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Role of Vitamin D in Wound Healing and Its Research Progress

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Abstract

Vitamin D, a fat-soluble vitamin, has been shown to play an important biological role in wound healing in recent years. Wound healing is a complex biological process involving multiple cell types and their interactions. Vitamin D plays a key role in this process by regulating immune responses, affecting inflammation levels, promoting cell proliferation and differentiation, and promoting collagen synthesis. Although there have been many studies on the role of vitamin D in wound healing, there are still some problems such as the optimal dosage, application timing and different effects of different types of wounds. This paper narrative reviews the molecular mechanism of vitamin D in wound healing and its research progress in clinical application to provide theoretical basis and guidance for future clinical practice. It is expected to bring new enlightenment and ideas for the research and development of wound healing field.

Keywords

Vitamin D, Wound Healing, Mechanism of Action, Immune Regulation, Clinical Application

1. Introduction

Vitamin D, as an important fat-soluble vitamin, has received more and more attention in recent years. Its importance and physiological function in the body have been gradually recognized by researchers. Vitamin D not only plays an important role in the metabolism of calcium and phosphorus, but also participates in the regulation of many physiological processes such as cell proliferation and differentiation of immune system and anti-inflammatory response [1] [2]. Recent studies have shown that vitamin D plays a key role in wound healing, and its correspond-

ing mechanism has been gradually revealed. Vitamin D regulates gene expression in a variety of cell types through its receptor (VDR), affecting cell proliferation, differentiation and migration, which are essential for promoting wound healing, especially in chronic wounds, diabetic feet and burns [3] [4].

Wound healing is a complex biological process, which can be divided into three stages: inflammation, proliferation and remodeling. In the inflammatory stage, the immune response is regulated by vitamin D, and the release of inflammatory mediators is reduced to promote wound healing. Studies have shown that vitamin D inhibits the expression of pro-inflammatory factors, such as IL-6 and TNF-α, and increases the level of anti-inflammatory factor IL-10 to promote the polarization of M1 macrophages to M2, which is very important for wound healing [5] [6]. Lack of vitamin D during the proliferation phase slows cell migration and proliferation, thus affecting the formation of new tissues [7]. Vitamin D also enhances angiogenesis by promoting the expression of angiogenic factors such as VEGF and PDGF, helping to provide nutrients and oxygen necessary for healing [5].

With the in-depth study of the role of vitamin D in wound healing, more and more clinical evidence shows that its supplementation can improve the healing effect of chronic wounds. For example, in one study, the incidence of infection in vitamin D supplementation group was significantly lower than that in control group, and at the same time, the wound healing speed was significantly accelerated, which gave new ideas and methods for the treatment of chronic wounds [3]. Vitamin D supplementation has been found to improve glycemic control and promote wound healing in diabetic foot studies, highlighting its potential value in diabetes-related wound management [4]. The purpose of this article is to systematically summarize the molecular mechanism of vitamin D in wound healing and its clinical application, and to discuss the future research direction and the possibility of clinical promotion. Through reviewing the existing literature, we will further explore the different mechanisms of vitamin D in wound healing and its potential for clinical application, especially in the fields of chronic wound and diabetic foot. With further understanding of vitamin D function, future research may lead to new therapeutic strategies for wound healing management.

2. Biological Function of Vitamin D and Its Relationship with Wound Healing

2.1. Vitamin D Metabolism and Active Forms

Vitamin D synthesis depends on the conversion of 7-dehydrocholesterol to vitamin D3 (cholecalciferol) by the skin under UV irradiation, followed by hydroxylation in the liver and kidneys to form its active form 1,25-dihydroxyvitamin D3 (1,25(OH) 2D3) [8]. Vitamin D regulates gene expression through its receptor (VDR) and thus affects cell functions. For example, in skin fibroblasts and keratinocytes, VDR activity is directly related to cell proliferation and migration [9]. Abnormal vitamin D metabolism is closely related to many chronic diseases and wound healing disorders. Studies have shown that vitamin D deficiency not

only affects bone health, but may also delay wound healing and increase the risk of chronic wounds [10]. Therefore, vitamin D metabolism and its active form are important in wound healing.

2.2. Cellular Targets of Vitamin D in Wound Healing

Vitamin D receptors are widely expressed in fibroblasts, keratinocytes and immune cells of the skin, and are involved in regulating multiple processes of wound healing. Vitamin D plays a key role in the initial stage of wound healing, accelerating epidermal regeneration by promoting keratinocyte proliferation and migration. [6] At the same time, vitamin D has a regulatory effect on collagen synthesis of fibroblasts, promoting the repair process of the dermal layer, and thus accelerating the entire healing process. These cells are able to participate more effectively in all stages of wound healing under the action of vitamin D, including inflammatory proliferation and remodeling. [7] Therefore, vitamin D is a key cellular target, and further research on its mechanism will help to develop new wound healing treatment strategies.

