int Wound J* **2023**;*20*(8):3417-3434. https://doi.org/10.1111/iwj.14196.
61. Pedersen BK: Anti-inflammatory effects of exercise: role in diabetes and cardiovascular disease. *Eur J Clin Invest* **2017**;*47*(8):600–611. https://doi.org/10.1111/eci.12781.
62. Herder C, Peltonen M, Koenig W, Sütfels K, Lindström J, Martin S et al. Anti-inflammatory effect of lifestyle changes in the Finnish Diabetes Prevention Study. *Diabetologia* **2009**;*52*:433–442. https://doi.org/10.1007/s00125-008-1243-1.
63. Yates T, Davies MJ, Gorely T, Talbot D, Bull F, Sattar N et al. The effect of increased ambulatory activity on markers of chronic low-grade inflammation: evidence from the PREPARE programme randomized controlled trial. *Diabet Med* **2010**;*27*:1256–1263. https://doi.org/10.1111/j.1464-5491.2010.03091.x.
64. Zheng G, Qiu P, Xia R, Lin H, Ye B, Tao J et al. Effect of aerobic exercise on inflammatory markers in healthy middle-aged and older adults: a systematic review and meta-analysis of randomized controlled trials. *Front Aging Neurosci* **2019**;*11*:98. https://doi.org/10.3389/fnagi.2019.00098.
65. Taherkhani S, Suzuki K, Castell L. A short overview of changes in inflammatory cytokines and oxidative stress in response to physical activity and antioxidant supplementation. *Antioxidants* **2020**;*9*:1–18. https://doi.org/10.3390/antiox9090886.
66. Pedersen BK, Åkerström TCA, Nielsen AR, Fischer CP. Role of myokines in exercise and metabolism. *J Appl Physiol* **2007**;*103*:1093–1098. https://doi.org/10.1152/japplphysiol.00080.2007.
67. Sharma S, Schaper N, Rayman G. Microangiopathy: is it relevant to wound healing in diabetic foot disease? *Diabetes Metab Res Rev* **2020**;*36*:e3244. https://doi.org/10.1002/dmrr.3244.
68. Versey Z, da Cruz Nizer WS, Russell E, Zigic S, DeZeeuw KG, Marek JE et al. Biofilm-innate immune Interface: contribution to chronic wound formation. *Front Immunol* **2021**;*12*:648554. https://doi.org/10.3389/fimmu.2021.648554.
69. Lin BS, Chang CC, Su CL, Li J-R, Chen M-L, Chen M-Y et al. The assessment of Buerger's exercise on dorsal foot skin circulation in patients with vasculopathic diabetic foot ulcer by using wireless near-infrared spectroscope: a cohort prospective study. *Lasers Med Sci* **2018**;*33*(5):977-982. https://doi.org/10.1007/s10103-017-2420-6.
70. Chang CC, Chen MY, Shen JH, Lin YB, Hsu WW, Lin BS. A quantitative real-time assessment of Buerger exercise on dorsal foot peripheral skin circulation in patients with diabetes foot. *Medicine (Baltimore)* **2016**;*95*(46):e5334. https://doi.org/10.1097/MD.0000000000005334.
71. Chang CF, Chang CC, Hwang SL, Chen MY. Effects of Buerger Exercise Combined Health-Promoting Program on Peripheral Neurovasculopathy Among Community Residents at High Risk for Diabetic Foot Ulceration. *Worldviews Evid Based Nurs* **2015**;*12*(3):145-153. https://doi.org/10.1111/wvn.12091.
72. Chao CYL, Zheng Y-P, Cheing GLY. Epidermal thickness and biomechanical properties of plantar tissues in diabetic foot. *Ultrasound Med Amp Biol* **2011**;*37*(7):1029-1038. https://doi.org/10.1016/j.ultrasmedbio.2011.04.004.
73. Goldsmith JR, Lidtke RH, Shott S. The effects of range-of-motion therapy on the plantar pressures of patients with diabetes mellitus. *J Am Podiatr Med Assoc* **2002**;*92*:483–490. https://doi.org/10.7547/87507315-92-9-483.
74. Jarl G, van Netten JJ, Lazzarini PA, Crews RT, Najafi B, Mueller MJ. Should weight-bearing activity be reduced during healing of plantar diabetic foot ulcers, even when using appropriate

 doi:10.20944/preprints202506.0367.v1

offloading devices? *Diabetes Res Clin Pract* **2021**;*175*:108733. doi: 10.1016/j.diabres.2021.108733. Epub 2021 Mar 10. PMID: 33713722.

