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Estrogen deficiency and wound healing

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Abstract

Background: Wound healing is a complex process involving hemostasis, inflammation, proliferation, and remodeling, which can be delayed by factors like hormonal changes. Estrogen plays a crucial role in regulating inflammation, collagen production, and angiogenesis during healing. In postmenopausal women, the decline in estrogen levels due to ovarian function cessation often leads to impaired healing, increased chronic inflammation, and a higher risk of infection. These challenges highlight the need to further explore the relationship between estrogen deficiency and wound healing, especially in the aging population where chronic wounds are more common.

Objectives: To review the relationship between estrogen deficiency, particularly in menopausal women, and its impact on the wound-healing process.

Conclusion: Estrogen deficiency delays wound healing by disrupting key processes like inflammation regulation and re-epithelialization, while increasing infection risk. Addressing this imbalance is crucial for improving recovery, especially in menopausal women.

Keywords: Estrogen; Wound Healing; Chronic Inflammation, Public Health; Health Risk

1. Introduction

Wound healing is a physiological process, involving hemostasis, inflammation, proliferation and remodeling phases to maintain skin integrity after trauma, either accidental or procedural. Disruption or unbalanced distribution of these processes can result in delayed wound healing. Estrogen deficiency, for example in menopausal women, is often associated with delayed wound healing, as estrogen can influence collagen production to accelerate wound healing. Menopause is the natural and permanent cessation of menstruation caused by estrogen deficiency without association with pathological conditions. Menopausal women may experience delayed wound healing, taking longer for the wound healing process than non-menopausal women [1][2].

Wound healing is a complex physiological process that involves a series of phases, namely hemostasis, inflammation, proliferation and remodeling. This process is essential to restore the integrity of tissues damaged by trauma or medical procedures. However, interference with this process can lead to delayed wound healing, which often occurs in certain conditions such as estrogen deficiency. One group that is prone to this is postmenopausal women, where estrogen levels drop dramatically due to the cessation of ovarian function [3].

Estrogen plays an important role in various stages of wound healing, including regulation of the inflammatory response, stimulation of collagen production, and acceleration of re-epithelialization. A deficiency of this hormone not only slows

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down the process of tissue regeneration but also increases the risk of infection and chronic inflammation. This is of particular concern, given the growing number of older women who experience chronic wounds due to various conditions, such as surgical procedures or inflammatory diseases [4].

This study aims to explore and explain the relationship between estrogen deficiency, particularly in menopausal women, and the wound healing process. The study highlights how reduced estrogen levels can inhibit various stages of wound healing, such as the inflammatory response, re-epithelialization, extracellular matrix production, and hemostasis, as well as its impact on infection risk and overall delay in wound healing. This study also aims to provide insight into the importance of considering hormonal factors in wound care in elderly patients.

2. Material and Method

This research was carried out by systematically searching for several kinds of literatures relevant to the topic discussed as references. This type of research is Literature Review design. The research was done audaciously in January 2025.

2.1. Research Strategy

Search for literature and data from journals or articles using keywords and Boolean Operators (AND, OR, and AND NOT). Article searches are limited to the year the article was published, namely within the last 5 years from 2019-2025. The keywords used in this systematic review are "Estrogen and Wound Healing" which aims to specify the search so as to make it easier to determine the literature used.

2.2. Inclusion and Exclusion Criteria

In this study, the inclusion criteria is literature that is available in full text and open access in English, has been published, and uses an original research design within the last 5 years.

The exclusion criteria used in this research is literature that uses languages other than English, literature reviews or systematic reviews, literature that is not available in full-text or open access and more than 5 years.

2.3. Synthetic Data

Literature collected through full-text understanding and extraction, including research title, author, year of publication, research objectives, methods, and conclusions. Subsequently, the data is analyzed to draw conclusions and recommendations that can answer research questions and objectives. Literature was selected through keyword searches and filtered based on title and abstract. The full text of each piece of literature was screened to determine its relevance to the inclusion and exclusion criteria established in this study.

3. Result and Discussion

Chronic inflammation is often characterized by prolonged pain. The propensity for chronic inflammation to develop is closely related to a reduction in estrogen levels, particularly in patients who have transitioned into menopause. Menopause, which marks the cessation of ovarian function, is characterized by a marked reduction in the number of ovarian follicles, primarily due to atresia and the cessation of ovulation. This depletion of follicles leads to a significant decline in the secretion of various hormones, including estrogen. As women age, the diminished production of estrogen results in a variety of physiological changes, one of the most notable being a reduction in the hormone's protective and anti-inflammatory effects. In addition to these immunomodulatory functions, estrogen plays a crucial role in wound repair, particularly by promoting re-epithelialization and stimulating the production of extracellular matrix (ECM) components. Therefore, the decline in estrogen levels that occurs in postmenopausal women severely impairs the efficiency of these reparative processes [5][6].

