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REVIEW ARTICLE

The Impact of Nicotine on Wound Healing: A Comparative Review of Cigarettes, Vaping, and Nicotine Patches with Insights into Pathophysiological Mechanisms

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1. ABSTRACT

Nicotine, a key component of tobacco products, significantly impacts wound healing through its effects on vascular response, inflammation, and cellular functions critical to tissue repair. The introduction of alternative nicotine delivery systems, such as e-cigarettes and transdermal patches, has raised questions about their relative safety compared to traditional cigarettes. This review explores the effects of nicotine delivery methods on wound healing, focusing on the mechanisms of nicotine-induced vasoconstriction, oxidative stress, angiogenesis, and immune modulation.

Cigarettes impair wound healing due to the combined effects of nicotine, carbon monoxide, and tar, which disrupt oxygen delivery, increase inflammation, and weaken collagen remodeling. E-cigarettes, while combustion-free, still hinder wound repair through nicotine's effects on keratinocyte migration and mitochondrial function. Nicotine patches, though safer than smoking, have complex effects depending on dose and duration. While preoperative smoking cessation significantly improves surgical outcomes, careful management of nicotine replacement therapies is critical to minimizing adverse effects. This review highlights the need for further research into the long-term impact of vaping and strategies to optimize nicotine cessation in surgical care.

2. Introduction

Nicotine, a highly addictive alkaloid primarily associated with tobacco products, is one of the most widely used substances worldwide[1]. Its impact on human health has been rigorously studied, with well-documented consequences on cardiovascular and respiratory systems[2-3]. However, its specific effects on wound healing depending on the delivery are less thoroughly understood. Wound healing is a complex, multi-stage process involving hemostasis, inflammation, tissue proliferation, and remodeling. Any disruption to these stages can prolong recovery, increase complication risks, and, in surgical settings, lead to higher rates of morbidity. The rise of alternative nicotine delivery systems, such as e-cigarettes and nicotine patches, brings a new dimension to understanding nicotine's impact on wound healing, as each method differs in bioavailability, associated chemical exposure, and systemic effects.

Historically, cigarette smoking has been shown to negatively affect wound healing due to its combined exposure to nicotine, carbon monoxide, and thousands of other toxic compounds. However, the popularity of vaping and transdermal nicotine patches has grown in recent years, with these alternatives marketed as "safer" options. These methods deliver nicotine in distinct forms, with vaping offering a combustion-free inhalation of aerosolized nicotine and patches providing controlled, gradual absorption through the skin. This variability in nicotine delivery raises important questions about how each method influences wound repair processes and whether alternative methods mitigate the known adverse effects of traditional cigarette smoking.

This review aims to critically examine the effects of nicotine on wound healing, comparing cigarettes, vaping, and nicotine patches, and exploring the underlying pathophysiological mechanisms. By delving into how nicotine interacts with immune modulation, vascular response, cellular migration, and oxidative stress, this paper seeks to provide an evidence-based understanding of nicotine's role in wound healing. The ultimate goal is to highlight potential clinical implications, identify gaps in current research, and offer guidance on nicotine management for optimal patient outcomes in wound care settings.

3. Methodology

The study consists of a systematic review of the focused topic via different databases. The participants will carefully read and review literature from reliable resources, such as pubmed, NIH, and other reliable educational platforms. The information obtained will be organized in a logical pattern, and will later on be analyzed in order to reveal an evidence-based conclusion.

4. Mechanisms of Nicotine in Wound Healing

Nicotine has complex effects on wound healing pathways, influencing cell migration, inflammation, angiogenesis, and epithelialization. The literature provides insights into these effects:

Cell Migration and Epithelialization: Nicotine has been shown to inhibit keratinocyte migration, which is crucial for re-epithelialization during wound healing. This inhibition is mediated through nicotinic acetylcholine receptors (nAChRs) and involves modulation of calcium influx and intracellular calcium concentration, which are critical for keratinocyte locomotion. This suggests that nicotine can delay wound re-epithelialization by affecting keratinocyte migration[4].

Inflammation: Nicotine has a complex role in modulating the inflammatory response as it appears to have a dual role in the inflammatory cascade. Some studies show that when nicotine is administered at low doses, endothelial cell progenitors may be stimulated and aid in the initial phases of wound healing. However, when administered at increasing dosages, the deleterious effects of nicotine were seen[10]. Nicotine can attenuate the inflammatory response by reducing inflammatory cell chemotactic

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responsiveness and migratory function, as well as oxidative bactericidal mechanisms. Xanthohuela et. al., 2013, describe how in microvascular endothelial cells, nicotine inhibits TNF-induced NF-κB activation, to suppress adhesion molecule and chemokine expression. Nicotine was also found to reduce adhesion of leukocytes to activated endothelium and ultimately reduced inflammation. In stressed mice, nicotine administration was associated with decreased inflammatory cell infiltration and altered cytokine expression, such as decreased transforming growth factor-β (TGF-β) and increased tumor necrosis factor-α (TNF-α). However, nicotine's impact on inflammatory mediators like TNF, IL-6, and IL-12 was minimal in some models, while it down-regulated growth factors such as VEGF, PDGF, and TGF-β1[5-8]. Lei and colleagues, 2017, also describe how TGF-β1 induced fibroblast to myofibroblast differentiation as well as myofibroblast contractility is inhibited by nicotine by inducing mitochondrial stress. The effect on fibroblasts, a key component of wound healing, was seen even when delivered through e-cigarettes. These mechanisms that lead to altered inflammatory response can overall impair the initial phases of wound healing, which rely on a robust inflammatory response to clear debris and pathogens[8].

