

# Potential mechanisms of exercise in maintaining skin homeostasis disrupted by protein deficiency (Review)

FAYSAL KASTELLA<sup>1</sup>, VITA MURNIATI TARAWAN<sup>2</sup>, IWAN SETIAWAN<sup>2</sup>, DECKY GUNAWAN<sup>3</sup>,  
 DIANA KRISANTI JASAPUTRA<sup>4</sup>, HANNA GOENAWAN<sup>2,5</sup>, JULIA WINDI GUNADI<sup>3,6</sup> and RONNY LESMANA<sup>2,5</sup>

<sup>1</sup>Postgraduate Program of Biomedical Science, Faculty of Medicine, Universitas Padjadjaran, Kota Bandung, West Java 40161; <sup>2</sup>Department of Biomedical Sciences, Faculty of Medicine, Universitas Padjadjaran, Kabupaten Sumedang, West Java 45363; Departments of <sup>3</sup>Physiology, and <sup>4</sup>Pharmacology, Faculty of Medicine, Universitas Kristen Maranatha, Kota Bandung, West Java 40164; <sup>5</sup>Biological Activity Division, Central Laboratory, Universitas Padjadjaran, Kabupaten Sumedang, West Java 45363; <sup>6</sup>Maranatha Biomedical Research Laboratory, Faculty of Medicine, Universitas Kristen Maranatha, Kota Bandung, West Java 40164, Indonesia

Received November 18, 2023; Accepted March 1, 2024

DOI: 10.3892/wasj.2024.235

**Abstract.** Skin homeostasis processes can be negatively affected by protein deficiency, which can cause the thinning of the epidermis and decrease collagen production in the dermis. It has been proven that exercise has benefits for skin health; however, the mechanisms of exercise as regards skin homeostasis and regeneration caused by protein deficiency are not yet fully understood. The present narrative review focuses on the potential mechanisms of exercise in maintaining skin homeostasis disrupted by protein deficiency, predominantly with the processes that take place in the epidermis and dermis. Normal homeostasis can be disrupted by protein deficiency, which is associated with histological, physiological and metabolic changes that may lead to organ impairment. Protein malnutrition may decrease the number of epidermal stem cells, which leads to epidermal thinning. Nevertheless, protein deprivation decreases the mRNA and protein levels of collagenase. This process decreases dermal collagen levels. Exercise promotes the excretion of certain cytokines and the expression of certain genes that function in skin tissue regeneration, which include peroxisome proliferator-activated receptor (PPAR)- $\gamma$  coactivator-1 $\alpha$ , transforming growth factor- $\beta$ 1, matrix metalloproteinase-9, interleukin (IL)-5, IL-15 and sirtuin-6, and inhibits C-X-C motif chemokine ligand 10. These genes affect skin tissue homeostasis and regeneration. Exercise can also enhance blood flow by increasing angiogenesis, and stimulating vasodilation to supply oxygen and nutrients. This is a vital factor in the synthesis of collagen. Moreover, exercise can modulate some pathways and

stimulate anti-inflammatory and antioxidant effects, contributing to skin regeneration and the healing process.

## Contents

1. Introduction
2. Epidermal and dermal homeostasis and healing
3. Importance of exercise in skin alterations following several diseases
4. Mechanisms of exercise in maintaining skin homeostasis disrupted by protein deficiency
5. Conclusion and future perspectives

## 1. Introduction

The skin, being the largest organ of the human body, has critical functions, which include the synthesis of vitamin D, controlling temperature, regulating water homeostasis, and protecting from hazardous chemicals and pathogens (1,2). As a part of homeostasis, the skin undergoes the complete substitution of damaged tissues with new ones through a continuous processes of regeneration. A high turnover of cell differentiation determines the mechanisms of regeneration in normal processes. Skin tissue is regenerated through the extensive proliferation and migration of a massive number of new cells (3).

The skin has three layers. The epidermis is the first layer and has no vascularization. This stratum is intricately stratified, which constitutes an external barrier. Consisting of lipid-rich structures and non-viable cells, this layer serves as a protective boundary. The epidermis is generated from the basal stratum germinativum via keratinocyte proliferation and the differentiation process. The dermis, which is the second layer, comprises connective tissue, primarily of fibroblasts. These cells are mesenchymal, which function as a skin scaffold. These cells secrete the extracellular matrix (ECM), which is characterized as a fibrous and elastic component. The main components of

---

*Correspondence to:* Dr Julia Windi Gunadi, Department of Physiology, Faculty of Medicine, Universitas Kristen Maranatha, Jalan Suria Sumantri No. 65, Kota Bandung, West Java 40164, Indonesia  
 E-mail: julia.windi@maranatha.ac.id

**Key words:** exercise, skin, homeostasis, regeneration, protein deficiency

the ECM are collagen types I and III, which confer elasticity and strength. From the total amount of collagen, 80-90% is represented by type I collagen and 8-12% by collagen type III. The hypodermis, which is the third layer, is a subcutaneous tissue, composed of blood vessels, lymph, and adipose tissue. This layer secretes various cytokines and chemokines. These layers play roles in certain important homeostasis processes, which include thermoregulation, metabolism and immune functions (4).