75. Coombes BK, Sierra-Silvestre E, Bisset LM, Mielke GI, Ware RS, Coombes JS et al. Pain exacerbation following physical activity in adults with diabetic neuropathy: Ecological momentary assessment of foot symptoms. *Aust J Gen Pract* **2024**;*53*(3):93-98. https://doi.org/10.31128/AJGP-05-23-6821.
76. Franklin BA, Eijsvogels TMH, Pandey A, Quindry J, Toth PP. Physical activity, cardiorespiratory fitness, and cardiovascular health: A clinical practice statement of the ASPC Part I: Bioenergetics, contemporary physical activity recommendations, benefits, risks, extreme exercise regimens, potential maladaptations. *Am J Prev Cardiol* **2022**;*12*:100424. https://doi.org/10.1016/j.ajpc.2022.100424.
77. Keylock KT, Vieira VJ, Wallig MA, DiPietro L, Schrementi M, Woods JA. Exercise accelerates cutaneous wound healing and decreases wound inflammation in aged mice. *Am J Physiol Regul Integr Comp Physiol* **2008**;*294*(1):179–184. https://doi.org/10.1152/ajpregu.00177.2007
78. Zogaib FG, Monte-Alto-Costa A. Moderate intensity physical training accelerates healing of full-thickness wounds in mice. *Braz J Med Biol Res* **2011**;*44*(10):1025–1035. https://doi.org/10.1590/s0100-879x2011007500115.
79. Zhou W, Liu GH, Yang SH, Mi BB, Ye SN. Low-intensity treadmill exercise promotes rat dorsal wound healing. *J Huazhong Univ Sci Technolog Med Sci* **2016**;*36*(1):121–126. https://doi.org/10.1007/s11596-016-1553-3.
80. Zhang J, Yuan T, Wang JH. Moderate treadmill running exercise prior to tendon injury enhances wound healing in aging rats. *Oncotarget* **2016**;*7*(8):8498–8512. https://doi.org/10.18632/oncotarget.7381.
81. Emery CF, Kiecolt-Glaser JK, Glaser R, Malarkey WB, Frid DJ. Exercise accelerates wound healing among healthy older adults: a preliminary investigation. *J Gerontol A Biol Sci Med Sci* **2005**;*60*(11):1432–1436. https://doi.org/10.1093/gerona/60.11.1432.
82. Lin X, Zhang X, Guo J, Roberts CK, McKenzie S, Wu W-C et al. Effects of Exercise Training on Cardiorespiratory Fitness and Biomarkers of Cardiometabolic Health: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *J Am Heart Assoc* **2015**;4(7):e002014. https://doi.org/10.1161/JAHA.115.002014.
83. Hoffman MD, Sheldahl LM, Buley KJ, Sandford PR. Physiological comparison of walking among bilateral above-knee amputee and able-bodied subjects, and a model to account for the differences in metabolic cost. *Arch Phys Med Rehabil* **1997**;*78*(4):385-392. https://doi.org/10.1016/s0003-9993(97)90230-6.
84. Amaro-Gahete FJ, Sanchez-Delgado G, Alcantara JMA, Martinez-Tellez B, Acosta FM, Merchan-Ramirez E et al. Energy expenditure differences across lying, sitting, and standing positions in young healthy adults. *PLoS One* **2019**;*14*(6):e0217029. https://doi.org/10.1371/journal.pone.0217029.
85. Keyser RE, Rasch EK, Finley M, Rodgers MM. Improved upper-body endurance following a 12-week home exercise program for manual wheelchair users. *J Rehabil Res Dev* **2003**;*40*(6):501-510. https://doi.org/10.1682/jrrd.2003.11.0501.
86. Vokac Z, Bell H, Bautz-Holter E, Rodahl K. Oxygen uptake/heart rate relationship in leg and arm exercise, sitting and standing. *J Appl Physiol* **1975**;*39*(1):54-59. https://doi.org/10.1152/jappl.1975.39.1.54.
87. Olivier N, Legrand R, Rogez J, Berthoin S, Prieur F, Weissland T. One-leg cycling versus arm cranking: which is most appropriate for physical conditioning after knee surgery? *Arch Phys Med Rehabil* **2008**;*89*(3):508-512. https://doi.org/10.1016/j.apmr.2007.11.013.
88. Hill M, Puddiford M, Talbot C, Price M. The validity and reproducibility of perceptually regulated exercise responses during combined arm + leg cycling. *Eur J Appl Physiol* **2020**;*120*(10):2203-2212. https://doi.org/10.1007/s00421-020-04444-z.
89. Moran J, Murphy A, Murphy D, Austin A, Moran D, Cronin C et al. The energy expenditure of non-weight bearing crutch walking on the level and ascending stairs. *Gait Posture* **2015**;*42*(1):23-26. https://doi.org/10.1016/j.gaitpost.2014.10.024.

