Pharmacogn J. 2024; 16(2): 485-491
A Multifaceted Journal in the field of Natural Products and Pharmacognosy
www.phcogj.com

Review Article

Vitamin D and Wound Recovery: Illuminating the Path to Enhanced Healing in Diabetic Patients

Aditya Chrisdianto[1], Prananda Surya Airlangga[2]*, Belindo Wirabuana[2], Regina Purnama Dewi Iskandar[3]

ABSTRACT

Wound healing is a highly coordinated biological event as a response to injured skin. It commonly takes 14 days for a wound to be completely healed. However, the duration of wound healing may vary between individuals due to certain factors. One major factor that delays the wound-healing process is Diabetes Mellitus. Delayed wound healing with poor prognosis commonly occurs in diabetic patients. Chronic hyperglycemia may affect macrophage polarisation, which is essential in the wound healing mechanism. The macrophage polarisation enables the pro-inflammatory M1 phenotype to switch to the anti-inflammatory M2 phenotype. Thus, pro-inflammatory M1 phenotype prevails persistently in diabetic wounds, while the anti-inflammatory M2 phenotype remains deficient. It results in significantly elevated levels of pro-inflammatory cytokines triggered by the M1 phenotype. Prolonged wound healing times increase the risk of infection, which can lead to more severe complications. Vitamin D is widely recognized for its essential role in regulating calcium levels and supporting bone health, as well as its positive effects on the immune system. This vitamin has the potential to skew macrophages towards the M2 phenotype and promote a regenerative and anti-inflammatory environment.

Keywords: Vitamin D, Diabetes Mellitus, Wound Healing, Macrophage Polarisation.

Aditya Chrisdianto[1], Prananda Surya Airlangga[2]*, Belindo Wirabuana[2], Regina Purnama Dewi Iskandar[3]

[1]Master Program of Clinical Medicine, Faculty of Medicine, Universitas Airlangga, Surabaya, INDONESIA.

[2]Department of Anaesthesiology, Faculty of Medicine, Universitas Airlangga, Surabaya, INDONESIA.

[3]Department of Orthodontics, Faculty of Dental Medicine, Universitas Airlangga, Surabaya, INDONESIA.

Correspondence

Prananda Surya Airlangga

Department of Anaesthesiology, Faculty of Medicine, Universitas Airlangga, Surabaya, INDONESIA.

E-mail: prananda-s-a@fk.unair.ac.id

History

- Submission Date: 16-03-2024;
- Review completed: 12-04-2024;
- Accepted Date: 18-04-2024.

DOI : 10.5530/pj.2024.16.77

Article Available online

http://www.phcogj.com/v16/i2

INTRODUCTION

The restoration of tissue integrity and functionality after injury or damage involves a fascinating and complex cascade of orchestrated events known as wound healing. This process encompasses a finely tuned orchestration of cellular and molecular interactions, among which immune cells play a pivotal role. Among immune cells, macrophages have emerged as central players in the dynamic and complex journey of tissue repair. In three sequential stages, the process unfolds: inflammation initiates, followed by proliferation, and concludes with maturation.[1] In the inflammatory phase, clot formation halts bleeding, while inflammatory cells infiltrate the wound, initiating the debridement process, preventing infection, and releasing cytokines. These cytokines not only promote inflammation but also stimulate fibroblast and keratinocyte proliferation and migration. Re-epithelialization of the wound commences with the proliferation and migration of keratinocytes, while fibroblasts proliferate and migrate to reconstruct the collagen matrix, providing the framework for re-epithelialization to take place. During the maturation phase, the epidermis is restored, and collagen cross-linking occurs within the healing wound matrix. Failure of these events to occur promptly results in chronic skin wounds.[2]

Macrophages exhibit remarkable plasticity, adopting different activation states and functions depending on the microenvironment in which they operate. M1 macrophages, once activated, are recognized for their pro-inflammatory and antimicrobial functions, whereas M2 macrophages, upon activation, assume roles linked to anti-inflammatory responses as well as tissue repair and remodeling. The balance and transition between these distinct macrophage phenotypes are critical determinants of the efficiency and quality of the wound healing process.[3]

Characterized by polyphagia, polydipsia, and hyperglycemia, diabetes mellitus (DM) stands as a chronic metabolic disorder. DM consists of Type 1 (T1DM), Type 2 (T2DM), and gestational diabetes. The worldwide incidence of DM in adults increased from 4.7% (1980) to 8.5%.[4] Delayed wound healing commonly occurs in diabetic patients due to hyperglycemia and impaired macrophage polarisation.[5] Elevated blood sugar levels can impair various cellular and molecular processes involved in wound healing. High glucose levels can results in microvascular dysfunction, inflammation, and oxidative stress that are able to hinder the body's ability to repair damaged tissue. Moreover, diabetes-related complications such as neuropathy and reduced blood circulation further exacerbate the problem by impairing the sensation of pain and reducing the delivery of essential nutrients to the wound site.[6] Impaired macrophage polarisation is characterized by increased M1 expression during the wound-healing process. It leads to disturbed angiogenesis and a lack of collagen levels that affect the outcome of wound healing.[3]