Proteins play a crucial role in maintaining skin homeostasis, which serve as essential substrates for key biological components, including enzymes, hormones, cytokines and growth factors. Protein deficiency can result in a decrease in the expression of certain genes and the production of certain cytokines and growth factors. Cytokines and growth factors are essential substances in skin homeostasis. Therefore, protein malnutrition can occur, which causes skin malfunction, leading to the thinning of the epidermis and decreasing collagen production in the dermis. Moreover, it can affect the healing process of wounds, as it impairs angiogenesis and fibroblast proliferation. Tissue regeneration begins with a proliferation of fibroblasts and then continues with a synthesis of collagen from fibroblasts. These two processes use proteins as substrates; hence, protein deficiency causes impairment of these stages. Some research has examined the effects of protein deficiency on skin homeostasis and wound healing. The study by Sugiyama *et al* (5) revealed that protein deficiency impaired the structure and functions of the skin epidermis. Their study found a decrease in the thickness of the epidermis and in the proliferative activity of epidermal cells. Another conclusion is that protein deficiency affects both the synthesis and degradation of skin collagen.

The status of dermal collagen is also affected by protein deficiency. Protein deprivation significantly reduces skin collagen (6). A previous study demonstrated that insufficient protein intake causes a decrease in collagen and elastin synthesis; the efficiency of enzymes, such as matrix metalloproteinases (MMPs) that degrade old proteins is also affected (7). The study by Alves *et al* (8) examined open acute wound healing and demonstrated that malnutrition impaired regeneration by decreasing the mRNA levels of transforming growth factor- $\beta$ 1 (TGF- $\beta$ 1).

As a complementary medicine, exercise is an activity that has benefits on health. This function takes place in all body systems, which include the skin. Additionally, exercise has been employed as a complementary therapy to accelerate skin wound healing. Although exercise has been proven to be beneficial for skin health, the mechanisms of exercise in skin homeostasis and regeneration caused by protein deficiency remain poorly understood. The present review highlights the potential mechanisms of exercise in maintaining skin homeostasis disrupted by protein deficiency, placing particular emphasis on the processes that occur in the epidermis and dermis.

## 2. Epidermal and dermal homeostasis and healing

The main cellular component of the epidermis includes keratinocytes, which comprise almost 95% of the epidermal cell population. Epidermal homeostasis is associated with keratinocyte regulation. Moreover, epidermal homeostasis is tightly

regulated. Through a regulated proliferation and differentiation program, the epidermis maintains tissue homeostasis. In this program, stem cell self-renewal and the differentiation process take place and interact. During this process, the undifferentiated keratinocytes from the basal layer are regenerated to form the stratum spinosum, stratum granulosum, and stratum corneum. Those cells move suprabasally to permanently withdraw from the cell cycle, and alter their biological activity and morphology. The outermost epidermal layer is comprised of corneocytes. The corneocytes consist of dead, flattened, non-nucleated keratinocytes (9).

Mitotic cell types of keratinocytes and epidermal stem cells (EpiSCs) are in the basal layer. Keratinocyte function is regulated by growth factors that trigger intracellular signaling pathways. Several types of growth factors have been explored, which include the epidermal growth factor family and the TGF- $\beta$  family, which are considered to be key regulators (10). Keratinocyte stem cells are characterized by their normally slow-cycle mitotic cells *in vivo*; they can self-renew and are involved in maintaining tissue (11). EpiSCs located in the basal layer of the epidermis have been shown to be key sources of cells for regeneration, metabolism and wound healing of the skin. The sources of EpiSCs may be derived from the regeneration of mesenchymal cells and the migration of other stem cells to the skin tissue. When the skin is damaged, the niches affect the regulation of the migration, proliferation and differentiation of stem cells, by activating multiple signaling pathways. EpiSC differentiation processes occur, which include changes in the number of repair cells, the concentration of cytokines and components of the ECM (12).

Several studies on the factors that influence the epidermis have been carried out. Aging and nutritional status are regarded as two factors that can influence epidermal homeostasis. The study by Lintzeri *et al* (13) concluded that the epidermis was thinner in aged skin. The epidermis tends to become thinner with aging and does not appear to be influenced by sex (13). The study by Leite *et al* (14) concluded that a significant difference existed in mean dermal thickness values in the malnourished group in comparison to the well-nourished group. Nonetheless, no difference was found in mean epidermal thickness between these groups (14).

Skin injury stimulates re-epithelialization, which involves the migration and proliferation of keratinocytes. It begins with the migration of keratinocytes and continues with proliferation. Several growth factors stimulate this process; two such growth factors are TGF- $\beta$  and fibroblast growth factor (FGF). To enhance proliferation, growth factors are produced to stimulate keratinocyte proliferation. Proliferation is required in order to supply keratinocytes, which may be sufficient to cover the wound surface. The proliferation of keratinocytes takes place in basal EpiSCs. This process continues even following epithelial wound closure (15).

Dermal homeostasis is related to collagen production and degradation process. The amount of gross protein content in the skin is ~22%. To maintain the collagen framework that has been established, as well as the synthesis of the new collagen, the amino acid intake must be sufficient (7). Collagen has a triple-helix structure. This substance can initiate and be responsible for the interaction between cells and the matrix. To date, almost 30 different types of collagen have been identified. One

of the most common types of protein is collagen type I (Col-I), which is commonly found in the skin. Col-I is comprised of the genes COL1A1 and COL1A2, known as  $\alpha 1$  and  $\alpha 2$ , respectively (16).

A decrease or loss in the amount of collagen in the skin can have an unfavorable effect. Collagen is the main type of fibrous connective tissue of the dermis. Types I and III collagen are primarily responsible for the tensile strength of the skin. Types I and III collagen are degraded by the collagenases, from the MMP family, which are produced by skin fibroblasts. Collagenases are the main enzymes in the breakdown process of collagen (6). Collagenases degrade collagen I, II and III at distinct sites. MMPs are produced by several cell types, and their production is regulated by cytokines. They participate in cell migration, growth and differentiation, tissue remodeling and angiogenesis (17). The inhibitors that control the activity of these enzymes are tissue inhibitors of metalloproteinases (TIMPs), which comprise of four members (TIMP-1, TIMP-2, TIMP-3 and TIMP-4) (6).

