**NAME: AKINTEYE ESTHER FOLAKEMI**

**MATRIC NUMBER: 15/MHS01/015**

**ASSIGNMENT TITLE: WOUND HEALING**

**COURSE TITLE: INTRODUCTION TO HISTOPATHOLOGY**

**COURSE CODE: ANA 404**

**QUESTION: 1. WRITE ON CYTOKINE SIGNALLING AND ITS ROLE IN WOUND HEALING.**

**2. WHEN IS WOUND HEALING REFFERED TO AS IMPAIRED AND WHY?**

**3. EXAMINE THE ROLE OF OXIDATIVE STRESS IN THE DEVELOPMENT AND PROGRESSION OF IMPAIRED WOUND HEALING.**

**ANSWERS:**

**1. Cytokine signalling**

Cytokine signalling is an important part of the human body regulation, it is an important element that regulates development of the hematopoietic cells in general and T cells in particular.

Cytokine signalling in oesophageal epithelial cells may play a critical role in the initial steps of the trans differentiation process of BE. NFkB is important for Cdx1 and Cdx2 transcriptional induction. Induction of NFκB by cytokine stimulation (and prostaglandin activity) has been established in many cell types and has pleiotropic effects on the cell, including the induction of cell survival pathways as well as transcriptional activation of target genes. Recent reports suggest that NFκB transcriptional activity may play a causal role in BE. Acid and bile salts can induce Cdx1 and Cdx2 protein in esophageal cells and in EAC cells. This induction is dependent upon NFκB activity and may be regulated by PI3K signaling. Interestingly, two NFκB binding sites have been identified in the promoter of Cdx2, suggesting a potential for NFκB in directly linking inflammation with Cdx2 expression. However, the complete mechanism by which acids, bile, and PI3K signalling regulate NFκB and Cdx gene expression is not fully understood.

**Role of cytokine signalling in wound healing**

The response to injury is a phylogenetically primitive, yet essential innate host immune response for restoration of tissue integrity. Tissue disruption in higher vertebrates, unlike lower vertebrates, results not in tissue regeneration, but in a rapid repair process leading to a fibrotic scar. Wound healing, whether initiated by trauma, microbes or foreign materials, proceeds via an overlapping pattern of events including coagulation, inflammation, epithelialization, formation of granulation tissue, matrix and tissue remodeling. The process of repair is mediated in large part by interacting molecular signals, primarily cytokines, that motivate and orchestrate the manifold cellular activities which underscore in  
Response to injury is frequently modeled in the skin,1 but parallel coordinated and temporally regulated patterns of mediators and cellular events occur in most tissues subsequent to injury. The initial injury triggers coagulation and an acute local inflammatory response followed by mesenchymal cell recruitment, proliferation and matrix synthesis. Failure to resolve the inflammation can lead to chronic nonhealing wounds, whereas uncontrolled matrix accumulation, often involving aberrant cytokine pathways, leads to excess scarring and fibrotic sequelae. Continuing progress in deciphering the essential and complex role of cytokines in wound healing provides opportunities to explore pathways to inhibit/enhance appropriate cytokines to control or modulate pathologic healing.  
Wound healing is a complex process encompassing a number of overlapping phases, including inflammation, epithelialization, angiogenesis and matrix deposition. During inflammation, the formation of a blood clot re-establishes hemostasis and provides a provisional matrix for cell migration. Cytokines play an important role in the evolution of granulation tissue through recruitment of inflammatory leukocytes and stimulation of fibroblasts and epithelial cells.  
  
Most types of injury damage blood vessels, and coagulation is a rapid-fire response to initiate hemostasis and protect the host from excessive blood loss. With the adhesion, aggregation and degranulation of circulating platelets within the forming fibrin clot, a plethora of mediators and cytokines are released (Table 1), including transforming growth factor beta (TGF-beta), platelet derived growth factor (PDGF), and vascular endothelial growth factor (VEGF), that influence tissue edema and initiate inflammation. VEGF, a vascular permeability factor, influences the extravasation of plasma proteins to create a temporary support structure upon which not only activated endothelial cells, but also leukocytes and epithelial cells subsequently migrate. Angiopoietin-1 (Ang-1), the ligand for Tie-2 receptors, is a natural antagonist for VEGF’s effects on permeability, a key regulatory checkpoint to avoid excessive plasma leakage.  
Latent TGF-beta1, released in large quantities by degranulating platelets, is activated from its latent complex by proteolytic and non-proteolytic mechanisms3 to influence wound healing from the initial insult and clot formation to the final phase of matrix deposition and remodeling.4 Active TGF-beta1 elicits the rapid chemotaxis of neutrophils and monocytes to the wound site5 in a dose-dependent manner through cell surface TGF-beta serine/threonine type I and II receptors and engagement of a Smad3-dependent signal.6 Autocrine expression of TGF- beta 1 by leukocytes and fibroblasts, in turn, induces these cells to generate additional cytokines including tumor necrosis factor alpha (TNF-a), interleukin 1 beta (IL-1 beta) and PDGF, as well as chemokines, as components of a cytokine cascade.7 Such factors act to perpetuate the inflammatory cell response, mediating recruitment and activation of neutrophils and monocytes. In response to TGF- beta and other cytokines, which engage their respective cell surface receptors, intracellular signaling pathways are mobilized to drive phenotypic and functional responses in target cell populations.8 Among the upstream signaling cascades engaged in acute tissue injury are NF-?B, Egr-1, Smads, and MAP kinases, which result in activation of many cognate target genes, including adhesion molecules, coagulation factors, cytokines and growth factors.