Clinical implications of delayed wound healing in diabetes are substantial. Due to the effects of diabetes on the microvascular and macrovascular systems, people with diabetes are more likely to experience difficulties during or after surgery.[7] Prolonged wound healing times increase the risk of infection, which can lead to more severe complications, such as cellulitis, abscess formation, or even limb amputation in extreme cases. The economic burden associated with chronic wounds in diabetes is significant, as it often necessitates prolonged

Cite this article: Chrisdianto A, Airlangga PS, Wirabuana B, Iskandar RPD. Vitamin D and Wound Recovery: Illuminating the Path to Enhanced Healing in Diabetic Patients. Pharmacogn J. 2024;16(2): 485-491.

hospitalizations, multiple surgeries, and costly wound care products.[8] In the perioperative period, during severe treatment, and in the Intensive Care Unit, patients with Vitamin D deficiency are frequently encountered by specialists in Anesthesiology and Reanimation. While hypovitaminosis D has been associated with unfavorable clinical outcomes in the general population, there is a lack of studies examining this relationship specifically in surgical patients. Assessing the impact of Vitamin D levels on postoperative mortality, a retrospective study analyzed 3,509 patients undergoing noncardiac surgery and found a correlation between Vitamin D levels below 13 ng/ml and heightened mortality and morbidity.[9]

The importance of Vitamin D, a secosteroid hormone, as a regulator of the immune response and inflammation has gained increasing recognition in recent years, reflecting a growing body of research. Beyond its well-documented functions in maintaining calcium balance and promoting bone health, this vitamin is now recognized for its multifaceted effects on immune cells, including macrophages. In particular, it has been implicated in the regulation of macrophage polarization, with the potential to skew macrophages towards the M2 phenotype and promote a regenerative and anti-inflammatory environment.[10] This literature review aims to analyze the promising role of Vitamin D as a regulator of macrophage polarization and offers a foundation for further research into its therapeutic potential in promoting optimal wound healing.

Vitamin D: An Overview

Vitamin D comprises a group of fat-soluble secosteroids, with the term commonly referring to two main forms: vitamin D2 (ergocalciferol), derived from plant sterol ergosterol, and vitamin D3 (cholecalciferol), derived from animal 7-dehydrocholesterol.[11] Dietary sources provide a small amount of vitamin D, encompassing both vitamin D2 and vitamin D3. The primary source of circulating vitamin D, predominantly vitamin D3, is synthesized in the skin from 7-dehydrocholesterol (7-DHC) upon exposure to sunlight. In humans, vitamin D undergoes a two-step hydroxylation process catalyzed by 25-hydroxylase and 1α-hydroxylase enzymes. This process occurs successively, resulting in the conversion of vitamin D into 1.25-dihydroxyvitamin D (1.25(OH)2D) in the kidney and 25-hydroxyvitamin D (25(OH)D) in the liver. Although 25-hydroxyvitamin D (25(OH)D) is the principal form circulating in the body and is a reliable indicator of overall vitamin D levels, 1.25-dihydroxy vitamin D (1.25(OH)2D) functions as the metabolically active form of vitamin D.[12]

Through both genomic and nongenomic mechanisms, Vitamin D demonstrates its effects. In the genomic pathway, 1.25(OH)2D, serving as a ligand, attaches to the vitamin D receptor (VDR), a ligand-dependent nuclear receptor. This receptor acts as a transcription factor, forming a heterodimer with the retinoid X receptor (RXR) following ligand binding. In a context-dependent manner, gene expression is activated or repressed by the VDR/RXR complex through recognition of vitamin D-responsive elements (VDRE), which are direct tandem repeats of two hormone response elements found in the regulatory regions of target genes. Coregulatory partners, such as chromatin remodelers, co-activators, and co-repressors, play a crucial role in tightly regulating the downstream effects of VDR.[14]

Although the connection between vitamin D and the immune system is not fully understood, available evidence suggests that vitamin D significantly influences both innate and adaptive immune functions. Specifically, vitamin D directly affects the function of monocytes, macrophages, and dendritic cells (DCs), as well as the secretion of associated cytokines, thereby regulating the innate immune response. Moreover, vitamin D modulates T and B cell activation, proliferation, and differentiation, influencing the development and progression of numerous autoimmune diseases, thus impacting the adaptive immune response.[15]

Vitamin D is sourced naturally from two primary outlets: food and sunlight. When acquired through dietary means, vitamin D undergoes mixing with bile and subsequent absorption by the intestine, facilitated partially by certain cholesterol transporters. Dietary sources of vitamin D encompass a range of foods such as fish, eggs, red meat, fatty foods, and dairy products, with fish serving as a predominant source. Meanwhile, sunlight exposure prompts the skin to synthesize vitamin D upon exposure to ultraviolet B (UVB) radiation. Remarkably, sunlight exposure alone can fulfill up to 90% of the body's vitamin D requirements.[10]

