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The Influence of GLP-1 Receptor Agonists on Wound Healing After Surgery: What Current Evidence Tells Us

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ABSTRACT

Introduction. Glucagon-like peptide-1 receptor agonists (GLP-1 receptor agonists, GLP-1 RAs) currently represent one of the most rapidly developing classes of pharmacological agents used in the treatment of metabolic diseases. Initially, their primary indication was the management of type 2 diabetes mellitus; however, in recent years, due to the growing recognition of obesity as a disease rather than merely a lifestyle factor, their use has significantly expanded. The most commonly used agents in this class include liraglutide, semaglutide, dulaglutide, and exenatide.

Aim. The aim of this study is to review current evidence regarding the impact of GLP-1 receptor agonists on postoperative wound healing and surgical complications, as well as to analyze potential biological mechanisms underlying the observed clinical effects.

Methodology. The literature review was based on publications retrieved from PubMed and Google Scholar using English-language keywords related to GLP-1 receptor agonists and postoperative

wound healing. The analysis primarily included review articles, original research studies, and selected sections of scientific books. Particular emphasis was placed on publications from the past several years describing both the mechanisms of action of GLP-1 receptor agonists and their relationship with wound healing processes.

Results. The results of clinical studies assessing the impact of GLP-1 receptor agonists on postoperative wound healing remain inconclusive. A substantial proportion of studies in general surgery, hand surgery, orthopedics, and chronic wound management indicate a beneficial effect of GLP-1 analogues on wound healing. In contrast, in plastic and reconstructive surgery, an association has been observed between GLP-1 analogue use and an increased risk of delayed healing, wound dehiscence, and local complications.

Conclusions. The use of GLP-1 analogues may influence the wound healing process, potentially reducing the risk of complications; however, in certain plastic surgical procedures, it may be
associated with delayed tissue regeneration. An individualized approach to the patient is recommended, along with further research to clearly determine the safety of their use in the perioperative period.
Keywords: GLP-1 receptor agonists; postoperative wound healing; diabetes and wound healing; health education; patient education; diabetes self-management education; health promotion; clinical decision-making; perioperative management; wound care; healthcare education; evidence- based medicine

Introduction

GLP-1 receptor agonists (GLP-1 RAs) represent one of the fastest-growing classes of pharmacological agents used in the treatment of metabolic disorders. Initially introduced for the management of type 2 diabetes mellitus, they act as incretin-based therapies that improve glycemic control by enhancing glucose-dependent insulin secretion, suppressing glucagon secretion, and delaying gastric emptying. Additionally, these agents influence central appetite-regulating mechanisms, leading to reduced food intake and, ultimately, weight reduction.

Applications of GLP-1 receptor agonists

For this reason, their use has significantly expanded beyond the treatment of type 2 diabetes and now also includes pharmacotherapy of obesity [1]. Clinical practice data indicate a marked increase in prescriptions for GLP-1 receptor agonists in recent years, with semaglutide accounting for the largest proportion among new therapies, particularly in the treatment of obesity in patients without diabetes [2]. The growing popularity of GLP-1 receptor agonists has resulted in an increasing number of surgical patients receiving these medications. Consequently, there is growing interest in their potential impact on the perioperative course, including postoperative wound healing.

Wound healing is a complex biological process involving sequential phases of inflammation, proliferation, and tissue remodeling. Disruption at any stage may lead to surgical complications such as delayed wound healing, wound dehiscence, or surgical site infection.

GLP-1 receptor agonists and their impact on wound healing

In recent years, evidence has emerged suggesting that GLP-1 receptor agonists may influence tissue regeneration through modulation of inflammatory responses. Conversely, some clinical observations indicate a potential association between these agents and wound healing complications, which may be related to rapid weight loss or metabolic changes accompanying therapy. Given the increasing number of patients receiving this class of drugs and the limited number of studies evaluating their effects on postoperative wound healing, this issue is becoming increasingly relevant in surgical and perioperative practice.

Methods of Literature Review

The literature review was conducted based on scientific publications available in international databases, primarily PubMed and Google Scholar. To identify relevant publications, combinations of English-language keywords were used, including: “GLP-1 receptor agonists”, “postoperative wound healing”, “surgical wound”, and “diabetes and wound healing”. The analysis, mainly included review articles and original studies addressing the impact of GLP-1 receptor agonists on postoperative wound healing were included, primarily published within the past several years.

Physiology of Wound Healing

Wound healing is a complex biological process aimed at restoring the structural and functional integrity of damaged tissues. This process involves coordinated interactions among multiple cell types, inflammatory mediators, growth factors, and extracellular matrix components.