**Inflammation**Of the myriad of cytokines that have been investigated in terms of wound healing, TGF- beta 1 has undoubtedly the broadest effects. Despite the vast number of reports documenting the actions of TGF-beta in this context, both in vitro and in vivo, controversy remains as to its endogenous role. The paradoxical actions of TGF-beta are best appreciated in inflammation, where dependent upon the state of differentiation of the cell and the context of action, TGF-beta acts in a bi-directional manner.10 Moreover, this understanding of the nature of TGF-beta has led to the hypothesis that it may act as a therapeutic tool in some circumstances, but also a target for therapeutic intervention in others. Recent studies, in particular those utilizing genetically manipulated animal models, have highlighted the impact of TGF-beta on various aspects of wound healing, and surprisingly, not all of its effects are conducive to optimal healing. Intriguingly, mutations within the TGF-beta1 gene, or in the cell signalling intermediate Smad3, lead to normal or even accelerated cutaneous wound healing responses.6 The rate of healing of full-thickness wounds in Smad3 null mice was significantly greater than in their wild-type counterparts, associated with enhanced epithelialization and keratinocyte proliferation, and a markedly diminished inflammatory response. These observations have broad implications for understanding the role of TGF-beta in the endogenous wound healing response, in that an excess of TGF-beta may be a normal constituent of the response for rapid and optimal protection of the host. In the absence of infection, however, reduction of this overexuberant recruitment, inflammation and keratinocyte suppression may result in a more cosmetically acceptable scar. This knowledge may allow us to optimize the response by modulating selective cell pathways and to tailor therapy to specific cellular defects in pathological conditions such as chronic ulcers and fibrotic processes.  
With the initial barrage of mediators, including TGF-beta, a chain reaction is set in motion, with recruitment, proliferation and activation of the cellular participants. Among the first cells to respond are the vascular endothelial cells, which not only respond to cytokines, but release them as well. Cytokine-induced enhancement of adhesion molecules (VCAM-1, ELAM-1, ICAM-1) on the endothelium provides the platform upon which circulating leukocytes expressing counter-adhesion molecules (integrins, selectins, Ig superfamily members) tether, slowing them down to sense the microenvironment and respond to chemotactic signals at the site of tissue injury. Adhesion molecule interactions between blood leukocytes and endothelium enables transmigration from inside to outside the vessel wall in response to multiple chemotactic signals. In addition to the powerful chemotactic activity of TGF-beta1 for neutrophils and monocytes, multiple chemokines are released to entice leukocytes into the site of tissue injury. Chemokines are represented by several families of related molecules based on the spatial location of the cysteine residues. Deletion of genes for chemokines leads to specific alterations in wound healing, underlying their role in this process   
Migrating through the provisional matrix (scaffolding) provided by the fibrin-enriched clot, leukocytes release proteases and engage in essential functions including phagocytosis of debris, microbes and degraded matrix components. Proteolytic activity is not constitutive, but transcriptionally driven by the cytokines, TGF-beta, IL-1beta and TNF-&alhpa;, released from multiple cellular sources (Table 1). Neutrophil recruitment typically peaks around hours post wounding, followed by an increasing representation of monocytes which are essential for optimal wound healing. Activation of these cells in the context of the wound microenvironment results in enhanced release of chemokines, recruitment of reinforcements, and amplification of the response, with the further release of cytokines, TNF-a, IL-1 and IL-6, that act as paracrine, autocrine and potentially, endocrine mediators of host defense. Antigen stimulation drives lymphocytic recruitment and activation, but at a delayed pace compared to the rapid acute response essential to maintain tissue integrity. Beyond the neutrophil, monocyte/macrophage and lymphocyte participants, mast cells have become increasingly recognized as active participants with increased numbers noted at sites of cutaneous injury. Mast cells respond to monocyte chemotactic protein (MCP-1) and TGF-beta1, -beta2 and -beta3, and within the lesion, release mediators (histamine, proteoglycans, proteases, platelet activating factor, arachidonate metabolites) and cytokines, including TGF-beta and IL-4. Once the inflammatory cells are activated, they become susceptible to TGF-beta1 mediated suppression to reverse the inflammatory process.7,10 Moreover, IL-4 may also dampen the inflammatory response as the inciting agent/trauma is dealt with and promote collagen synthesis during the repair phase.  