The active form of vitamin D, calcitriol, is essential for maintaining calcium and phosphate balance in the body. It facilitates the absorption of calcium and phosphate in the intestines, encourages calcium reabsorption in the kidneys, and triggers the release of calcium from bones when needed. These actions help maintain proper mineralization of bones and teeth. Vitamin D also has immunomodulatory functions. It can affect the immune system by influencing the differentiation and function of immune cells. Adequate levels of vitamin D have been suggested by certain studies to help the immune system respond effectively to infections and prevent autoimmune diseases. Vitamin D, besides its involvement in bone health and the immune system, has been associated with various other physiological processes, including cell growth, regulation of blood pressure, insulin secretion, and mood regulation. A worldwide health issue has emerged due to the widespread occurrence of Vitamin D deficiency, with widespread implications for public health. In children, vitamin D deficiency can lead to rickets, while in adults, it can result in osteomalacia. Additionally, insufficient levels of vitamin D are associated with an elevated risk of fractures, autoimmune disorders, infectious diseases, and various chronic conditions.[16]

Wound Healing Process

Protecting the body from physical damage, pathogens, and fluid loss, the skin acts as a vital life-protective barrier and performs immune-neuroendocrine functions essential for maintaining body homeostasis. Prompt restoration of skin integrity post-injury is crucial to uphold its functions. This intricate process involves the coordinated participation of peripheral blood mononuclear cells, resident skin cells, the extracellular matrix, cytokines, chemokines, growth factors, and regulatory molecules in wound healing.[1]

Wound healing is a complex and highly coordinated biological process that the body undergoes to repair damaged tissue, such as cuts, abrasions, surgical incisions, or injuries. It typically occurs in several overlapping phases of hemostasis, inflammation, proliferation, and remodeling.[8] In the outset of wound healing, the phase of hemostasis occurs immediately after an injury to prevent excessive bleeding. It is a complex process involving the interaction of various components in the blood and blood vessel walls. At the site of injury, hemostasis focuses on forming a stable blood clot to seal the damaged blood vessel, thereby preventing additional blood loss.[17]

Following an injury to a blood vessel, the first response is vasoconstriction. It triggers the narrowing of blood vessels to reduce blood flow to the site of injury. Smooth muscle cell contraction within the blood vessel walls mediates this temporary measure aimed at minimizing blood loss.[18] During primary hemostasis, a temporary platelet plug forms at the injury site, with platelets—small cell fragments in the blood—playing a crucial role in this process. Platelets, upon exposure to collagen at the injury site, become activated and adhere to the exposed collagen. Various adhesive molecules and receptors facilitate this adhesion. Once adhered to the site of injury, platelets become activated and change shape, releasing granules containing factors that promote platelet aggregation and vasoconstriction. This activation helps stabilize the initial platelet plug. Activated platelets recruit more platelets to