Angiogenesis: Despite its negative effects on other aspects of wound healing, nicotine can promote angiogenesis, a critical component of wound healing. The angiogenic properties of nicotine have been described to result from stimulation of endothelial cell migration, proliferation, and tube formation. This effect is mediated through the activation of endothelial nAChRs, particularly the alpha7 subtype, which stimulate well described angiogenic pathways. In diabetic mice, nicotine accelerated wound healing by enhancing neovascularization, comparable to the effects of basic fibroblast growth factor (bFGF). Low concentrations of nicotine have been shown to synergize with bFGF[9-11]. Although this angiogenic effect can enhance neovascularization, which is beneficial for wound healing, some studies hypothesize it may also contribute to pathological conditions such as tumor growth and atherosclerosis[9-11].

Overall, while nicotine can promote angiogenesis, its vasoconstrictive effects, inhibition of keratinocyte migration, and alteration of the inflammatory response generally result in impaired wound healing.

5. Mechanisms of Nicotine-Induced Vasoconstriction

Nicotine is a potent vasoconstrictor, which reduces blood flow to the skin and other tissues. This vasoconstriction is mediated through the amplification of norepinephrine-induced vasoconstriction and impairment of endothelium-dependent vasorelaxation, as both vascular endothelial cells and vascular smooth muscle express multiple α and β subunits of the nicotinic acetychline receptor. Stimulation of this receptor from the presence of nicotine elicits multiple vasoconstrictive pathways from vasoactive products such as endothelin-1, impairing endothelium-dependent vasodilation[7]. The reduced blood flow limits the delivery of oxygen and nutrients essential for tissue repair[8-9].

6. Comparative Analysis of Nicotine Delivery Systems

The impact of smoking on wound healing is well-documented, with several components of cigarette smoke, including nicotine, carbon monoxide, and tar, playing significant roles in impairing physiological processes essential for wound repair. Nicotine acts as a potent vasoconstrictor, reducing peripheral blood flow and limiting oxygen delivery to tissues, which can result in tissue ischemia and impaired healing. This vasoconstriction is particularly detrimental in the inflammatory and proliferative phases of wound healing, where oxygen is critical for cellular processes such as collagen synthesis and angiogenesis[12]. Additionally, nicotine increases platelet adhesiveness, potentially leading to microvascular occlusion and reduced tissue perfusion. Beyond vascular effects, nicotine also suppresses key cellular functions by inhibiting the proliferation and activity of fibroblasts, macrophages, and keratinocytes, which are critical for granulation tissue formation and immune responses necessary for wound dosure and infection prevention[12].

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Carbon monoxide, another major component of cigarette smoke, exacerbates hypoxia by competing with oxygen for binding sites on hemoglobin. Its affinity for hemoglobin is approximately 200 times greater than that of oxygen, significantly reducing the oxygen-carrying capacity of blood and worsening tissue oxygenation in already ischemic wound environments[12]. Meanwhile, tar introduces a complex mixture of carcinogens, polycyclic aromatic hydrocarbons, and other toxins into the system, which amplify tissue damage and perpetuate inflammation by stimulating pro-inflammatory cytokine production. These combined effects create a hostile environment for cellular repair mechanisms, delaying wound healing and increasing the risk of complications such as infection, dehiscence, and chronic wounds[12].

Regarding e-cigarettes or vaping, the primary concern is nicotine, which is present in these products at varying concentrations. Studies suggest that nicotine from e-cigarettes shares many of the deleterious effects observed in traditional smoking, particularly its ability to impede wound healing by disrupting cellular energy metabolism and tissue repair processes. For example, nicotine has been shown to inhibit myofibroblast differentiation, a process essential for wound contraction and closure. Additionally, it interferes with mitochondrial oxidative phosphorylation, a critical pathway for cellular energy production needed during wound healing[13]. However, unlike traditional cigarettes, e-cigarettes do not produce combustion products such as carbon monoxide and tar, which might reduce the overall burden of tissue damage and inflammation. Despite this potential advantage, the impact of nicotine alone remains significant. Animal studies investigating e-cigarette vapor exposure have reported impaired biomechanical properties of healing tendons, indicating that nicotine alone can compromise structural integrity and functional recovery of tissues[14].