2.3. Effects of Vitamin D on Immune Regulation and Inflammatory Response

Vitamin D plays an important role in regulating immune and inflammatory responses. It can regulate the function of macrophages, dendritic cells and T cells, thus balancing pro-inflammatory and anti-inflammatory responses [10]. Studies have shown that vitamin D has an inhibitory effect on inflammatory responses and reduces the release of inflammatory mediators, which is extremely important for the transition of wounds to proliferative phase [6]. In addition, vitamin D also enhances local immune defense and prevents infection by regulating the expression of antibacterial peptides during wound healing, which is particularly important [9]. Therefore, the speed of wound healing can not only be improved by the immunomodulatory effect of vitamin D, but also the risk of infection can be reduced, providing a new idea for wound management.

3. Advances in Molecular Mechanism of Vitamin D in Wound Healing

3.1. Signaling Pathway of Vitamin D Regulating Cell Proliferation and Differentiation

Vitamin D mediates a series of signal transduction pathways in cells through its receptor (VDR), and then affects cell proliferation and differentiation. Specifically, vitamin D can activate Wnt/β-catenin and MAPK.(mitogen-activated protein kinase) and PI3K/Akt (Phosphatidylinositol 3-kinase/Akt), which play an important role in cell proliferation, migration and differentiation. Emerging evidence suggests that vitamin D may facilitate keratinocyte and fibroblast proliferation and migration via modulation of the Wnt signaling pathway, potentially contributing to enhanced wound epithelialization and repair [8]. With respect to

MAPK signaling, the vitamin D receptor (VDR) appears to serve dual regulatory functions: mediating non-genomic activation through p38/ERK pathways to promote cellular proliferation, while concurrently exerting genomic suppressive effects through phosphatase induction and inflammatory signal attenuation to dampen sustained stress responses [11] [12]. Regarding the PI3K/Akt cascade, VDR activation has been implicated in augmenting cell survival and proliferative signaling, fostering the expansion and appropriate differentiation of epidermal stem cells and fibroblasts, which may substantially facilitate the wound healing process [13]. In addition, VDR expression is reduced due to vitamin D deficiency, which further delays wound healing [6]. By regulating these signaling pathways, vitamin D not only promotes cell growth and repair, but also plays a key role in tissue healing.

3.2. Effect of Vitamin D on Collagen Synthesis and Matrix Remodeling

Vitamin D plays an important role in collagen synthesis and matrix remodeling. Studies have shown that vitamin D can promote the expression of type I and type III collagen, thereby improving the stability and structural integrity of wound matrix [7]. In the process of wound repair, the balance of matrix metalloproteinases (MMPs) and their inhibitors (TIMPs) is critical for matrix remodeling. Vitamin D modulates matrix remodeling processes involving the expression of MMPs and TIMPs with the ultimate goal of promoting wound healing [9]. In addition, vitamin D improves the microenvironment for wound healing by modulating the composition of extracellular matrix to enhance healing effectiveness.

3.3. Role of Vitamin D in Mitigating Oxidative Stress

Vitamin D plays a key role in antioxidant stress.(Nuclear factor E2-related factor 2) signaling pathway, vitamin D can enhance the antioxidant capacity of cells and reduce the damage caused by oxidative stress to wound cells [14]. Studies have shown that the survival rate and functional recovery of cells can be improved by vitamin D supplementation, and the stability of wound healing environment can also be maintained [3]. Oxidative stress is closely related to wound healing. Vitamin D can promote cell proliferation and migration by reducing oxidative damage, thus providing support for the smooth development of wound healing process. In summary, vitamin D not only plays a role in promoting cell proliferation and differentiation and collagen synthesis in wound healing, but also supports the recovery of cell function by antioxidant mechanism.