Growth factor production is involved in skin homeostasis and wound healing. Naturally, cells secrete growth factor proteins, and the protein then interacts with cell surface receptors. The binding triggers various processes, which stimulate cell signal transduction pathways. Skin healing involves these growth factor-stimulated cellular responses (18).

TGF- $\beta$ 1 is considered to play an essential role in wound healing. TGF- $\beta$ 1 mediates fibroblast proliferation, collagen production, ECM deposition and myofibroblast differentiation in wound healing (19-21). During this process, TGF- $\beta$  is secreted by fibroblasts and is released from storage sites in the disrupted ECM. TGF- $\beta$ 1 signaling has some effects, including promoting the proliferation of fibroblasts, the synthesis of ECM components such as Col-I and fibronectin by fibroblasts, and the transition of fibroblasts to a myofibroblast wound phenotype. TGF- $\beta$  signaling also involves crosstalk between the dermis and epidermis (22-25).

Several studies have concluded that other than TGF- $\beta$ , under physiological conditions, fibrosis keratinocytes stimulate fibroblasts through the production of interleukin (IL)-1, inducing keratinocyte growth factor and metalloproteinases. Fibroblasts have been shown to modulate keratinocyte proliferation and differentiation (26). As high metabolic rates affect tissues, mesenchymal stem cells (MSCs) are the first to be affected by protein deficiency (1). MSCs can differentiate into keratinocytes in the human epidermis (27). Protein deprivation increases collagenase activity by suppressing the gene expression of two of the TIMPs. Protein deprivation decreases the active form of collagenase. This process also decreases the levels of dermal collagen (6).

### 3. Importance of exercise in skin alteration following several diseases

Exercise is considered to play a crucial role in skin health. Some reviews and research have suggested that several skin disorders are related to exercise. Exercise plays crucial roles in certain skin disorders, which include aging-related skin disorders (cancer), inflammatory disorders (psoriasis and dermatitis) and nutritional disorders, such as protein deficiency (delayed wound healing) (28). Exercise habits have been shown to have several beneficial effects on skin health. Exercise can enhance the structure, moisturizing and

hydration function of the skin (29). Briefly, the known skin benefits of exercise include improving blood flow to nourish cells and remove toxins from the skin; preventing the signs of aging by boosting collagen, elasticity, tone/turgor and the skin barrier; inhibiting the anti-inflammatory actions of oxidative stress; decreasing stress by increasing dermal resilience; and maintaining improved overall skin well-being (30).

Exercise may be an effective preventive strategy against psoriasis. A joint guideline review between the Journal of the Academy of Dermatology and the National Psoriasis Foundation published in 2019 recommended that dermatologists should give regular exercise advice to patients with psoriasis to reduce the risk of associated comorbidities, including metabolic syndrome (31). The study by Lai *et al* (32) demonstrated that moderate and vigorous levels of physical activity appeared to be beneficial for dermatitis. Hence, patients with active hand dermatitis must be advised to remain physically active (32).

The study by Nishikori *et al* (29) demonstrated that resistance exercise exerted effects on skin aging and skin rejuvenation. Some studies have reported that exercise accelerates wound healing (29,33-35). The review by Yeh *et al* (36) examined the preventive and therapeutic roles of exercise in various skin diseases. Their review demonstrated that exercise was recommended for the attenuation of skin aging, the prevention of psoriasis and the improvement of venous leg ulcers (36).

The aforementioned findings indicate that exercise has several benefits on skin health. Nevertheless, the mechanisms through which exercise exerts its effects are not completely understood. The present review discusses how exercise contributes to the maintenance of skin homeostasis, particularly under conditions of protein deficiency.

### 4. Mechanisms of exercise in maintaining skin homeostasis disrupted by protein deficiency

In the present review, as demonstrated in Table I, 12 articles on the mechanisms of exercise in maintaining skin homeostasis were identified. Exercise has been explored in various research to prove its effects on skin health, which include effects on wound healing and the aging process. Below, various studies on the effects of exercise on skin health are presented and the findings from these are discussed. Exercise is classified as acute or chronic; aerobic or anaerobic; endurance or resistance type; and mild, moderate and high intensity. The mechanisms include the role of cytokines, growth factors, oxygenation and angiogenesis.

The study by Riyahi *et al* (2) on the elderly concluded that exercise has some positive effects on skin regeneration in wound healing. These effects are mediated by circulating IL-15. IL-15 is an essential mitochondrial signal, that increases the growth of keratinocytes and fibroblasts (2). These results are supported by the study by Nishikori *et al* (29), which demonstrated that aerobic exercise stimulated the release of IL-15, which reduced skin aging by supporting mitochondrial biogenesis in the skin. Regular training can inhibit skin aging, such as deteriorations in skin elasticity, upper dermal structure and dermal thickness. Nevertheless, acute training enhances skin elasticity and upper dermal structure, but not dermal thickness (29).

Exercise affects inflammation in the skin. Length and intensity are two factors that determine the effects of exercise on inflammation. Aerobic exercise with moderate intensity can

Table I. Studies on exercise related to skin health.