Transdermal nicotine delivery, such as nicotine patches, offers a combustion-free method of nicotine administration and is widely used as a form of nicotine replacement therapy (NRT). While nicotine patches eliminate harmful byproducts of combustion, the effects of nicotine itself on wound healing remain complex and dose-dependent. Some studies suggest that at low concentrations, nicotine may modestly attenuate inflammation and enhance cellular proliferation in specific contexts, potentially supporting aspects of tissue repair[15,16]. However, these effects are inconsistent and do not outweigh the negative impacts observed at higher nicotine doses. A study examining the use of nicotine patches in post-operative patients found no significant adverse effects on wound healing outcomes compared to those who continued smoking. This finding suggests that the absence of combustion products may mitigate some of the harmful effects associated with smoking, though nicotine itself still poses risks to the healing process[17].

Comparative analyses and systematic reviews have provided additional insight into the differential impacts of smoking, vaping, and nicotine patches on wound healing. Sørensen et al. conducted a systematic review that emphasized the rapid restoration of tissue oxygenation and partial reversal of inflammatory cell dysfunction following smoking cessation[15]. The review highlighted that while smoking cessation improves oxygen delivery and reduces the inflammatory burden, certain aspects of the healing process, such as proliferative responses, remain impaired for a prolonged period. Importantly, the review suggested that nicotine replacement therapy, although not completely risk-free, is significantly less harmful than continued smoking[15]. This aligns with broader evidence indicating that while nicotine itself can impede wound healing through its vasoconstrictive and cellular inhibitory effects, the absence of combustion products in NRT and e-cigarettes may represent a less detrimental alternative to traditional cigarettes. Nonetheless, the risks associated with nicotine exposure, irrespective of the delivery method, warrant caution, particularly in patients undergoing surgical or trauma-related wound care[15-17].

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7. Clinical Implications and Recommendations

The impact of smoking, vaping, and nicotine patches on surgical outcomes, particularly wound healing complications, infection rates, and overall recovery, is extensively documented in the medical literature. Smoking remains a significant risk factor for impaired wound healing and increased postoperative complications. The pathophysiological mechanisms underlying these risks include reduced tissue oxygenation, impaired inflammatory response, and altered collagen synthesis, all of which contribute to delayed healing, increased infection rates, and a higher likelihood of wound dehiscence or chronic wounds[18-21].

Nicotine, a key component of cigarette smoke, is particularly harmful due to its vasoconstrictive properties, which reduce peripheral blood flow and oxygen delivery to tissues. Adequate oxygenation is critical during the inflammatory and proliferative phases of wound healing, where cellular energy demands are high for processes such as angiogenesis and collagen deposition[20]. By increasing platelet adhesiveness, nicotine further contributes to microvascular occlusion, exacerbating tissue ischemia[20]. In addition to vascular effects, nicotine impairs the function of fibroblasts and macrophages, which are essential for granulation tissue formation, wound contraction, and the immune response needed to prevent infections[17,20]. Furthermore, nicotine disrupts the synthesis of type I collagen, a primary structural protein in wound repair, leading to weaker scar formation and delayed recovery[17,20].

Smoking cessation is strongly recommended preoperatively to mitigate these risks. Evidence indicates that cessation for at least four weeks before surgery can significantly reduce the risk of wound healing complications and infections, as well as improve surgical outcomes overall[19,21]. This period allows for partial restoration of tissue oxygenation and a reduction in the inflammatory burden caused by cigarette smoke[21]. However, even shorter durations of smoking cessation have been associated with improved outcomes, making it a critical recommendation in preoperative care[19].

Nicotine replacement therapy (NRT), such as nicotine patches, is a common strategy to assist smoking cessation and offers a safer alternative to smoking. NRT provides a combustion-free source of nicotine, eliminating exposure to harmful toxins such as carbon monoxide and tar found in traditional cigarette smoke[22]. However, its impact on wound healing remains complex. Some studies suggest that while nicotine may impair the inflammatory phase of wound healing, it can stimulate the proliferative phase by enhancing keratinocyte migration and fibroblast activity. These effects result in a marginal impact overall, particularly when compared to the detrimental effects of smoking[18,22]. Importantly, NRT is generally considered safer than continued smoking, especially in the perioperative period, where its use can help maintain cessation and reduce overall surgical risks[22].

Vaping, or the use of electronic cigarettes, delivers nicotine without many of the harmful combustion byproducts associated with traditional cigarettes. This has led to the perception that vaping might pose fewer risks to surgical outcomes. However, evidence remains limited, and concerns about nicotine's well-established effects on vasoconstriction, inflammation, and collagen synthesis still apply[20,22]. Studies have highlighted that nicotine exposure via e-cigarettes can inhibit myofibroblast differentiation and impair mitochondrial energy production, both of which are critical for tissue repair[19]. Although the absence of toxicants such as tar and carbon monoxide might reduce some of the risks, the long-term effects of vaping on surgical outcomes and wound healing require further investigation[22].

In summary, smoking significantly impairs surgical outcomes, particularly wound healing and infection rates, by disrupting tissue oxygenation, inflammation, and collagen synthesis[18-21]. Preoperative smoking cessation is a critical intervention for improving surgical outcomes, with evidence supporting cessation for at least four weeks to achieve

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significant benefits[19-21]. While NRT may have some minor effects on wound healing, it is considerably safer than continued smoking and can be effectively integrated into perioperative care plans[22]. Vaping, although free of combustion-related toxins, remains a concern due to the presence of nicotine and its detrimental effects on wound healing processes, underscoring the need for further research into its surgical implications[19-22].