In the elderly, delayed and impaired wound healing is often observed and is closely associated with a prolonged inflammatory response. This response is characterized by an increased recruitment of inflammatory cells, yet the reaction itself is delayed in comparison to younger individuals. This dysregulated inflammatory response is compounded by the excessive secretion of pro-inflammatory cytokines, such as tumor necrosis factor alpha (TNFα), which further exacerbates the inflammatory milieu [6][7]. Estrogen has been well-documented for its role in modulating the early stages of acute wound healing by controlling the inflammatory response. Specifically, estrogen dampens the early inflammatory cascade by inhibiting neutrophil infiltration into the wound site through a reduction in the expression of adhesion molecules. Additionally, estrogen is involved in enhancing neutrophil oxidative metabolism, which is essential for the pathogen-killing functions of neutrophils. Therefore, estrogen deficiency in the elderly not

only diminishes the phagocytic capacity of neutrophils but also increases susceptibility to infections and contributes to delayed wound healing [8].

Estrogen exerts direct effects on monocytes and macrophages, as these cells possess both nuclear and membrane-bound estrogen receptors (ERs). During the inflammatory phase of wound healing, estrogen deficiency hinders the differentiation of monocytes into tissue-resident macrophages, thereby leading to an upregulation of protease expression. These proteases, including elastase and matrix metalloproteinases (MMPs), contribute to tissue degradation, further impeding the healing process. Estrogen's presence, on the other hand, reduces the secretion of these tissue-damaging proteases, which results in an overall improvement in collagen and fibronectin deposition within the dermis. Impaired wound healing in elderly individuals is often linked to a reduced expression of growth factors, diminished keratinocyte proliferation, and an enhanced sensitivity to inhibitory cytokines. These alterations collectively contribute to delayed re-epithelialization, which is particularly evident in postmenopausal women due to estrogen deficiency. In addition to its direct effects on epithelial migration and proliferation, estrogen also indirectly influences matrix deposition by mesenchymal cells. Estrogen stimulates the secretion of transforming growth factor-beta 1 (TGF-β1) by dermal fibroblasts, a critical factor that promotes the synthesis and deposition of collagen and fibronectin within the ECM [4][9].

Furthermore, estrogen plays an important role in angiogenesis, which is essential for the formation of granulation tissue. Estrogen directly stimulates endothelial cells, promoting the development of new blood vessels within the wound site. This angiogenic effect supports the creation of a vascular network that is crucial for the delivery of nutrients and oxygen to the healing tissue, facilitating overall wound repair. Additionally, estrogen modulates the synthesis of interleukin-1 (IL-1) by tissue macrophages, a key cytokine involved in the formation of granulation tissue [4][10].

The deposition of collagen, a critical component of the ECM, is also influenced by estrogen, and its reduction in postmenopausal women can have profound effects on the hemostasis phase of wound healing. Collagen, when exposed due to blood vessel damage, interacts with specific receptors on platelets, thereby triggering platelet activation and morphological changes. This process is vital for the formation of a platelet plug, which serves as the initial seal for the wound. However, in the absence of adequate collagen, platelet activation is hindered, resulting in an imperfectly formed platelet plug. Such an incomplete platelet plug leads to a reduction in fibrin thread production and prolongs the coagulation activation period. As a result, the hemostasis phase is delayed, which in turn affects subsequent stages of wound healing, further contributing to the overall delay in the healing process [11][12].