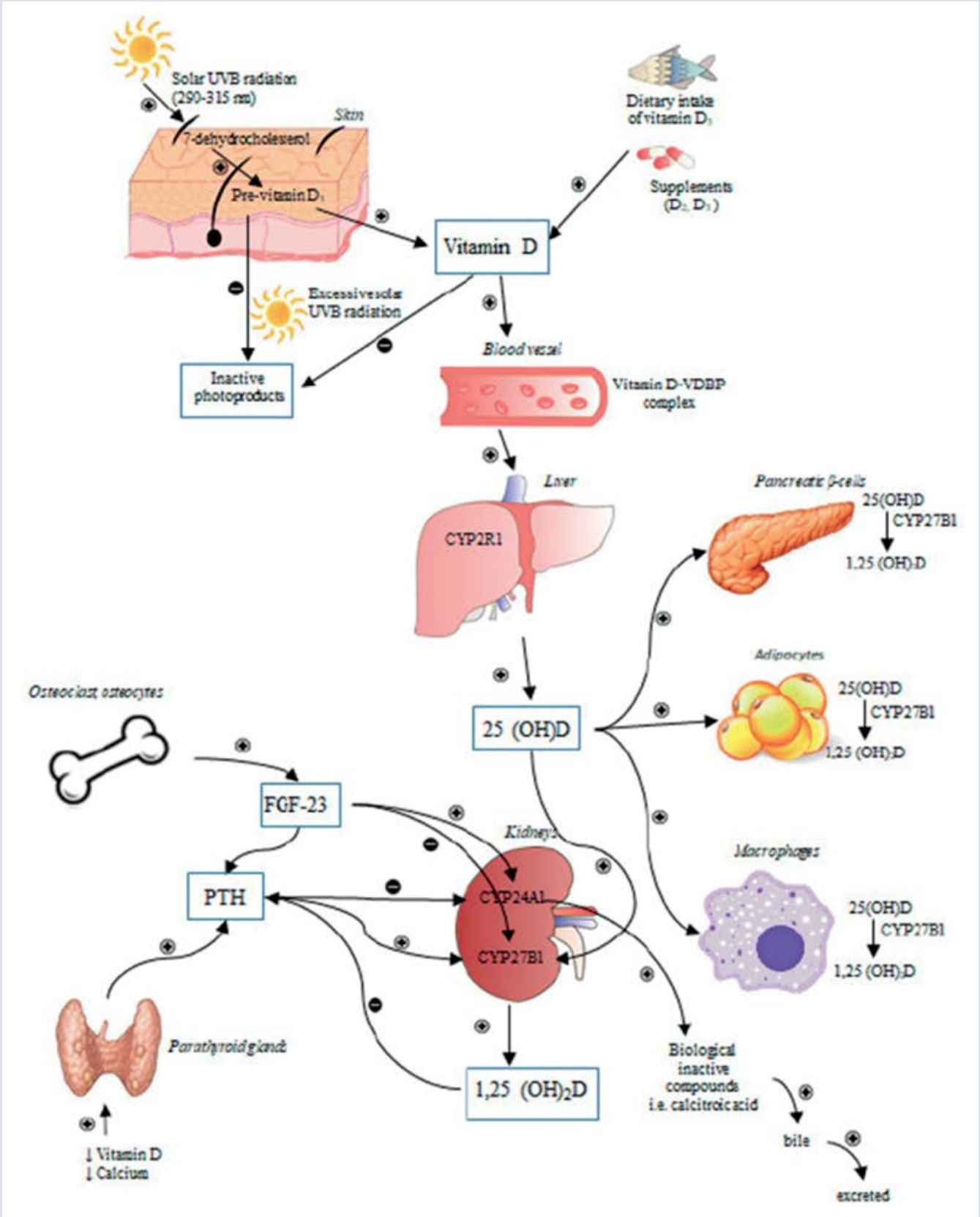

Figure 1: The Synthesis and Metabolism of Vitamin D.[13]

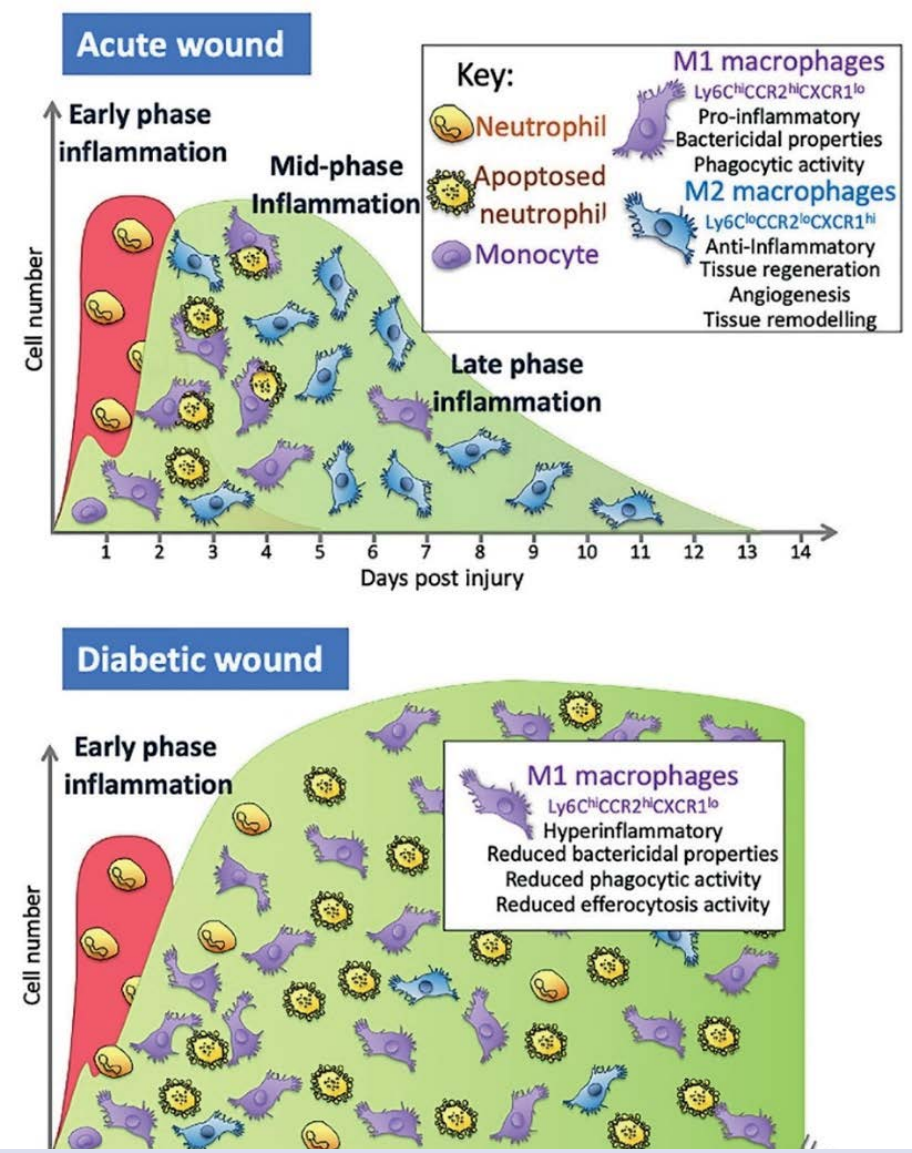

Figure 2: The difference between diabetic and non-diabetic wound healing mechanisms.[26]

the injury site by adhering to each other, forming a larger and more stable platelet plug. The activation of the coagulation cascade, which comprises a sequence of enzymatic reactions, leads to the formation of a fibrin clot during secondary hemostasis. This clot reinforces the platelet plug and stabilizes it.[17]