The management of nicotine use in surgical patients is crucial for optimizing wound healing outcomes and reducing postoperative complications. Evidence-based recommendations emphasize the importance of preoperative smoking cessation, ideally starting at least four weeks before surgery, to significantly reduce the risk of wound healing complications and infections[23-25]. This timeline allows for the reduction of nicotine and carbon monoxide levels, which are known to impair wound healing through various mechanisms, including vasoconstriction and reduced oxygen delivery to tissues[25].

Nicotine replacement therapies (NRT), such as patches, gums, or lozenges, are effective aids for smoking cessation and are generally considered safe in the perioperative period. They help manage withdrawal symptoms and increase the likelihood of successful cessation without significantly impacting wound healing outcomes[25-26]. While some basic science studies suggest potential negative effects of nicotine on wound healing, human studies have not demonstrated significant detrimental effects when NRT is used[26].

Protocols for counseling and supporting patients in nicotine cessation before surgery often involve a combination of behavioral interventions and pharmacotherapy. The "Ask, Advise, Connect" strategy is a practical approach that can be implemented in preoperative clinics. This involves asking patients about their smoking status, advising them to quit, and connecting them to counseling resources such as quitlines or primary care providers[5]. Intensive interventions, including multiple counseling sessions and pharmacotherapy, are recommended when feasible, as they have been shown to reduce postoperative complications and increase long-term abstinence rates[23,27].

Healthcare providers play a critical role in ensuring adherence to nicotine cessation guidelines. They should initiate discussions about smoking cessation as soon as surgery is planned, emphasizing the benefits of quitting both preoperatively and postoperatively[24,26]. Providers can enhance adherence by integrating smoking cessation interventions into preoperative care plans and by collaborating with anesthesiologists, primary care physicians, and surgeons to provide comprehensive support[23,26]. This multidisciplinary approach is essential for optimizing surgical outcomes and promoting long-term health benefits for patients.

8. Pharmacokinetics and Pharmacodynamics of Nicotine Delivery Systems

Nicotine binds to nicotinic-cholinergic receptors found in the adrenal medulla, autonomic ganglia, and brain, promoting stimulatory effects primarily in the locus coeruleus and rewarding effects within the mesolimbic pathway[28]. Likewise, nicotine is able to affect both the peripheral and central nervous systems, increasing heart rate and blood pressure, while constricting blood vessels in the skin and coronary arteries. Therefore, this alkaloid is a key physiological mediator in its users.

Nicotine can be absorbed through the respiratory tract, mucous membranes in the mouth, and the skin. Given its pKa of 7.9, nicotine remains in its non-ionized form in basic environments, facilitating passage through membranes[29]. A basic environment is therefore necessary for optimal nicotine absorption. This emphasizes the role of pH in evaluating various nicotine formulations.

Nicotine is cleared from the system at a relatively high rate, approximately 0.8–1.5 L/min, and this rate is influenced by liver blood flow. It is predominantly

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metabolized in the liver by the CYP450 isoform CYP2A6 into cotinine, its major metabolite. To a lesser extent, nicotine is also metabolized in the lung and kidneys[29].

Recent research indicates that the high pH of cigarette smoke particles favors the non-ionized form of nicotine[30]. This facilitates the rapid absorption of nicotine from cigarette smoke through the lungs, aided by the large surface area of the alveoli and small airways. Nicotine dissolves in the lung's fluid at pH 7.4, ensuring rapid transfer into the bloodstream and optimal bioavailability[30]. Upon inhalation, nicotine is quickly distributed to the brain. In contrast, absorption through the skin via transdermal routes leads to a slower, more gradual increase in nicotine levels in both the brain and peripheral tissues. Nicotine's high lipophilicity enables effective dermal absorption. However, transdermal nicotine can take 2-10 hours to reach peak concentrations, with bioavailability (F) ranging from 68–82%[31]. Compared to smoking, plasma nicotine levels fluctuate less with transdermal systems, making them the least similar to those produced by smoking[32]. Dermal absorption is slower and undergoes first-pass metabolism, and as with other nicotine delivery methods, pH significantly influences absorption, with higher pH increasing the absorption rate through skin or mucosal surfaces.

A 2004 review examined the effects of nicotine from smoking on dermal cells and their impact on wound healing. It notes that while nicotine can promote keratinocyte adhesion and differentiation by modulating nicotinic acetylcholine receptors (nAChRs), it also has the potential to induce apoptosis and impede cell migration. It can be concluded that nicotine can operate on a spectrum as its effects seem to be dose-dependent through a bimodal influence that may act through different nAChR subtypes or alternate cellular pathways. This implied that varying bioavailability or exposure durations (acute vs. chronic) could lead to different responses in cells like keratinocytes. Thus, short, controlled doses of nicotine might stimulate dermal cells, promoting cell migration and potentially aiding wound healing. This suggested that short-term therapeutic use may have distinct effects in comparison to prolonged harmful exposure[33].