Author(s), year of publication	Title	Type of study and method	Conclusion	(Refs.)
Coletti <i>et al</i> , 2013	Restoration vs. reconstruction: Cellular mechanisms of skin, nerve and muscle regeneration compared	Review	Moderate-intensity exercise improves tissue oxygen to accelerate the wound healing process, and mild hypoxia stimulates angiogenesis, collagen formation, and cell survival	(3)
Lo Presti <i>et al</i> , 2017	Gelatinases and physical exercise: A systematic review of evidence from human studies	Systematic review	MMP-9 gene transcription occurs as a result of acute exercise, whereas MMP-2 and TIMP transcription result from the regular repetition of exercise over time; a single bout of exercise and regular training appear to have opposite effects on blood MMP-9 levels	(17)
Hoffmann and Weigert, 2017	Skeletal Muscle as an Endocrine Organ: The Role of Myokines in Exercise Adaptations	Review	After acute exercise or training, the mRNA abundance of TGF- $\beta$ 1 and TGF- $\beta$ 2 receptor 2 is increased	(49)
Ishihara, 2019	Mild hyperbaric oxygen: mechanisms and effects.	Review	Keratinocyte proliferation and epidermal cell regeneration may be effective for damage repair in the epidermis and are activated by exposure to mild hyperbaric oxygen.	(45)
Riyahi <i>et al</i> , 2021	Reviewing the Physiology of Cutaneous Wound Healing and Evaluating the Effect of Exercise on It	Review	Exercise increases circulatory IL-15 levels, which increases keratinocytes and fibroblasts; exercise affects inflammation in the skin; the effect of exercise on inflammation depends on its length and intensity; regular exercise improves angiogenesis and increases local blood flow providing oxygen and nutrients to wound tissue, which is important in the synthesis of connective tissue; regular exercise can prevent oxidative stress and accelerate healing by potentiating the body's systemic antioxidative defense	(2)
Han <i>et al</i> , 2021	Increase in Free and Total Plasma TGF- $\beta$ 1 Following Physical Activity	Experimental study, which measured plasma concentrations of free and total TGF- $\beta$ 1, TGF- $\beta$ 2 and TGF- $\beta$ 3 in 40 subjects	Light physical activity was associated with a significant increase in free and total TGF- $\beta$ 1 and TGF- $\beta$ 2 plasma concentrations; the function of TGF- $\beta$ was indicated in several processes of skin process such as angiogenesis, inflammation, fibroblast proliferation, and collagen synthesis in wound healing	(22)



Table I. Continued.

Author(s), year of publication	Title	Type of study and method	Conclusion	(Refs.)
Ishikawa <i>et al</i> , 2021	Hot yoga increases SIRT6 gene expression, inhibits ROS generation, and improves skin condition	Original article	Hot yoga increases blood SIRT6 gene expression and inhibits plasma ROS production	(37)
Oizumi <i>et al</i> , 2021	The association between activity levels and skin moisturising function in adults	A cross-sectional, observational study was conducted in Japan with 86 participants; the study analyzed two skin moisturising function parameters based on data from self-administered questionnaires concerning participant exercise habits	Higher-intensity exercise may promote skin-moisturising function; endurance exercise induces IL-5, and IL-5 promotes the biosynthesis of the mitochondria; thus, skin construction improves	(48)
Ishiuichi-Sato and Nedachi, 2021	Possible involvement of CXCL10 chemokine ligand 10 in exercise-induced collagen production of mouse dermal fibroblasts	Experimental study on mice were subjected to forced treadmill running. (15 cm/sec for 30 min)	Exercise reduces the expression of myokine CXCL10 so that the skin apoptosis process is reduced	(50)
Barzegari <i>et al</i> , 2022	The effect of three different exercise methods HIIT, HIT and MIT on the expression of FGF and TGF genes in liver tissue of male Wistar rats	Experimental study on 32 male Wistar rats that participated in moderate-intensity training, high-intensity training, and high-intensity intermittent training; the amount of TGF and FGF gene changes was determined using real-time PCR	MIT, HIT and HIIT increase the expression of TGF and FGF	(52)
Chen <i>et al</i> , 2022	Molecular mechanisms of exercise contributing to tissue regeneration	Review	Exercise strongly induces the overexpression of PGC-1 $\alpha$ . PGC-1 $\alpha$ in both human and rodent muscle and may trigger the remodeling of the satellite cell niche by altering the extracellular matrix composition	(53)
Nishikori <i>et al</i> , 2023	Resistance training rejuvenates aging skin by reducing circulating inflammatory factors and enhancing dermal extracellular matrices	An experimental study to compare the effects of acute training and regular training on skin aging in a 16-week intervention in 61 healthy middle-aged Japanese women with a sedentary lifestyle	Regular training counteracts skin aging such as deteriorations in skin elasticity, upper dermal structure, and dermal thickness. Acute training also had positive effects on skin elasticity and upper dermal structure, but it did not improve dermal thickness	(29)

MMP, matrix metalloproteinase; TIMP, tissue inhibitor of metalloproteinase; TGF, transforming growth factor; IL, interleukin; SIRT6, sirtuin 6; ROS, reactive oxygen species; CXCL10, C-X-C motif chemokine ligand 10; MIT, medium-intensity training; HIIT, high-intensity interval training; PGC-1 $\alpha$ , peroxisome proliferator-activated receptor (PPAR)- $\gamma$  coactivator-1 $\alpha$ .