In secondary hemostasis, clotting factors are activated, leading to the conversion of fibrinogen, a soluble protein, into insoluble fibrin strands. These fibrin strands intertwine to form a meshwork that ensnares red blood cells and fortifies the platelet plug, thereby establishing a durable blood clot. Following clot formation, it begins to contract, drawing the edges of the injured blood vessel nearer. This contraction aids in reducing the wound's size and halting additional bleeding.[19] As the wound begins to heal, a process called fibrinolysis occurs to break down the fibrin clot. Plasmin, an enzyme, is responsible for degrading the fibrin clot, allowing for the eventual dissolution of the clot as the wound heals. Hemostasis is a tightly regulated process, and imbalances in the system can lead to bleeding disorders (hemorrhagic conditions) or clotting disorders (thrombotic conditions). The wound-healing process, once hemostasis is successfully achieved, proceeds to the inflammatory phase.[20]

Following hemostasis, the body initiates an inflammatory response. This involves the release of various signaling molecules, including cytokines and chemokines, which attract immune cells to the wound site.[21] White blood cells, primarily neutrophils and macrophages, are essential for modulating the inflammation phase. Neutrophils and macrophages help to clear debris, such as dead cells, foreign materials, and bacteria, from the wound site. This is achieved through a process called phagocytosis, where these immune cells engulf and digest foreign particles. Inflammatory mediators cause blood vessels near the wound to dilate (expand) and become more permeable. This helps facilitate the delivery of immune cells and essential nutrients to the injured area, promoting the healing process.[22]

The immune cells present at the wound site not only remove debris but also play a role in initiating an immune response against potential pathogens. During wound healing, this helps to protect the body from infection. Excessive or prolonged inflammation, although necessary for

the wound-healing process, can result in delayed healing and potential complications. Once the inflammation has served its purpose, the process transitions into the proliferative phase, where new tissue is generated and the wound begins to close. Eventually, this leads to the remodeling phase, during which the tissue matures and strengthens.[21]

After the inflammatory and proliferative phases, the final stage of wound healing is the remodeling phase. It typically starts around three weeks after the initial injury and can continue from several months to potentially years, contingent on the magnitude and severity of the wound. Collagen is produced in this phase. It is a protein that provides strength and structure to the wound. However, the type of collagen changes from type III to type I, which is stronger and more durable. This transition helps to increase the tensile strength of the healing tissue. The tissue at the wound site gradually undergoes reorganization, resulting in the formation of a scar.[22]

Loss of tissue function or restricted mobility in the affected area can occur due to the inferior strength and elasticity of scar tissue compared to the original tissue. As time progresses, changes in texture, color, and flexibility are observed in scar tissue, eventually becoming more similar to the surrounding healthy tissue. This process can take months or even years to complete.[23] Initially, the scar may appear red, raised, and firm, but it typically becomes less noticeable as it matures. In addition to collagen, other components of the wound, such as blood vessels, nerves, and other cell types, also continue to evolve and adapt during the remodeling phase. This can help improve the overall function and appearance of the healed area. As the collagen remodels and the scar matures, the wound site gradually regains its strength and stability. However, it may not reach the same level of strength as the original tissue.[24]

During the remodeling phase, the objective is to restore as much functionality and cosmetic appearance to the wound site as possible. It's important to note that while the wound may appear fully healed during this phase, it's still a dynamic process that continues beneath the surface, and it's essential to protect the area from excessive stress or trauma to prevent disruption of the healing process and promote optimal scar formation.[23]

Acute and chronic are the two main types of wounds. In healthy individuals, acute wounds usually heal fully within 2 to 3 weeks, transitioning to a remodeling phase with minimal scarring. However, if a wound remains stagnant in any phase for 6 to 8 weeks, it is classified as chronic.[22] Beyond the visible area, chronic wounds typically involve a broader scope of tissue damage, affecting not just the immediate site but also the surrounding tissues, increasing the risk of ulceration.[25]

Chronic wounds, unlike acute wounds, are linked to particular ailments such as diabetes and display an aberrant healing trajectory. They are characterized by their failure to promptly heal. During the initial phases of wound healing, the scarcity of macrophages disrupts the typical processes of inflammation and proliferation, resulting in compromised re-epithelialization, impaired granulation tissue formation, or hemorrhaging.[18] The M1 subset of macrophages drives the production of pro-inflammatory mediators and engages in phagocytic activity, while the M2 subset is linked to extracellular matrix (ECM) production and the generation of anti-inflammatory mediators. Failure to transition between M1 and M2 states leads to chronic wounds, such as venous ulcers and diabetic wounds, which often remain stuck in the inflammation phase. The duration of this phase depends on factors like bacterial load and the presence of necrotic tissue at the wound site.[20]

Vitamin D and Wound Healing Mechanism

Vitamin D is essential for numerous physiological functions in the body, such as immune function and bone health. While its direct role in wound healing is not as well-established as some other factors, Emerging evidence suggests a potential contribution of vitamin D to the overall process.[27] Vitamin D is recognized for its role in modulating the immune system. It can enhance the function of immune cells like macrophages, crucial for initiating wound healing, particularly in its early stages by removing debris and pathogens. Adequate vitamin D levels may support a more effective immune response during the healing process.[28]