E-cigarettes deliver nicotine as an aerosol, which contains fewer toxicants than cigarette smoke. Pharmacokinetic studies on first-generation e-cigarettes in new users show that nicotine exposure is more similar to that of nicotine gum, a nicotine inhaler, or even an unlit cigarette than to combustible cigarette exposure[34]. Research on second-generation or "advanced" e-cigarette devices used by experienced users has shown higher plasma nicotine levels compared to first-generation devices[35]. Therefore, a comparison can be made between first and second-generation e-cigarette devices but none can compare to the overwhelming bioavailability of nicotine from combustible cigarette exposure.

In a review article from 2014 encompassing electronic cigarettes, automated smoking machine data showed that e-cigarettes deliver less nicotine per puff than traditional cigarettes[35]. Clinical studies suggested that e-cigarettes produce modest nicotine concentrations in inexperienced users. However, experienced users can reach nicotine and/or cotinine levels comparable to those from smoking traditional cigarettes. This indicates that user experience plays a significant role in nicotine bioavailability as well.

9. Impact of Nicotine on Immune Response to Wound Healing

Smoking has been shown to markedly increase the risk of complications following surgery, especially those involving wound healing, though researchers are still uncovering the precise mechanisms behind this. Smokers have consistently been found to face higher incidences of tissue necrosis, wound reopening, infection, and chronic problems like fistulas and hernias, regardless of the type of surgery[36]. Therefore, investigation is merited regarding immunological pathways that are disrupted during these phenomena.

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When a wound is created, the body initially responds by forming a clot to halt bleeding and stabilize the area. In smokers, this process is affected by heightened platelet activity and increased fibrinogen levels, which hasten clot formation. However, these clotting alterations also change the structure of the clot itself, diminishing the availability of certain cytokines essential for signaling during wound repair. Cytokines play a vital role in drawing immune cells to the wound site, so the reduction in these molecules leads to impaired immune cell migration, compromising the wound's defense against infections and slowing the clearance of damaged tissue[36].

Nicotine adds another layer of complexity by disrupting immune function, notably through reduced cytokine secretion, weakened T-cell receptor activity, and impaired antibody production. This drop in immune function in nicotine-exposed tissues can create a substantial barrier to wound healing, as the immune system becomes less responsive where nicotine is concentrated. Smoking also shifts immune cell levels, elevating certain white blood cells and TCD8+ cells while decreasing TCD4+ cells and natural killer cells, which are important for a well-coordinated immune response[37].

Nicotine can also influence the rate of wound contraction, sometimes accelerating this phase of healing, potentially due to increased activity of myofibroblasts driven by higher levels of fibrinogen and fibronectin. However, faster wound contraction alone doesn't necessarily prevent infection or other complications. Over time, smoking disrupts fibroblast function, leading to lower collagen production and restricted new blood vessel formation. This weakened support structure delays complete wound closure and increases the likelihood of complications like wound dehiscence and hernias[36].

On a cellular level, smoking releases reactive oxygen species (ROS) into the body, which cause direct damage to cells, fuel inflammation, and reduce the wound's ability to fight bacterial infections. Smokers also tend to have lower levels of essential antioxidants such as vitamins C and E, both necessary for counteracting ROS and aiding collagen production. This lack of antioxidant support destabilizes collagen, causing delayed and more fragile healing, and heightens the risk of complex complications. Although quitting smoking may restore some immune function and reduce infection risk, the lasting impacts of nicotine and other smoking-related damage to wound healing often persist. As previously noted, nicotine directly suppresses immune responses, continuing to pose a risk for wound healing even after cessation[36].

In summary, smoking creates numerous, interconnected challenges for post-surgical wound healing. Its effects on immune function, clot structure, wound contraction, collagen stability, and ROS damage collectively raise the likelihood of post-surgical complications. While quitting smoking can reduce some risks, the residual effects, especially from nicotine exposure, may still influence the wound healing process in former smokers.

10. Role of Nicotine in Angiogenesis and Tissue Perfusion

- **Angiogenic Pathways**: Explore the effect of nicotine on angiogenesis (e.g., VEGF, endothelial cell migration).

  From previous studies we know that endothelial nicotinic Acetylcholinesterase Receptors (nAChR) modulate blood vessel formation, remodeling, and mediate the effect of nicotine on angiogenesis. Nicotine's specific binding to nAChR deregulates various biological processes. Some of those being regulation of cell proliferation, apoptosis, migration, invasion, angiogenesis, inflammation and cell-mediated immunity, embryonic and adult stem cells, and adult tissues as well as cancer cells. These deregulations can eventually lead to malignant and pathological angiogenesis[38]. An interdependence has been found between angiogenic pathways mediated by growth factor receptors, and

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the pathway mediated by endothelial nAChRs. In the wounded endothelial monolayer, activation of nicotinic acetylcholine receptors triggers growth factors like VEGF or bFGF to accelerate endothelial cell migration. Likewise, researchers have identified convergent genomic responses of ECs to nicotine, VEGF and bFGF(2) by focusing on specific receptors. α7-nAChR specifically plays an important role in cholinergic angiogenesis.