**Re-epithelialization**  
Clearance of debris, foreign agents, and/or infectious organisms promotes resolution of inflammation, apoptosis, and the ensuing repair response that encompasses overlapping events involved in granulation tissue, angiogenesis, and re-epithelialization. Within hours, epithelial cells begin to proliferate, migrate and cover the exposed area to restore the functional integrity of the tissue. Re-epithelialization is critical to optimal wound healing not only because of reformation of a cutaneous barrier, but because of its role in wound contraction. Immature keratinocytes produce matrix metalloproteases (MMPs) and plasmin to dissociate from the basement membrane and facilitate their migration across the open wound bed in response to chemoattractants. The migration of epithelial cells occurs independently of proliferation, and depends upon a number of possible processes including growth factors, loss of contact with adjacent cells, and guidance by active contact. TGF-beta1 stimulates migration of keratinocytes in vitro,6,19 possibly by integrin regulation and/or provisional matrix deposition.20 Behind the motile epidermal cells, basal cell keratinocyte proliferation is mediated by the local release of growth factors, with a parallel up-regulation of growth factor receptors including TNF-a, heparin-binding epidermal growth factor (EGF) and keratinocyte growth factor (KGF or FGF-7). Such growth factors are released not only by keratinocytes themselves, acting in an autocrine fashion, but also by mesenchymal cells and macrophages, as paracrine mediators. Numerous animal models in which cytokine genes have been deleted or over-expressed have provided further evidence that such factors are involved in the process of epithelialization. TGF-beta1, and -beta2 are potent inhibitors of keratinocyte proliferation, with the Smad3 pathway implicated as the negative modulator.6 Since epithelialization is significantly accelerated in mice null for the Smad3 gene, with unchecked keratinocyte proliferation, but impaired migration in response to TGF-beta1, the implication is that the early proliferative event is critical to normal epithelialization.6 Once contact is established with opposing keratinocytes, mitosis and migration stop, and in the skin, the cells differentiate into a stratified squamous epithelium above a newly generated basement membrane. Other factors secreted by keratinocytes may exert paracrine effects on dermal fibroblasts and macrophages. One such factor is a keratinocyte-derived non-glycosylated protein termed secretory leukocyte protease inhibitor (SLPI), which inhibits elastase, mast cell chymase, NF-?B and TGF-beta1 activation. In rodents, SLPI is a macrophage-derived cytokine with autocrine and paracrine activities, but production by human macrophages has not yet been demonstrated. In mice, an absence of this mediator of innate host defense (SLPI null) is associated with aberrant healing.26  
The remodeling phase (i.e. re-epithelialization and neovascularization) of wound healing is also cytokine-mediated. Degradation of fibrillar collagen and other matrix proteins is driven by serine proteases and MMPs under the control of the cytokine network. Granulation tissue forms below the epithelium and is composed of inflammatory cells, fibroblasts and newly formed and forming vessels.   
Granulation tissue forms below the epithelium and is composed of inflammatory cells, fibroblasts and newly formed and forming vessels. This initial restructuring of the damaged tissue serves as a temporary barrier against the hostile external environment. Within granulation tissue, angiogenesis (i.e. the generation of new capillary blood vessels from pre-existing vasculature to provide nutrients and oxygen) is potentiated by hypoxia, nitric oxide (NO), VEGF and fibroblast growth factor 2 (FGF-2) and by the chemokines, MCP-1 and macrophage inflammatory protein (MIP-1a). VEGF, released from wound epithelium and from the extracellular matrix by endothelial-derived proteases, stimulates endothelial cell proliferation and increases vascular permeability.2,30,31 VEGF may be transcriptionally up-regulated in response to NO, which also influences vasodilatation, an early step in angiogenesis. In a cyclic fashion, VEGF also drives nitric oxide synthase (NOS) in endothelial cells. Endothelial cells express high affinity receptors for VEGF, VEGF R1 (Flt-1) and VEGF R2 (Flk-1), and represent a primary target of this angiogenic and vascular permeability factor.31 Mice heterozygous for targeted inactivation of VEGF or homozygous for inactivation of its receptors are embryonically lethal, confirming the essentiality of VEGF in angiogenesis.32,33 Besides VEGF, FGFs transduce signals via four protein tyrosine kinase receptors34 to mediate key events involved in angiogenesis. FGFs recruit endothelial cells, and also direct their proliferation, differentiation and plasminogen activator synthesis. Clearly a multifactorial process, the cellular events underlying neovascularization are also impacted by TGF-beta1, EGF, TGF-a, endothelin 1, leptin, and indirectly, TNF-a and IL-1beta.  