Vitamin D has anti-inflammatory properties, and inflammation is a natural part of the wound healing process. Proper regulation of inflammation is essential for effective wound healing. Balancing the inflammatory response, Vitamin D aids in preventing excessive inflammation, which might otherwise hinder the healing process.[29] Vitamin D plays a regulatory role in cell proliferation and differentiation. These processes are critical for tissue repair and regeneration. Skin cells are among the various cell types involved in wound healing that possess vitamin D receptors. Vitamin D may contribute to the formation and maintenance of healthy skin.[30]

Connective tissue relies on collagen as a vital component for effective wound healing. There is evidence from some studies suggesting that vitamin D may influence collagen synthesis, which could impact the strength and integrity of the healing tissue.[27] Maintaining adequate vitamin D levels through exposure to sunlight, diet, or supplements may be beneficial for overall health, including supporting the body's ability to heal wounds. However, for personalized advice tailored to individual health circumstances, it is recommended to seek guidance from a healthcare professional.[31]

Macrophages are key immune cells involved in the different phases of wound healing. They can exhibit different functional states or polarization, commonly categorized into two main types: M1 (classically activated or pro-inflammatory) and M2 (alternatively activated or anti-inflammatory).[3] Achieving a delicate equilibrium between M1 and M2 macrophages is crucial for an effective and controlled wound-healing response. Diabetes-related wound healing issues are brought on by compromised neutrophil and macrophage function. In diabetics, an imbalance in the polarization of M1 and M2 leads to an increase in the expression of pro-inflammatory cytokines by M1, including IL-1β and TNF-α. Furthermore, it can reduce anti-inflammatory cytokines like IL-10 produced by M2. Excessive production of pro-inflammatory cytokines and reduced production of anti-inflammatory cytokines contribute to a protracted inflammatory process that might cause uncontrollable tissue damage.[32] Research has demonstrated that Vitamin D exhibits immunomodulatory properties and can influence macrophage polarization.[33]

The complex process of macrophage polarization involves multifactorial interactions regulated by various signaling molecules and pathways. Currently, research has focused on five well-established signaling pathways: JAK/STAT, PI3K/Akt, C-Jun N-terminal kinase (JNK), Notch, and B7-H3/STAT3.[34] Macrophages play pivotal roles in systemic metabolism, hematopoietic function, angiogenesis, apoptosis, and tumour formation. Investigating the regulation of macrophage polarization offers novel insights into treating macrophage-related diseases. The findings revealed a gradual decrease in plasma IL-6 concentration with increasing levels of 25(OH)D, accompanied by a rise in TGF-β secretion by M2 macrophages. Additionally, the results indicated a shift towards an M2 phenotype in peripheral blood macrophages with increasing serum 25(OH)D levels, characterized by a decrease in the M1/M2 ratio.[29]

Belonging to the mononuclear phagocyte system, macrophages constitute a diverse population of cells. Research suggests that Vitamin D has contrasting effects on macrophage behavior: it suppresses M1 macrophage infiltration while promoting the activation of M2 macrophages. Treatment with Calcitriol significantly curbed macrophage infiltration and dampened the production of

proinflammatory cytokines. Vitamin D is renowned for its ability to reduce inflammation, and it can modulate the production of cytokines. This can potentially favor the M2 macrophage phenotype, typically linked to anti-inflammatory and tissue repair functions.[35] Studies have demonstrated the ability of Vitamin D to boost the phagocytic activity of macrophages. This is important for clearing debris and dead cells during the resolution phase of inflammation, contributing to the overall wound healing process. M2 macrophages play a pivotal role in tissue repair and remodeling. Vitamin D may contribute to this process by promoting the M2 phenotype, which is associated with tissue repair functions.[36]

In intestinal regulation, the vitamin D/VDR axis plays a significant role in governing the activation of monocytes/macrophages. When exposed to various environmental cues, macrophages typically adopt either a pro-inflammatory (M1) or anti-inflammatory (M2) phenotype.[35] The induction of macrophage phenotype transition by Vitamin D favors M2 over M1 polarization, aligning with reduced production of pro-inflammatory cytokines.[37] The implication here is that vitamin D plays a protective role in colitis by influencing the biology of macrophages.

CONCLUSION AND FUTURE DIRECTIONS

Delayed wound healing in diabetic patients is caused by impaired macrophage polarisation, which leads to persistent inflammation. Vitamin D exerts a positive influence on enhancing the outcome of wound healing in diabetic patients by inducing a shift in macrophage phenotype from the pro-inflammatory M1 to the anti-inflammatory M2, resulting in a reduction in the production of pro-inflammatory cytokines. Despite numerous large-scale clinical trials, the clinical efficacy of vitamin D supplements in the prognosis of wound healing in diabetic patients has not been demonstrated. Further research in this field would be of great help in producing the desired wound-healing outcome in diabetic patients.

ACKNOWLEDGEMENTS

The authors would like to thank the staff of the Department of Anaesthesiology and Reanimation, Faculty of Medicine, Airlangga University for supporting this study.

FUNDING

There was no specific funding from governmental, commercial, or non-profit entities for this study.

DISCLOSURE

The authors have stated their absence of any conflict of interest regarding this study.

AUTHORS' CONTRIBUTION

All authors contributed to article preparation and paper revision and have collectively assumed responsibility for all aspects of this study.

ETHICAL CONSIDERATION

Ethical committee approval for this study was obtained from the Faculty of Medicine at Airlangga University. The approval certificate number is 340/EC/KEPK/FKUA/2023.