When α7-nAChR is upregulated, the proliferation process of subconfluent endothelial cells gets started. Subsequently, selective inhibition of this receptor can put a hold on endothelial tube formation[39]. In a previous study[40], pharmacological inhibition of this nAChR, or genetic disruption of α7-nAChR expression, significantly inhibited angiogenesis in a number of animal models, including angiogenesis in response to inflammation, ischemia, and tumor growth. The pathological angiogenesis can be stimulated by endogenous acetylcholine, such as those mentioned previously, but also exogenously in the form of nicotine. This in turn can lead to an uncontrolled angiogenesis resulting in malignancy or other pathological processes.

- **Comparative Impact on Blood Flow and Oxygenation**: Discuss how the delivery method affects blood flow to healing tissues and the implications for tissue repair.

The toxic constituents of cigarette smoke--particularly nicotine, carbon monoxide, and hydrogen cyanide-- have proven mechanisms by which smoking may undermine wound repair. It is well known that nicotine is a vasoconstrictor which in turn reduces blood flow to skin layers, resulting in tissue ischemia and impaired healing of injured tissue[41]. It also raises the risk of thrombotic microvascular occlusion and tissue ischemia by increasing platelet adhesiveness, and reduces proliferation of red blood cells, fibroblasts, and macrophages. Carbon monoxide diminishes oxygen transport and metabolism, whereas hydrogen cyanide inhibits the enzyme systems necessary for oxidative metabolism and oxygen transport at the cellular level[41]. Toxic effects and insufficient tissue oxygenation caused by smoking are thought to be among the factors that could explain the impaired healing of surgical wounds in smokers[42].

11. Impact of Nicotine on Skin Cells and Connective Tissue

- **Keratinocytes and Fibroblasts**: Examine nicotine's influence on keratinocyte proliferation and fibroblast function across different delivery methods.

Nicotine appears as a mediator for keratinocyte adhesion and motility. It exerts inhibitory effects on keratinocyte migration, while calcium serves as a second messenger in the signaling pathway[43]. ACh signaling through a7 nAChR channels controls late stages of keratinocyte development. The process works in the epidermis by regulating expression of the cell cycle stages; progression, apoptosis, and terminal differentiation genes. These effects are mediated, in part,by alterations in transmembrane Calcium influx. Elimination of the a7 component of nicotinergic signaling in keratinocytes has been shown to decrease relative amounts of pro-apoptotic factors, such as Bad and Bax[43]. This suggests that a7 nAChR is related to stimulation of keratinocyte apoptosis. In conclusion, nicotine enhances keratinocyte adhesion, differentiation, apoptosis and inhibits keratinocyte migration, limiting the wound healing process.

Nicotine also affects fibroblast mechanisms, especially by working on specific subunits. A3, a5, a7, b2, and b4 nAChR subunits are detected in human fibroblasts. Exposure of

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these cells to nicotine increases mRNA and protein levels of the cell-cycle regulators p21, cyclin D1, Ki-67, and PCNA which lead to increased apoptosis regulators like Bcl-2 and caspase 3[43].

- **Collagen Synthesis and Matrix Remodeling:** Review how nicotine impacts extracellular matrix formation, collagen deposition, and remodeling, crucial for wound strength.

  The exposure of human skin fibroblasts to nicotine has been shown to decrease biosynthesis of type I and III collagens. Furthermore, tobacco smoke extract has been shown to reduce fibroblast-mediated collagen gel contraction in vitro, which affects wound healing. Nicotine also increases levels of matrix metalloproteinases (MMPs), which are enzymes that break down collagen, thus impairing overall collagen turnover and skin integrity[42]; contributing to premature skin aging and impaired wound healing.

  A recent study involving nicotine a3 nAChR knockout mice, results show alterations in fibroblast growth and function that are opposite to those observed in fibroblasts treated with nicotine. There were decreased amounts of extracellular matrix proteins, collagen 1, elastin and metalloproteinase-1 in knockout mice compared to others. Nicotine is involved in reduced proliferation of red blood cells, fibroblasts, and macrophages. Its main effect on wound healing is inhibiting keratinocyte migration and differentiation, and the second phase of wound healing: re-epithelization[43].

12. Conclusion

This review highlights the complex role of nicotine in wound healing and the differential impacts of cigarettes, vaping, and nicotine patches. Cigarettes remain the most detrimental due to the combined effects of nicotine, carbon monoxide, and tar, which impair oxygen delivery, increase inflammation, and disrupt collagen synthesis. E-cigarettes, though free of combustion byproducts, still hinder wound repair due to the harmful effects of nicotine on angiogenesis, cellular migration, and oxidative stress. Nicotine patches provide a safer alternative but must be used cautiously as nicotine's impact on inflammatory and proliferative pathways can still delay healing in high doses.

Clinical evidence underscores the importance of preoperative smoking cessation for at least four weeks to reduce complications. Nicotine replacement therapies can aid cessation efforts but should be tailored to minimize adverse effects on wound repair. Future research should focus on the long-term implications of vaping on wound healing, the mechanisms underlying nicotine's dose-dependent effects, and strategies for optimizing nicotine management in surgical patients. By addressing these gaps, clinicians can better support patient outcomes in wound care and surgical recovery.