 doi:10.20944/preprints202506.0367.v1

90. Carter SE, Jones M, Gladwell VF. Energy expenditure and heart rate response to breaking up sedentary time with three different physical activity interventions. *Nutr Metab Cardiovasc Dis* **2015**;*25*(5):503-509. https://doi.org/10.1016/j.numecd.2015.02.006.
91. Volkers KM, van Dijk T CW, Eggermont LH, Hollander AP, Scherder E JA. The intensity of chair-assisted exercises in cognitively healthy older adults. *J Aging Phys Act* **2013**;*21*(3):260-71. https://doi.org/10.1123/japa.21.3.260.
92. Mollà-Casanova S, Muñoz-Gómez E, Sempere-Rubio N, Inglés M, Aguilar-Rodríguez M, Page A et al. Effect of virtual running with exercise on functionality in pre-frail and frail elderly people: randomized clinical trial. *Aging Clin Exp Res* **2023**;*35*(7):1459-1467. https://doi.org/10.1007/s40520-023-02414-x.
93. Kim JC, Lee HM. EEG-based evidence of mirror neuron activity from app-mediated stroke patient observation. *Medicina (Kaunas)* **2021**;*57*:979. https://doi.org/10.3390/medicina57090979.
94. Gandhi D, Sterba A, Khatter H, Pandian J. Mirror therapy in stroke rehabilitation: current perspectives. *Ther Clin Risk Manag* **2020**;*16*:75–85. https://doi.org/ 10.2147/TCRM.S206883.
95. Maggio MG, Torrisi M, Buda A, De Luca R, Piazzitta D , Cannavò A et al. Effects of robotic neurorehabilitation through Lokomat plus virtual reality on cognitive function in patients with traumatic brain injury: a retrospective case-control study. *Int J Neurosci* **2020**;*130*:117–123. https://doi.org/10.1080/00207454.2019.1664519.
96. Abbruzzese G, Marchese R, Avanzino L, Pelosin E. Rehabilitation for Parkinson's disease: current outlook and future challenges. *Parkinsonism Relat Disord* **2016**;*22*:60–64. https://doi.org/10.1016/j.parkreldis.2015.09.005.
97. Caligiore D, Mustile M, Spalletta G, Baldassarre G. Action observation and motor imagery for rehabilitation in Parkinson's disease: a systematic review and an integrative hypothesis. *Neurosci Biobehav Rev* **2017**;*72*:210–222. https://doi.org/10.1016/j.neubiorev.2016.11.005.