DATA AVAILABILITY

The article contains all the necessary data to support the results; no supplementary source data is needed.

REFERENCES

1. Cañedo-Dorante L, Cañedo-Ayala M. Skin Acute Wound Healing: A Comprehensive Review. International Journal of Inflammation. 2019:3706315.
2. Davanso MR, Crisma AR, Braga TT, Masi LN, Amaral CL, Leal VNC, de Lima DS, et al. Macrophage Inflammatory State in Type 1 Diabetes: Triggered By NLRP3/Inos Pathway And Attenuated By Docosahexaenoic Acid. Clinical Science. 2021. 135: 19–34 https://doi.org/10.1042/CS20201348.
3. Louiselle AE, Niemiec SM, Zgheib C, and Liechty KW. Macrophage Polarization and Diabetic Wound Healing. Translational Research. 2021;236:109-116. https://doi.org/10.1016/j.trsl.2021.05.006.
4. Purwanti OS, Novitasari E. The Correlation of Knowledge of Prevention With Neuropathy Treatment In Diabetes Mellitus Patients In Sukoharjo Regency. *Bali Medical Journal*. 2021;10(3) Special Issue ICONURS: 1342-1346. DOI: 10.15562/bmj.v10i3.2910
5. Ackerman JE, Geary MB, Orner CA, Bawany F, Loiselle AE. Obesity/Type II Diabetes Alters Macrophage Polarization Resulting in A Fibrotic Tendon Healing Response. *PLoS ONE*. 2017;12(7): e0181127. https://doi.org/10.1371/journal. pone.0181127.
6. Orliaguet L, Dalmas E, Drareni K, Venteclef N, Alzaid F. Mechanisms of Macrophage Polarization in Insulin Signaling and Sensitivity. Frontiers in Endocrinology. 2020;11:1–23. https://doi.org/10.3389/fendo.2020.00062.
7. Julhijrianto Y, Novida H. Pre-operative Management of A Patient with Tubo Ovarian Abscess and Diabetic Ketoacidosis. *Bali Medical Journal*. 2023;12(3): 3331-3336. DOI: 10.15562/bmj.v12i3.4817
8. Spampinato SF, Caruso GI, De Pasquale R, Sortino MA, Merlo S.. The Treatment of Impaired Wound Healing in Diabetes: Looking Among Old Drugs. Pharmaceuticals. 2020;13(4), 1–17. https://doi.org/10.3390/ph13040060.
9. Tas N, Noyan T, Yagan Ö, Hanci V, Çanakçi E. Preoperative Vitamin D Levels and Respiratory Complications of General Anaesthesia. Niger J Clin Pract. 2018;21:1278-83. doi: 10.4103/njcp.njcp_102_18. PMID: 30297559.
10. Santos HO, Martins CEC, Forbes SC, Delpino FM. A Scoping Review of Vitamin D for Nonskeletal Health: A Framework for Evidence-based Clinical Practice. Clinical Therapeutics. 2023;45(5).
11. Lubis HH, Nababan KA, Paramita DA. Correlation of Low Vitamin D Status with Atopic Dermatitis Severity in Children. *Bali Medical Journal*. 2021;10(1): 291-295. DOI: 10.15562/bmj.v10i1.2203
12. Cutuli SL, Cascarano L, Tanzarella ES, Lombardi G, Carelli S, Pintaudi G, Grieco DL, De Pascale G, Antonelli M. Vitamin D Status and Potential Therapeutic Options in Critically Ill Patients: A Narrative Review of the Clinical Evidence. Diagnostics. 2022;12(11):2719. https://doi.org/10.3390/diagnostics12112719
13. Szymczak-Pajor I, Śliwińska A. Analysis of Association between Vitamin D Deficiency and Insulin Resistance. Nutrients. 2019;11(4):794. https://doi.org/10.3390/nu11040794
14. Hanel A, Malmberg HR, Carlberg C. Genome-wide effects of chromatin on vitamin D signalling. J. Mol. Endocrinol. 2020;64:R45–R56.
15. Zhang Y, Fang G, Tang J, Jia L, Feng Y, Xu, P, Faramand A. Association between vitamin D supplementation and mortality: systematic review and meta-analysis. BMJ.2019;366: l4673.
16. Wu J, Atkins A, Downes M, Wei Z. Vitamin D in Diabetes: Uncovering the Sunshine Hormone's Role in Glucose Metabolism and Beyond. Nutrients. 2023;15:1997. https://doi.org/10.3390/nu15081997
17. Wilkinson HN, Hardman MJ. Wound Healing: Cellular Mechanisms and Pathological Outcomes. *Open Biol.* 2020;10:200223. http://dx.doi.org/10.1098/rsob.200223
18. Naskar A, Kim KS. Recent Advances In Nanomaterial-Based Wound-Healing Therapeutics. *Pharmaceutics*. 2020;12(6):499-500.
19. Zaidi A, Green L. 2019 Physiology of haemostasis. Anaesth. Intensive Care Med. 20, 152–158. (doi:10. 1016/j.mpaic.2019.01.005)

20. Krzyszczyk P, Schloss R, Palmer A, Berthiaume F. The Role of Macrophages in Acute and Chronic Wound Healing and Interventions to Promote Pro-wound Healing Phenotypes. Front Physiol. 2018;9:419. doi: 10.3389/fphys.2018.00419.