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13. References:

1. Benowitz NL. Nicotine addiction. *N Engl J Med.* 2010;362(24):2295-2303. doi:10.1056/NEJMra0809890

2. Price LR, Martinez J. Cardiovascular, carcinogenic and reproductive effects of nicotine exposure: a narrative review of the scientific literature. *F1000Res.* 2019;8:1586. doi:10.12688/f1000research.20062.2

3. Walser T, Cui X, Yanagawa J, et al. Smoking and lung cancer: the role of inflammation. *Proc Am Thorac Soc.*2008;5(8):811-815. doi:10.1513/pats.200809-100TH

4. Zia S, Ndoye A, Lee TX, Webber RJ, Grando SA. Receptor-mediated inhibition of keratinocyte migration by nicotine involves modulations of calcium influx and intracellular concentration. *J Pharmacol Exp Ther.*2000;293(3):973-981.

5. Sørensen LT. Wound healing and infection in surgery: the pathophysiological impact of smoking, smoking cessation, and nicotine replacement therapy: a systematic review. *Ann Surg.* 2012;255(6):1069-1079. doi:10.1097/SLA.0b013e31824f632d

6. de Almeida TF, Romana-Souza B, Machado S, Abreu-Villaça Y, Monte-Alto-Costa A. Nicotine affects cutaneous wound healing in stressed mice. *Exp Dermatol.* 2013;22(8):524-529. doi:10.1111/exd.12186

7. Whitehead AK, Erwin AP, Yue X. Nicotine and vascular dysfunction. Acta Physiol (Oxf). 2021 Apr; 231(4):e13631. doi: 10.1111/apha.13631. Epub 2021 Feb 24. PMID: 33595878; PMCID: PMC8026694.

8. Xanthoulea S, Deliaert A, Romano A, et al. Nicotine effect on inflammatory and growth factor responses in murine cutaneous wound healing. *Int Immunopharmacol.* 2013;17(4):1155-1164. doi:10.1016/j.intimp.2013.10.022

9. Jacobi J, Jang JJ, Sundram U, et al. Nicotine accelerates angiogenesis and wound healing in genetically diabetic mice. *Am J Pathol.* 2002;161(1):97-104. doi:10.1016/S0002-9440(10)64161-2

10. Morimoto N, Takemoto S, Kawazoe T, Suzuki S. Nicotine at a low concentration promotes wound healing. *J Surg Res.* 2008;145(2):199-204. doi:10.1016/j.jss.2007.05.031

11. Martin JW, Mousa SS, Shaker O, Mousa SA. The multiple faces of nicotine and its implications in tissue and wound repair. *Exp Dermatol.* 2009; 18(6):497-505. doi:10.1111/j.1600-0625.2009.00854.x

12. Silverstein P. Smoking and wound healing. *Am J Med.* 1992;93(1A):22S-24S. doi:10.1016/0002-9343(92)90623-j

13. Lei W, Lerner C, Sundar IK, Rahman I. Myofibroblast differentiation and its functional properties are inhibited by nicotine and e-cigarette via mitochondrial OXPHOS Complex III. *Sci Rep.* 2017;7:43213. doi:10.1038/srep43213

14. Kennedy P, Saloky K, Yadavalli A, et al. Nicotine exposure via electronic cigarettes significantly impedes biomechanical healing properties of tendon healing in a rat model. *Arthroscopy.* 2021; 37(10):3170-3176. doi:10.1016/j.arthro.2021.03.071

15. Sørensen LT. Wound healing and infection in surgery: the pathophysiological impact of smoking, smoking cessation, and nicotine replacement therapy: a systematic review. *Ann Surg.* 2012;255(6):1069-1079. doi:10.1097/SLA.0b013e31824f632d

16. Jin MF, Campbell EH, Somani AK. Is there a smoking gun for nicotine? A review of the role of nicotine in dermatologic surgery. *Dermatol Surg.* 2022;48(11):1171-1175. doi:10.1097/DSS.0000000000003547

17. Sørensen LT, Toft BG, Rygaard J, et al. Effect of smoking, smoking cessation, and nicotine patch on wound dimension, vitamin C, and systemic markers of collagen metabolism. *Surgery.* 2010;148(5):982-990. doi:10.1016/j.surg.2010.02.005

18. Sørensen LT. Wound healing and infection in surgery: the pathophysiological impact of smoking, smoking cessation, and nicotine replacement therapy: a systematic review. *Ann Surg.* 2012;255(6):1069-1079. doi:10.1097/SLA.0b013e31824f632d

19. Rinker B. The evils of nicotine: an evidence-based guide to smoking and plastic surgery. *Ann Plast Surg.*2013;70(5):599-605. doi:10.1097/SAP.0b013e3182764fcd

20. Silverstein P. Smoking and wound healing. *Am J Med.* 1992;93(1A):22S-24S. doi:10.1016/0002-9343(92)90623-j

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21. Fan Chiang YH, Lee YW, Lam F, et al. Smoking increases the risk of postoperative wound complications: a propensity score-matched cohort study. *Int Wound J.* 2023;20(2):391-402. doi:10.1111/iwj.13887