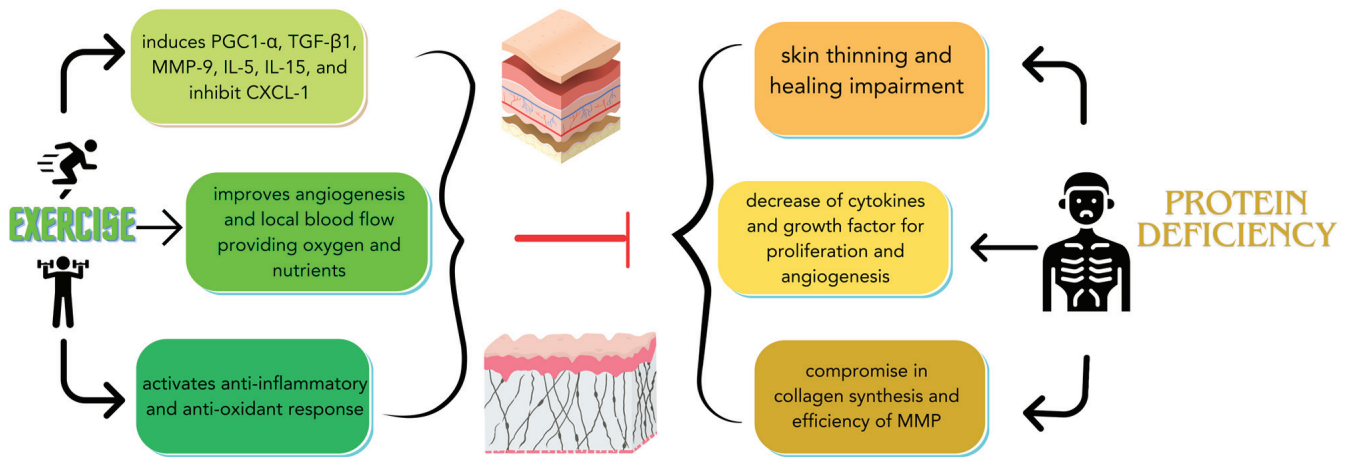


Figure 1. Potential mechanisms of exercise in maintaining skin homeostasis disrupted by protein deficiency. PGC-1 $\alpha$ , peroxisome proliferator-activated receptor (PPAR)- $\gamma$  coactivator-1 $\alpha$ ; TGF- $\beta$ 1, transforming growth factor  $\beta$ 1; IL-5, interleukin 5; IL-15, interleukin 15; MMP-9, matrix metalloproteinase 9; CXCL-10, C-X-C motif chemokine ligand 10.

reduce oxidative stress by increasing antioxidant enzyme activities. Regular exercise potentiates the systemic antioxidative defense of the body to prevent oxidative stress and accelerate healing. Exercise supports vascular growth and increases tissue vascularization by regulating reactive oxygen species (ROS). Regular exercise improves angiogenesis and increases local blood flow, providing oxygen and nutrients to wound tissue. Sufficient oxygen and nutrients support the synthesis of skin connective tissue (2).

The study by Ishikawa *et al* (37) reported that continuous hot yoga exercise protected against ROS-induced senescence by modulating sirtuin (SIRT) 6 expression. Several studies have provided evidence that the SIRT family is involved in the regulation of longevity (38-43). Hot yoga may enhance the activation of SIRT6 via a mechanism mediated by shear stress. The study by Ishikawa *et al* (37) also reported that continuous hot yoga exercise can suppress catecholamines and thus promote blood flow. Exercise under appropriate heat stress and high humid conditions is expected to increase cutaneous blood flow with skin temperature (37).

Moderate-intensity exercise has been proven to improve tissue oxygen to accelerate the wound healing process. Tissue oxygenation is an essential factor in the healing process; angiogenesis, collagen formation and cell survival can be stimulated by mild hypoxia. Oxygen is critical for the synthesis of connective tissue. Exercise provides adequate oxygen supply to wound tissue and helps in healing (3). Hypoxia can occur physiologically by exercise. This condition stimulates cellular adaptation, which is mediated by key oxygen sensors, namely, hypoxia-inducible factors (HIFs). HIFs respond acutely and induce the production of endogenous metabolites and proteins to promptly regulate metabolic pathways that maintain oxygen supply (44). Keratinocyte proliferation and epidermal cell regeneration may be effective for the regeneration of the epidermis. Keratinocyte proliferation and epidermal cell regeneration are activated by exposure to mild hyperbaric oxygen (45). Hyperbaric oxygen has the same mechanism as exercise in enhancing oxidative metabolism.

Previous studies have revealed that the moderate-intensity training effect is superior to that of high intensity and

strenuous intensity in the skin healing process. The study by Heinen *et al* (46) on patients with diabetes reported that moderate-intensity exercise was the best option for wound healing. The study by Amatriain-Fernández *et al* (47) indicated that regular moderate-intensity exercise exerts anti-inflammatory and antioxidant effects, and can stimulate several signaling pathways (47). Aerobic exercise is more effective than anaerobic exercise in the skin healing process, although both exercises are effective. Nonetheless, anaerobic exercises may increase ROS production in wound tissue and delay regeneration (2).

Another potential mechanism of exercise in the skin regeneration process is by inducing MMPs. MMPs are involved in biological processes, which include angiogenesis. A previous study demonstrated that acute intense exercise caused an increase in circulating MMP-9 levels. MMP-9 is involved in the processes of angiogenesis, including proteolysis of the capillary basement membrane; ECM degradation induces the release of proangiogenic and antiangiogenic factors. Angiogenesis is a key factor in regeneration, including in skin tissue (17).