21. Rodrigues M, Kosaric N, Bonham CA, Gurtner GC. Wound Healing: A Cellular Perspective. Physiol Rev. 2019;99(1):665-706. doi: 10.1152/physrev.00067.2017.

22. Gushiken LFS, Beserra FP, Bastos JK, Jackson CJ, Pellizzon CH. Cutaneous Wound Healing: An Update from Physiopathology to Current Therapies. Life. 2021;1:665. https:// doi.org/10.3390/life11070665

23. Cangkrama M, Wietecha M, Werner S. Wound Repair, Scar Formation, and Cancer: Converging on Activin. Trends in Molecular Medicine. 2020;26(12): 1107-17.

24. Darby IA, Desmoulière A. Scar Formation: Cellular Mechanisms. In: Téot, L., Mustoe, T.A., Middelkoop, E., Gauglitz, G.G. (eds) Textbook on Scar Management. Springer. 2020. Cham. https://doi.org/10.1007/978-3-030-44766-3_3

25. Deng X, Gould M, Ali MA. A Review of Current Advancements for Wound Healing: Biomaterial Applications and Medical Devices. J Biomed Mater Res. 2022;110:2542–2573.

26. Aitcheson SM, Frentiu FD, Hurn SE, Edwards K, Murray RZ. Skin Wound Healing: Normal Macrophage Function and Macrophage Dysfunction in Diabetic Wounds. Molecules. 2021;26(16):4917. https://doi.org/10.3390/molecules26164917

27. Janoušek J, Pilařová V, Macáková K, Nomura A, Veiga-Matos J, da Silva DD, Remião F, Saso L, Malá-Ládová K, Malý J, Nováková L, Mladěnka P. Vitamin D: Sources, Physiological Role, Biokinetics, Deficiency, Therapeutic Use, Toxicity, and Overview of Analytical Methods for Detection of Vitamin D and its Metabolites. Critical Reviews in Clinical Laboratory Sciences. 2022;59:8:517-554, DOI: 10.1080/10408363.2022.2070595

28. Bouillon R, Manousaki D, Rosen C, Trajanoska K, Rivadeneira F, Richards JB. The Health Effects of Vitamin D Supplementation: Evidence From Human Studies. Endocrinology.2021;18: 97-110.

29. Zhang L, Wang Z, Wang X, Zhang N, Ke J, Yang L. Study on the relationship between vitamin D level and macrophage typing in patients with type 2 diabetes mellitus. International Journal of Diabetes in Developing Countries. 2023;43(5):792–800.

30. Pilz S, Zittermann A, Trummer C, Theiler-Schwetz V, Lerchbaum E, Keppel MH, Grübler MR, März W, Pandis M. Vitamin D Testing and Treatment: A Narrative Review of Current Evidence. Endocrine Connections. 2019;8(2):R27-R43. doi: 10.1530/EC-18-0432.

31. Hahn JM, Combs KA, Powell HM, Supp DM. A Role for Vitamin D and The Vitamin D Receptor In Keloid Disorder. Wound Rep Reg. 2023;31:563–575.

32. Hendrijantini N, Sitalaksmi RM, Ari MDA, Hidayat TJ, Putri PAN, Sukandar D. The expression of TNF-α, IL-1β, and IL-10 in the diabetes mellitus condition induced by the combination of spirulina and chitosan. *Bali Medical Journal*. 2020;9(1):22-26. DOI: https://dx.doi.org/10.15562/bmj.v9i1.1625

33. De Santa F, Vitiello L, Torcinaro A, Ferraro E. The role of metabolic remodeling in macrophage polarization and its effect on skeletal muscle regeneration. Antioxid Redox Signal. 2019;30(12):1553–98

34. Xia T, Zhang M, Lei W, Yang R, Fu S, Fan Z, Yang Y, Zhang T. Advances in The Role of STAT3 in Macrophage Polarization. Front Immunol. 2023;14:1160719. doi: 10.3389/fimmu.2023.1160719

35. Daryabor G, Gholijani N, Kahmini FR. A Review of The Critical Role of Vitamin D Axis on The Immune System. Experimental And Molecular Pathology. 2023;132-133:104866.

36. Infante M, Ricordi C, Sanchez J, Clare-Salzler MJ, Padilla N, Fuenmayor V, Chavez C, Alvarez A, Baidal D, Alejandro R, et al.. Influence of vitamin D on Islet Autoimmunity And Beta-Cell Function In Type 1 Diabetes. *Nutrients*. 2019;11(9):2185

37. Munoz-Garach A, Garcia-Fontana B, Munoz-Torres M. Vitamin D Status, Calcium Intake And Risk Of Developing Type 2 Diabetes: An Unresolved Issue. *Nutrients*. 2019. 11(3):642. doi: 10.3390/nu11030642

Cite this article: Chrisdianto A, Airlangga PS, Wirabuana B, Iskandar RPD. Vitamin D and Wound Recovery: Illuminating the Path to Enhanced Healing in Diabetic Patients. Pharmacogn J. 2024;16(2): 485-491.