Table 1 Summary of study results

No.	Author Name, Year	Objective	Research Result
1.	Lombardi, C., et al., 2022	The objective of this article is to review and highlight the heterogeneous roles of eosinophils in various eosinophil-related inflammatory conditions, as well as to explore the implications of targeted therapies on eosinophils based on different eosinophil subpopulations (tissue-resident eosinophils and inducible eosinophils). This article also aims to examine the importance of using biomarkers as predictors for selecting appropriate therapies and to gain a deeper understanding of the role of eosinophils in the regulation of homeostasis and inflammatory processes.	The results of this study indicate that eosinophils are not only destructive cells in Th2-oriented diseases, but also have regulatory functions in homeostatic processes. Identification of distinct eosinophil subpopulations, such as resident eosinophils (rEos) and inducible eosinophils (iEos), has a significant impact on the effectiveness of targeted therapies. This study also emphasizes the need for further development in understanding eosinophil biology through precision medicine approaches such as proteomics, transcriptomics, and metabolomics to improve therapeutic outcomes and understanding of eosinophils and related diseases.
2.	Vodegel EV,. et al., 2021	To determine the effects of oestrogen or oestrogen deprivation on vaginal wound healing. Impaired wound	Estrogen therapy has a positive effect on vaginal wound healing. The study found that estrogen increased neovascularization, microscopic wound

		healing following prolapse surgery may increase the risk of recurrent prolapse in the future. Vaginal oestrogen therapy may improve wound healing, hereby possibly improving surgical outcomes.	closure, collagen synthesis, and tissue strength in animals. In addition, estrogen increased granulation and accelerated macroscopic wound closure in both women and animals, and reduced the inflammatory response and transforming growth factor (TGF)-β1 levels in animals. All of these results were statistically significant, indicating the potential for estrogen therapy to improve surgical outcomes in the context of vaginal wound healing.
3.	Binder, R. L., et al., 2019	The study aimed to determine the effect of menopausal status and hormone therapy on the introitus and labia majora at the levels of histology and gene expression.	The results of this study show that introitus appears exquisitely sensitive to hormone status. Dramatic changes were observed in histology including a thinning of the epithelium in post-menopausal subjects with vaginal atrophy. Furthermore, there was differential expression of many genes that may contribute to tissue remodeling in the atrophic introitus. Levels of expression of genes associated with wound healing, angiogenesis, cell migration/locomotion, dermal structure, apoptosis, inflammation, epithelial cell differentiation, fatty acid, carbohydrate and steroid metabolism were significantly different in the cohort exhibiting atrophy of the introitus. While changes were also observed at the labia, that site was considerably less sensitive to hormone status. The gene expression changes observed at the introitus in this study were very similar to those reported previously in the atrophic vagina providing further evidence that these changes are associated with atrophy.
4.	Mukai K., et al., 2019	This article aims to evaluate the effects of topical estrogen on wound healing in 80-week-old female mice, including its effects on the rate of closure and healing time. This study also assesses the role of estrogen in the inflammatory, proliferative, and repair phases of wounds, as well as the mechanisms of delayed healing, by analyzing histological changes at the wound site.	The results of the study demonstrated that topical estrogen application to wounds in 80-week-old female mice resulted in delayed cutaneous wound healing. Specifically, the treated wounds exhibited slower closure rates compared to control wounds. Histological analysis revealed that estrogen application influenced the inflammatory phase, leading to prolonged inflammation. Additionally, the study observed alterations in collagen deposition and epithelialization, further contributing to the delay in wound healing. These findings suggest that while estrogen is typically associated with promoting healing in younger tissues, its topical application in aged mice may have the opposite effect, potentially due to age-related changes in estrogen receptor sensitivity and tissue response.
5.	Tanbo., et al., 2021	To examine the factors that influence the prediction of the time to menopause and explore the potential for accurately forecasting its onset. The study aims to assess various biological, environmental, and genetic determinants that could help predict the timing of menopause, as well as to	Predicting the time to menopause is a complex process influenced by various factors, including genetics, lifestyle, and reproductive history. The study found that certain markers, such as ovarian reserve and hormone levels, may provide useful indications of the timing of menopause. However, the researchers also noted that despite the potential of these markers, predictions remain imprecise due to the variability of individual

		evaluate the reliability and practicality of existing predictive models.	experiences. The study highlighted that while some predictive models show promise, they are not yet sufficiently reliable for widespread clinical application. Furthermore, the authors discussed the challenges in developing accurate tools for menopause prediction, given the biological and environmental variability among women.

4. Conclusion

A decrease in estrogen levels in elderly women, especially after menopause, can affect wound healing process by inhibiting the inflammatory responses, re-epithelialization, extracellular matrix production, and hemostasis. Estrogen deficiency leads to chronic inflammation, decreased phagocytic ability of neutrophils, increased risk of infection, decreased collagen production, and overall delayed healing. Therefore, it is important to pay attention to these hormonal factors and consider appropriate treatment strategies in elderly patients to facilitate optimal wound healing.

Compliance with ethical standards

Disclosure of conflict of interest

There is no conflict of interest declared by authors in this study.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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