In their study, Oizumi *et al* (48) examined the association between the activity level and skin-moisturizing function. The skin-moisturizing function is a key physiological parameter of the skin. Their study used an exercise habits questionnaire and examined the types of skin moisturizing. The results revealed that activity levels were associated with skin moisture levels. The moderate- and high-activity-level habit groups had higher skin moisture levels than the low-activity-level habit group. Moreover, the results suggested that higher-intensity exercise had a beneficial effect on increasing skin-moisturizing function. Endurance exercise enhanced skin health by inducing IL-5, which promoted the biosynthesis of the mitochondria (48).

Exercise induces the production of certain myokines from muscle contraction (49). The C-X-C motif chemokine ligand 10 (CXCL10) secretion from skeletal muscles can control collagen production in mouse dermal fibroblasts. CXCL10 is a myokine whose expression is reduced due to muscle contraction. CXCL10 promotes the apoptosis of endothelial cells. The reduction in CXCL10 expression in skeletal muscle through exercise can be considered to have a wide range of effects on the whole body, including the skin (50).

In another study, light physical activity was shown to be associated with a significant increase in free and total TGF- $\beta$ 1 and TGF- $\beta$ 2 plasma concentrations. TGF- $\beta$  was involved in several skin processes, such as angiogenesis, fibroblast proliferation and collagen synthesis (22). Following acute exercise or training, an increase in the mRNA levels of TGF- $\beta$ 1 and TGF- $\beta$ 2 receptor 2 was observed. The release of TGF- $\beta$  at the early stages of the healing process recruits inflammatory cells from the circulation into the wounded area. This process then continues with angiogenesis and collagen synthesis. TGF- $\beta$  stimulates the cells to increase the synthesis of ECM proteins and simultaneously decreases the levels of collagen proteases (49).

The effects of exercise on skin regeneration also may be mediated by the production of growth factors. Previous research has compared the effects of exercise on the expression of TGF and FGF in liver tissue, demonstrating that moderate-intensity training (MIT), high-intensity training (HIT) and high-intensity interval training (HIIT) increases the expression of TGF and FGF. However, it appears that the expression of these genes increases to a greater extent with MIT than with HIT and HIIT. The duration of MIT can be concluded to have been an effective factor in the expression of both genes; among the most critical factors in the expression of TGF and FGF are the intensity of training and its duration. This effect is very likely to occur in any organ in the body, including the skin, as the effects of growth factors are not limited to a specific organ (51,52).

In the body, particularly in muscle tissue, exercise strongly induces the overexpression of peroxisome proliferator-activated receptor (PPAR)- $\gamma$  coactivator-1 $\alpha$  (PGC-1 $\alpha$ ). PGC-1 $\alpha$  is a transcription coactivator, which in muscle, can alter the ECM composition and subsequently results in remodeling of the satellite cell niche; PGC-1 $\alpha$  promotes exercise-induced tissue regeneration and is involved in mitochondrial signaling. Thus, PGC-1 $\alpha$  functions as the key regulator of the crosstalk between mitochondrial biogenesis and exercise-induced regeneration. This mechanism potentially occurs in the skin regeneration process (53). The various mechanisms in the epidermis and dermis that could potentially explain the effects of exercise on skin homeostasis disrupted by protein deficiency are illustrated in Fig. 1.

A limitation of the present review is that references were not distinguished in terms of the type of exercise, research methods and subjects. In addition, the present review did not separate the mechanisms that occur physiologically (homeostasis) and pathologically (wound healing).

## 5. Conclusion and future perspectives

Exercise is beneficial for skin health, both under normal and wound conditions, by affecting the processes that take place in the epidermis and dermis. The mechanisms involved are complex and comprise process that include various cytokines and growth factors. Further research is warranted in order to determine the effects and mechanisms of exercise on the skin with more specific parameters, including distinguishing the types of exercise and various skin conditions, and examining any mechanisms, cytokines and growth factors involved in skin tissue hemostasis and regeneration.

## Acknowledgements

Not applicable.

## Funding

The present study was supported by scheme B internal grant from Universitas Kristen Maranatha (grant no. 013/SK/ADD/UKM/III/2023) and the Academic Leadership Grant from Universitas Padjadjaran (grant no. 1549/UN6.3.1/PT.00/2023).

## Availability of data and materials

Not applicable.

## Authors' contributions

DG, DKJ and FK conceived the study and searched the literature for studies to be included in the review. JWJ, DKJ, HG and VMT performed the screening and selection of articles to be included in the review. DG and FK drafted the manuscript. RL and IS confirmed the findings from the included studies and reviewed the drafted manuscript. All authors worked together in completing the final draft of the review article. All authors have read and approved the final manuscript. Data authentication is not applicable.

## Ethics approval and consent to participate

Not applicable.

## Patient consent for publication

Not applicable.

## Competing interests

The authors declare that they have no competing interests.

## References

1. dos Santos GG, Batool S, Hastreiter A, Sartori T, Nogueira-Pedro A, Borelli P and Fock RA: The influence of protein malnutrition on biological and immunomodulatory aspects of bone marrow mesenchymal stem cells. *Clin Nutr* 36: 1149-1157, 2017.
2. Riyahi F, Riahy S and Yousefpour M: Reviewing the Physiology of Cutaneous Wound Healing and Evaluating the Effect of Exercise on It: A Narrative Review Article. *Ann Mil Health Sci Res* 19: e115926, 2021.
3. Coletti D, Teodori L, Lin Z, Beranudin JF and Adamo S: Restoration versus reconstruction: Cellular mechanisms of skin, nerve and muscle regeneration compared. *Regen Med Res* 1: 4, 2013.
4. Mazini L, Rochette L, Hamdan Y and Malka G: Skin immunomodulation during regeneration: Emerging new targets. *J Pers Med* 11: 85, 2021.
5. Sugiyama A, Fujita Y, Kobayashi T, Ryu M, Suzuki Y, Masuda A, Ochi T and Takeuchi T: Effect of protein malnutrition on the skin epidermis of hairless mice. *J Vet Med Sci* 73: 831-835, 2011.
6. Oishi Y, Fu Z, Ohnuki Y, Kato H and Noguchi T: Effects of protein deprivation on alpha1(I) and alpha1(III) collagen and its degrading system in rat skin. *Biosci Biotechnol Biochem* 66: 117-126, 2002.