Wound healing is classically divided into four partially overlapping phases: hemostasis, inflammation, proliferation, and remodeling (scar maturation) [3].

Disruption of any stage of this tightly regulated process may result in delayed healing, pathological scarring, or the development of chronic wounds [4].

Hemostasis Phase

Hemostasis represents the initial phase of the body's response to tissue injury and begins immediately following damage [5]. Its primary objective is to stop bleeding and form a temporary matrix that enables the migration of cells involved in subsequent stages oftissue repair [6].

Damage to blood vessels leads to vasoconstriction and platelet activation. Platelets aggregate at the site of injury and initiate the coagulation cascade, resulting in the formation of a fibrin-platelet clot that stabilizes the wound and prevents further blood loss [7].

Activated platelets release numerous growth factors, including platelet-derived growth factor (PDGF), transforming growth factor-β (TGF-β), and vascular endothelial growth factor (VEGF), which stimulate the migration of fibroblasts, endothelial cells, and keratinocytes to the site of injury [5].

Inflammatory Phase

The inflammatory phase begins shortly after clot formation and typically lasts from several hours to a few days [9]. Its primary role is the elimination of microorganisms and removal of necrotic cells and damaged tissue debris [6].

This phase is characterized by increased vascular permeability and infiltration of immune cells into the wound site [5]. Neutrophils are the first cells to appear, removing bacteria and cellular debris through phagocytosis [8].

At later stages, macrophages become the dominant cell type. They not only participate in debris clearance but also secrete numerous cytokines and growth factors that regulate subsequent stages of wound healing [9]. Macrophages thus play a crucial role in the transition from the inflammatory phase to the proliferative phase [5].

An excessive or prolonged inflammatory response may impair the healing process and contribute to chronic wound formation [5].

Proliferative Phase

The proliferative phase begins after resolution of inflammation and typically lasts from several days to several weeks [9]. It is characterized by intensive cellular proliferation and reconstruction of the damaged tissue structure [6].

A key process in this phase is the formation of granulation tissue. Fibroblasts migrate to the site of injury and synthesize extracellular matrix components, including type III collagen, proteoglycans, and fibronectin [5]. Granulation tissue serves as a scaffold for further tissue regeneration [9].

Angiogenesis, the formation of new blood vessels from proliferating endothelial cells, is another essential component of this phase. The newly formed vascular network provides oxygen and nutrients necessary for tissue regeneration [5].

Simultaneously, re-epithelialization occurs, during which keratinocytes migrate from the wound edges and skin appendages and proliferate to restore epidermal continuity [7].
Wound contraction also takes place, driven by myofibroblasts that generate mechanical forces bringing the wound edges closer together [9].

Remodeling Phase

Remodeling represents the final stage of wound healing and may last from several weeks to many months [5]. During this phase, the extracellular matrix undergoes reorganization and the mechanical strength of the newly formed tissue gradually increases [6].

A key process involves the replacement of type III collagen with stronger type I collagen. Collagen fibers are reorganized and aligned along lines of mechanical tension in the skin [7].

During remodeling, the number of blood vessels and cells in the granulation tissue decreases, leading to the formation of a mature scar [5]. Despite this process, the tensile strength of the scar typically reaches only approximately 70–80% of that of uninjured skin [5].

Effects of GLP-1 Receptor Agonists on the Hemostasis Process

Data regarding the direct impact of GLP-1 receptor agonists on the hemostasis phase are limited. GLP-1 receptor agonists exhibit antiplatelet effects by inhibiting platelet activation and aggregation. Despite a potential minor influence on early hemostasis, their overall anti-inflammatory and endothelial-protective effects may support the wound healing process [10]. Also available evidence suggests that GLP-1 receptor agonists may favorably influence the postoperative course by reducing the risk of bleeding and postoperative hematoma formation [12].

Impact of GLP-1 Receptor Agonists on the Inflammatory Process

Findings from studies investigating GLP-1 receptor agonists and tissue regeneration indicate that these agents modulate inflammation through multiple mechanisms, including improvement of systemic metabolism, direct effects on immune cells, and influence on non- immune cells involved in intercellular signaling. It has also been observed that GLP-1 Ras reduce levels of inflammatory markers such as C-reactive protein (CRP) in patients with type 2 diabetes or obesity [11].