22. Jin MF, Campbell EH, Somani AK. Is there a smoking gun for nicotine? A review of the role of nicotine in dermatologic surgery. *Dermatol Surg.* 2022;48(11):1171-1175. doi:10.1097/DSS.0000000000003547

23. Fiddes RA, McCaffrey N. Preoperative smoking-cessation interventions to prevent postoperative complications: a quality assessment and overview of systematic review evidence. *Anesth Analg.* 2024. doi:10.1213/ANE.0000000000007187

24. Barua RS, Rigotti NA, Benowitz NL, et al. 2018 ACC expert consensus decision pathway on tobacco cessation treatment: a report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. *J Am Coll Cardiol.* 2018;72(25):3332-3365. doi:10.1016/j.jacc.2018.10.027

25. Rinker B. The evils of nicotine: an evidence-based guide to smoking and plastic surgery. *Ann Plast Surg.*2013;70(5):599-605. doi:10.1097/SAP.0b013e3182764fcd

26. Jin MF, Campbell EH, Somani AK. Is there a smoking gun for nicotine? A review of the role of nicotine in dermatologic surgery. *Dermatol Surg.* 2022;48(11):1171-1175. doi:10.1097/DSS.0000000000003547

27. Yousefzadeh A, Chung F, Wong DT, Warner DO, Wong J. Smoking cessation: the role of the anesthesiologist. *Anesth Analg.* 2016;122(5):1311-1320. doi:10.1213/ANE.0000000000001170

28. National Center for Biotechnology Information. PubChem Compound Summary for CID 89594, Nicotine. PubChem website. https://pubchem.ncbi.nlm.nih.gov/compound/Nicotine.

29. Olsson Gisleskog PO, Perez Ruixo JJ, Westin Å, et al. Nicotine population pharmacokinetics in healthy smokers after intravenous, oral, buccal and transdermal administration. *Clin Pharmacokinet.* 2021;60:541-561. doi:10.1007/s40262-020-00960-5

30. Benowitz NL, Hukkanen J, Jacob P III. Nicotine chemistry, metabolism, kinetics and biomarkers. *Handb Exp Pharmacol.* 2009;(192):29-60. doi:10.1007/978-3-540-69248-5_2

31. Gupta SK, Benowitz NL, Jacob P, Rolf CN, Gorsline J. Bioavailability and absorption kinetics of nicotine following application of a transdermal system. *Br J Clin Pharmacol.* 1993;36:221-227.

32. American Society of Health-System Pharmacists. *AHFS Drug Information 2009.* Bethesda, MD; 2009.

33. Martin JW, Mousa SS, Shaker O, Mousa SA. The multiple faces of nicotine and its implications in tissue and wound repair. *Exp Dermatol.* 2009;18(6):497-505. doi:10.1111/j.1600-0625.2009.00854.x

34. Yingst JM, Foulds J, Veldheer S, et al. Nicotine absorption during electronic cigarette use among regular users. *PLoS One.* 2019;14(7):e0220300. doi:10.1371/journal.pone.0220300

35. Schroeder MJ, Hoffman AC. Electronic cigarettes and nicotine clinical pharmacology. *Tob Control.* 2014;23(Suppl 2):ii30–ii35. doi:10.1136/tobaccocontrol-2013-051469

36. Sørensen LT. Wound healing and infection in surgery: the pathophysiological impact of smoking, smoking cessation, and nicotine replacement therapy: a systematic review. *Ann Surg.* 2012;255(6):1069-1079. doi:10.1097/SLA.0b013e31824f632d

37. Abtahi Froushani SM, Ajami M, Mahmoudzadeh M. Effect of nicotine on immune system function. *Adv Pharm Bull.* 2022. doi:10.34172/apb.2022.032

38. Cardinale A, Nastrucci C, Cesario A, Russo P. Nicotine: specific role in angiogenesis, proliferation and apoptosis. *Crit Rev Toxicol.* 2012;42(1):68-89. doi:10.3109/10408444.2011.623150

39. Cooke JP. Angiogenesis and the role of the endothelial nicotinic acetylcholine receptor. *Life Sci.* 2007;80(24-25):2347-2351. doi:10.1016/j.lfs.2007.01.061

40. Heeschen C, Weis M, Aicher A, Dimmeler S, Cooke JP. A novel angiogenic pathway mediated by non-neuronal nicotinic acetylcholine receptors. *J Clin Invest.* 2002;110(4):527-536. doi:10.1172/JCI14676

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41. Silverstein P. Smoking and wound healing. *Am J Med.* 1992;93(1A):22S-24S. doi:10.1016/0002-9343(92)90623-j

42. Knuutinen A, Kokkonen N, Risteli J, et al. Smoking affects collagen synthesis and extracellular matrix turnover in human skin. *Br J Dermatol.* 2002;146(4):588-594. doi:10.1046/j.1365-2133.2002.04694.x

43. Misery L. Nicotine effects on skin: are they positive or negative? *Exp Dermatol.* 2004;13(11):665-670. doi:10.1111/j.0906-6705.2004.00274.x

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