7. Garg S and Sangwan A: Dietary protein deficit and deregulated autophagy: A new Clinico-diagnostic perspective in pathogenesis of early aging, skin, and hair disorders. *Indian Dermatol Online J* 10: 115-124, 2019.
8. Alves CC, Torrinhas RS, Giorgi R, Brentani MM, Logullo AF and Waizberg DL: TGF- $\beta$ 1 expression in wound healing is acutely affected by experimental malnutrition and early enteral feeding. *Int Wound J* 11: 533-539, 2014.
9. Sciegłinska D, Krawczyk Z, Sojka DR and Gogler-Piğłowska A: Heat shock proteins in the physiology and pathophysiology of epidermal keratinocytes. *Cell Stress Chaperones* 24: 1027-1044, 2019.
10. Hashimoto K: Regulation of keratinocyte function by growth factors. *J Dermatol Sci* 24 (Suppl 1): S46-S50, 2000.
11. Lavker RM and Sun TT: Epidermal stem cells: Properties, markers, and location. *Proc Natl Acad Sci USA* 97: 13473-13475, 2000.
12. Yang R, Wang J, Chen X, Shi Y and Xie J: Epidermal stem cells in wound healing and regeneration. *Stem Cells Int* 2020: 9148310, 2020.
13. Lintzeri DA, Karimian N, Blume-Peytavi U and Kottner J: Epidermal thickness in healthy humans: A systematic review and meta-analysis. *J Eur Acad Dermatol Venereol* 36: 1191-1200, 2022.
14. Leite SN, Jordão Júnior AA, de Andrade TAM, Masson Ddos S and Frade MAC: Experimental models of malnutrition and its effect on skin trophism. *An Bras Dermatol* 86: 681-688, 2011 (In English, Portuguese).
15. Wang Y and Graves DT: Keratinocyte function in normal and diabetic wounds and modulation by FOXO1. *J Diabetes Res* 2020: 3714704, 2020.
16. Naomi R, Ridzuan PM and Bahari H: Current insights into collagen type I. *Polymers (Basel)* 13: 2642, 2021.
17. Lo Presti R, Hopps E and Caimi G: Gelatinases and physical exercise: A systematic review of evidence from human studies. *Medicine (Baltimore)* 96: e8072, 2017.
18. de Araújo R, Lôbo M, Trindade K, Silva DF and Pereira N: Fibroblast growth factors: A controlling mechanism of skin aging. *Skin Pharmacol Physiol* 32: 275-282, 2019.
19. Yin L, Zhao X, Ji S, He C, Wang G, Tang C, Gu S and Yin C: The use of gene activated matrix to mediate effective SMAD2 gene silencing against hypertrophic scar. *Biomaterials* 35: 2488-2498, 2014.
20. Liu S, Jiang L, Li H, Shi H, Luo H, Zhang Y, Yu C and Jin Y: Mesenchymal stem cells prevent hypertrophic scar formation via inflammatory regulation when undergoing apoptosis. *J Invest Dermatol* 134: 2648-2657, 2014.
21. Wang R, Ghahary A, Shen Q, Scott PG, Roy K and Tredget EE: Hypertrophic scar tissues and fibroblasts produce more transforming growth factor-beta1 mRNA and protein than normal skin and cells. *Wound Repair Regen* 8: 128-137, 2000.
22. Han AJ, Alexander LC Jr, Huebner JL, Reed AB and Kraus VB: Increase in free and total plasma TGF- $\beta$ 1 following physical activity. *Cartilage* 13 (1 Suppl): 1741S-1748S, 2021.
23. Shi A, Hillege MMG, Wüst RCI, Wu G and Jaspers RT: Synergistic short-term and long-term effects of TGF- $\beta$ 1 and 3 on collagen production in differentiating myoblasts. *Biochem Biophys Res Commun* 547: 176-182, 2021.
24. Hata S, Okamura K, Hatta M, Ishikawa H and Yamazaki J: Proteolytic and non-proteolytic activation of keratinocyte-derived latent TGF- $\beta$ 1 induces fibroblast differentiation in a wound-healing model using rat skin. *J Pharmacol Sci* 124: 230-243, 2014.
25. Konstantinou E, Zagoriti Z, Pyriochou A and Poulas K: Microcurrent stimulation triggers MAPK signaling and TGF- $\beta$ 1 release in fibroblast and osteoblast-like cell lines. *Cells* 9: 1924, 2020.
26. Russo B, Brembilla NC and Chizzolini C: Interplay between keratinocytes and fibroblasts: A systematic review providing a new angle for understanding skin fibrotic disorders. *Front Immunol* 11: 648, 2020.
27. Dos Santos JF, Borçari NR, da Silva Araújo M and Nunes VA: Mesenchymal stem cells differentiate into keratinocytes and express epidermal kallikreins: Towards an in vitro model of human epidermis. *J Cell Biochem* 120: 13141-13155, 2019.
28. Kaimal S and Thappa DM: Diet in dermatology: Revisited. *Indian J Dermatol Venereol Leprol* 76: 103-115, 2010.
29. Nishikori S, Yasuda J, Murata K, Takegaki J, Harada Y, Shirai Y and Fujita S: Resistance training rejuvenates aging skin by reducing circulating inflammatory factors and enhancing dermal extracellular matrices. *Sci Rep* 13: 10214, 2023.