4. Progress in Clinical Application of Vitamin D in Wound Healing

4.1. Clinical Study on Vitamin D Supplementation in the Treatment of Chronic Wounds

Vitamin D deficiency is extremely common in patients with chronic wounds, es-

pecially diabetic foot ulcers, and studies have shown a significant association with delayed wound healing. Low levels of 25-hydroxyvitamin D are associated with multiple hard-to-heal wound types, according to a systematic review of the literature (such as pressure ulcers, diabetic ulcers, and venous ulcers) [10]. Vitamin D levels in these patients were generally below the normal range, suggesting that vitamin D supplementation may be beneficial to improve wound healing. In addition, clinical trials have shown that vitamin D supplementation can effectively improve the healing rate of chronic wounds. In a study conducted by Gao *et al.* in patients with diabetic foot ulcers, the cohort receiving vitamin D supplementation appeared to demonstrate accelerated wound healing relative to the control group, with wound area reduction reaching approximately 60% [3]. Studies of different doses and administration routes also showed differences in the efficacy of vitamin D. Some studies showed that vitamin D supplementation of 2000IU daily could effectively increase the serum vitamin D level of patients and reduce the infection rate [3]. Overall, vitamin D supplementation in chronic wound healing shows good clinical prospects, but the specific optimal dose and mode of administration still need further study.

4.2. Application of Vitamin D in Burn and Surgical Wound Repair

Vitamin D has also been shown to promote burn and surgical wound healing. Studies have shown that vitamin D can accelerate the healing process of burn patients by enhancing immune function and promoting wound repair. The mechanism is related to the anti-inflammatory and immunomodulatory properties of vitamin D. For example, in one study of burn patients, vitamin D supplementation significantly increased serum antimicrobial peptides (e.g. cathelicidin), which in turn increases the body's resistance to infection [6]. In addition, vitamin D status after surgery is strongly associated with wound healing speed and the incidence of complications. A study of patients undergoing open carpal tunnel surgery showed that normal vitamin D levels were associated with faster wound healing, and vitamin D deficiency significantly increased the risk of delayed healing [15]. Therefore, vitamin D supplementation may play an important role in the recovery process after surgery, especially for those patients with relatively weak immune function. Appropriate vitamin D supplementation can help promote wound healing and reduce the incidence of complications.

4.3. Clinical Potential of Vitamin D in Combination with Other Therapeutic Strategies

Vitamin D is not only used as a single supplement in wound healing, but also shows excellent clinical potential in combination with other treatment strategies. For example, growth factors, stem cell therapy and combination of antibacterial therapy and vitamin D are gradually becoming research hotspots. Some studies show that vitamin D and growth factors can significantly improve wound healing, perhaps by promoting cell proliferation and migration, and reepithelialization [8].

In addition, the combination of stem cell therapy and vitamin D has shown excellent prospects. Research has found that vitamin D can improve the survival rate and function of stem cells, thus enhancing their role in wound repair [16]. In antibacterial therapy, the antibacterial properties of vitamin D can be combined with traditional antibiotics to enhance the ability to control drug-resistant strains and improve the success rate of wound healing [17]. In conclusion, the combination of vitamin D and other therapies provides a new idea for wound healing, and its synergistic effect and specific mechanism still need to be further explored.

5. Conclusions

Vitamin D plays an increasingly important role in wound healing, which is receiving increasing attention from the medical community. Related studies have shown that vitamin D can effectively promote wound healing through a variety of molecular mechanisms, including regulating immune response, promoting cell proliferation and differentiation, enhancing collagen synthesis, and resisting oxidative stress. These important theoretical foundations for vitamin D application in wound therapy are laid by these biological effects.

The results of clinical studies further confirm the excellent adjuvant effect of vitamin D supplementation on chronic wounds, diabetic feet and burns. Accumulating evidence suggests that vitamin D supplementation may facilitate wound healing while demonstrating a favorable safety profile, with no serious adverse effects reported. Daily oral administration of 2000 IU vitamin D3 appeared to be associated with significant improvements in reducing infection rates, facilitating wound healing, and enhancing immune function, while demonstrating a favorable safety profile without significant adverse events. This finding provides strong support for clinicians to introduce vitamin D supplementation in wound treatment, demonstrating its potential as a simple, economical and efficient adjuvant treatment.

However, despite the encouraging results of existing studies, there is still a need to further explore the optimal dosage, mode of administration and combination with other treatments of vitamin D. The resolution of these questions will provide more scientific guidance for clinical practice and help optimize wound healing management strategies. For example, vitamin D supplementation doses may vary from patient to patient. Knowing the vitamin D requirements under different pathological conditions will help to formulate personalized treatment plans. In addition, the combination of vitamin D and other treatments, such as antibiotic wound dressings or other factors that promote healing, is also the focus of future research.

Future experimental designs based on current research should focus on larger randomized controlled trials to verify the long-term effectiveness of vitamin D in wound healing and clearly define its mechanism of action. At the same time, to explore the relationship between patient vitamin D levels and treatment effects, it may provide new biomarkers for clinical use, thus optimizing treatment options.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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