Effect of GLP-1 Receptor Agonists on the Proliferative Phase

GLP-1 receptor agonists exert a multidirectional beneficial effect on the proliferative phase of wound healing, encompassing key regenerative processes such as re-epithelialization, angiogenesis, and extracellular matrix remodeling. They have been shown to stimulate keratinocyte migration and proliferation via activation of the PI3K/Akt signaling pathway [13], as well as enhance regenerative capacity under hyperglycemic conditions, among others by inhibiting ferroptosis through activation of the Nrf2 pathway [14].

Their effects on fibroblasts and extracellular matrix are complex and context-dependent. On one hand, they may support regeneration by increasing elastin synthesis; on the other hand, they exhibit antifibrotic properties by limiting excessive collagen production and extracellular matrix deposition under pathological conditions [15, 16].

Furthermore, regulation of matrix metalloproteinase activity (e.g., MMP-2) and TGF-β contributes to proper tissue remodeling in later stages of wound healing [17].

Clinical Studies on Beneficial Effects in Wound Healing

Current scientific literature available in PubMed and Google Scholar indicates that GLP-1 receptor agonists have a heterogeneous impact on postoperative wound healing, depending on the type of surgical procedure and patient population.

In large cohort analyses involving diabetic patients undergoing surgical procedures, GLP-1 receptor agonist use was associated with a significantly lower risk of postoperative wound dehiscence and hematoma, without an increased risk of infection or bleeding [18].

Furthermore, an analysis of 72,578 surgical procedures in diabetic patients demonstrated that GLP-1 receptor agonist use was associated with a reduced risk of wound dehiscence across all BMI categories and a lower risk of rehospitalization [19].

In a study including 138,980 patients undergoing major surgical procedures (CABG, colectomy, pancreatectomy, abdominal aortic aneurysm repair), propensity score matching showed that GLP-1 receptor agonist use was not associated with an increased risk of postoperative complications [20].

In orthopedics, meta-analyses have shown that these agents are associated with a lower risk of periprosthetic infection following arthroplasty [21], while no significant differences were observed in wound dehiscence or other healing-related complications [22].

Additionally, following Achilles tendon repair in obese individuals, GLP-1 RAs were associated with a lower risk of wound infection [23].

In hand surgery, GLP-1 receptor agonist use was not associated with an increased risk of infection or wound dehiscence, and a reduction in overall complications and reoperation rates was observed [24].

In the treatment of chronic wounds, such as diabetic foot ulcers, GLP-1 RAs demonstrate beneficial immunomodulatory and angiogenic effects, although clinical data remain limited. By addressing multiple aspects of the pathophysiology of diabetic foot ulcers, these agents may contribute to improved healing and prevention of recurrence [25].

Their use in diabetic patients undergoing soft tissue reconstruction for foot ulcers has been associated with lower rates of surgical site infection, reoperation, deep vein thrombosis, and overall mortality compared to patients not receiving these agents [26].

Clinical Studies on Complications

An increased risk of wound healing complications in patients using GLP-1 receptor agonists, particularly in plastic and reconstructive surgery, may result from several biological mechanisms.

The most important factor appears to be rapid weight loss leading to nutritional deficiencies, especially reduced levels of albumin and prealbumin, which impair tissue regeneration and contribute to delayed healing and wound dehiscence [27].

Additionally, reduction in subcutaneous fat volume leads to increased tissue fragility and susceptibility to fat necrosis, which is particularly relevant in procedures requiring high- quality tissue support, such as abdominoplasty or mastopexy [28].

GLP-1 receptor agonists may also influence tissue metabolism; however, in the context of plastic surgery, this effect may be overshadowed by nutritional deficiencies and structural changes in adipose tissue.

Studies have reported a higher risk of delayed healing, wound dehiscence, and local complications in patients without diabetes or obesity who use GLP-1 RAs primarily for weight loss [29].

Conclusions

The connection between GLP-1 receptor agonists and tissue regeneration is of growing clinical importance due to the increasing use of these agents among patients, including those undergoing surgical procedures. Analysis of available studies suggests that GLP-1 RAs have the potential to reduce the risk of wound healing complications (e.g., dehiscence, infection); however, in selected plastic surgical procedures, they may increase the risk of delayed healing.

An individualized approach to patient management and careful monitoring of postoperative wound healing are recommended. Further studies are necessary to determine the safety of these agents in the perioperative setting in clinical practice.

Disclosure

The authors declare that they have no financial or non-financial conflicts of interest that could be perceived as influencing the interpretation of the research findings or the content of this manuscript. This work was conducted independently without any external funding or support.

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The data presented in this study are available in the cited articles.

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