30. Knaggs H and Lephart ED: Enhancing skin anti-aging through healthy lifestyle factors. *Cosmetics* 10: 142, 2023.
31. Yeroushalmi S, Hakimi M, Chung M, Bartholomew E, Bhutani T and Liao W: Psoriasis and exercise: A review. *Psoriasis (Auckl)* 12: 189-197, 2022.
32. Lai YC and Yew YW: A relationship between physical activities and hand dermatitis: An epidemiology study of the USA population. *Indian J Dermatol* 60: 584-587, 2015.
33. Emery CF, Kiecolt-Glaser JK, Glaser R, Malarkey WB and Frid DJ: Exercise accelerates wound healing among healthy older adults: A preliminary investigation. *J Gerontol A Biol Sci Med Sci* 60: 1432-1436, 2005.
34. Pence BD and Woods JA: Exercise, obesity, and cutaneous wound healing: Evidence from rodent and human studies. *Adv Wound Care (New Rochelle)* 3: 71-79, 2014.
35. Kawanishi M, Kami K, Nishimura Y, Minami K, Senba E, Umamoto Y, Kinoshita T and Tajima F: Exercise-induced increase in M2 macrophages accelerates wound healing in young mice. *Physiol Rep* 10: e15447, 2022.
36. Yeh C, Flatley E, Elkattawy O, Berger L and Rao B: Exercise in dermatology: Exercise's influence on skin aging, skin cancer, psoriasis, venous ulcers, and androgenetic alopecia. *J Am Acad Dermatol* 87: 183-184, 2022.
37. Ishikawa T, Ito E, Okada T and Sumi T: Hot yoga increases SIRT6 gene expression, inhibits ROS generation, and improves skin condition. *Glycative Stress Res* 8: 123-135, 2021.
38. Sharples AP, Hughes DC, Deane CS, Saini A, Selman C and Stewart CE: Longevity and skeletal muscle mass: The role of IGF signalling, the sirtuins, dietary restriction and protein intake. *Aging Cell* 14: 511-523, 2015.
39. Giblin W, Skinner ME and Lombard DB: Sirtuins: Guardians of mammalian healthspan. *Trends Genet* 30: 271-286, 2014.
40. Satoh A and Imai S: Systemic regulation of mammalian ageing and longevity by brain sirtuins. *Nat Commun* 5: 4211, 2014.
41. Schmeisser K, Mansfeld J, Kuhlow D, Weimer S, Priebe S, Heiland I, Birringer M, Groth M, Segre A, Kanfi Y, *et al*: Role of sirtuins in lifespan regulation is linked to methylation of nicotinamide. *Nat Chem Biol* 9: 693-700, 2013.
42. Kanfi Y, Naiman S, Amir G, Peshti V, Zinman G, Nahum L, Bar-Joseph Z and Cohen HY: The sirtuin SIRT6 regulates lifespan in male mice. *Nature* 483: 218-221, 2012.
43. Imai S and Guarente L: It takes two to tango: NAD<sup>+</sup> and sirtuins in aging/longevity control. *NPJ Aging Mech Dis* 2: 16017, 2016.
44. Kumar H and Choi DK: Hypoxia inducible factor pathway and physiological adaptation: A cell survival pathway? *Mediators Inflamm* 2015: 584758, 2015.
45. Ishihara A: Mild hyperbaric oxygen: Mechanisms and effects. *J Physiol Sci* 69: 573-580, 2019.
46. Heinen M, Borm G, van der Vleuten C, Evers A, Oostendorp R and van Achterberg T: The Lively Legs self-management programme increased physical activity and reduced wound days in leg ulcer patients: Results from a randomized controlled trial. *Int J Nurs Stud* 49: 151-161, 2012.
47. Amatriain-Fernández S, Gronwald T, Murillo-Rodríguez E, Imperatori C, Solano AF, Latini A and Budde H: Physical exercise potentials against viral diseases like COVID-19 in the elderly. *Front Med (Lausanne)* 7: 379, 2020.
48. Ryosuke O, Yoshie S and Hiromi A: The association between activity levels and skin moisturising function in adults. *Dermatol Reports* 13: 8811, 2021.
49. Hoffmann C and Weigert C: Skeletal muscle as an endocrine organ: The role of myokines in exercise adaptations. *Cold Spring Harb Perspect Med* 7: a029793, 2017.
50. Ishiuchi-Sato Y and Nedachi T: Possible involvement of CXC motif chemokine ligand 10 in exercise-induced collagen production of mouse dermal fibroblasts. *Endocr J* 68: 1359-1365, 2021.
51. Yadav H and Rane SG: TGF- $\beta$ /Smad3 signaling regulates brown adipocyte induction in white adipose tissue. *Front Endocrinol (Lausanne)* 3: 35, 2012.
52. Barzegari A, Naghibi S, Dashty MH and Zafarabadi FK: The effect of three different exercise methods HIIT, HIT and MIT on the expression of FGF and TGF genes in liver tissue of male Wistar rats. *Appl Health Stud Sport Phys* 9: 100-113, 2022.
53. Chen J, Zhou R, Feng Y and Cheng L: Molecular mechanisms of exercise contributing to tissue regeneration. *Signal Transduct Target Ther* 7: 383, 2022.