Of necessity, angiogenesis is a tightly controlled process. It is characterized not only by the presence of endogenous inducers, but also inhibitors which mediate a decline in the process as the granulation tissue, named for the granular appearance of the blood vessels in the wound, matures and scar remodeling continues. Among the identified endogenous inhibitors of re-vascularization are thrombospondin (TSP-1), IFN-?, IP-10, IL-12, IL-4 and the tissue inhibitors of MMPs (TIMPs), in addition to the recently recognized activities of angiostatin and endostatin (reviewed in reference 2). Since loss of angiogenic control may have negative consequences as evident in tumors, rheumatoid arthritis, and endometriosis, identification of potential endogenous and therapeutic modulators continues.  
Matrix Production and Scar Formation  
With the generation of new vasculature, matrix-generating cells move into the granulation tissue. These fibroblasts degrade the provisional matrix via MMPs and respond to cytokine/growth factors by proliferating and synthesizing new extracellular matrix (ECM) to replace the injured tissue with a connective tissue scar. Although the stage is being set for tissue repair from the beginning (provisional matrix, platelet release of PDGF and TGF-beta, cytokine reservoir), fibroblasts migrate into the wound and matrix synthesis begins in earnest within a couple of days, continuing for several weeks to months. TGF-beta contributes to the fibrotic process by recruiting fibroblasts and stimulating their synthesis of collagens I, III, and V, proteoglycans, fibronectin and other ECM components.4,35 TGF-beta concurrently inhibits proteases while enhancing protease inhibitors, favoring matrix accumulation. In vivo studies have confirmed that exogenous TGF-beta1 increases granulation tissue, collagen formation, and wound tensile strength when applied locally or given systemically in animal models. Increased levels of TGF-beta are routinely associated with both normal reparative processes, as well as fibropathology. In Smad3 null mouse wounds, matrix deposition (fibronectin) could be restored by exogenous TGF-beta, implying a Smad3-independent pathway, whereas collagen deposition was not restored, suggesting a dichotomous Smad3-dependent regulation.6 The progressive increase in TGF-beta3 over time and its association with scarless fetal healing have implicated this member of the TGF-beta family in the cessation of matrix deposition. Other members of the TGF-beta superfamily may also contribute to the wound healing response. Activin A when over-expressed in basal keratinocytes stimulates mesenchymal matrix deposition, whereas BMP-6 over-expression inhibits epithelial proliferation.  
PDGF, released at the outset by degranulating platelets, represents a family of cytokines consisting of two polypeptide chains (A and B) which form the dimers PDGF-AA, AB and B.39 In addition to platelets, PDGF is released by activated macrophages, endothelial cells, fibroblasts and smooth muscle cells and is a major player in regulating fibroblast and smooth muscle cell recruitment and proliferation through PDGF specific receptor-ligand interactions.40 Beyond its role in fibroblast migration and matrix deposition, PDGF-A and -B also up-regulate protease production, in contrast to the anti-protease activity of TGF-beta. PDGF represents the only FDA approved cytokine/growth factor for the clinical enhancement of delayed wound healing. Also central to repair are the FGFs, which signal mitogenesis and chemotaxis, underlying granulation tissue formation, and the production of MMPs. FGF-1 (acidic FGF) and FGF-2 (basic FGF) have been the most intensely studied, but the additional members of this family may also support tissue repair and/or have clinical application.44 The role of FGF-2 has been confirmed in the FGF-2 null mouse which shows not only retarded epithelialization but also reduced collagen production.  
With many overlapping functional properties with FGFs, epidermal growth factor (EGF) orchestrates recruitment and growth of fibroblasts and epithelial cells in the evolution of granulation tissue. EGF and TGF-a, which share sequence homology, enhance epidermal regeneration and tensile strength in experimental models of chronic wounds.46 TNF-a and IL-1beta, key mediators of the inflammatory process, also contribute to the reparative phase either directly by influencing endothelial and fibroblast functions or indirectly, by inducing additional cytokines and growth factors. IL-6 has also been shown to be crucial to epithelialization and influences granulation tissue formation, as shown in the wound healing studies of mice null for the IL-6 gene.47 As repair progresses, fibroblasts display increased expression levels of adhesion molecules and assume a myofibroblast phenotype, mediated in part by TGF-beta and PDGF-A and -B, to facilitate wound contraction.48  
**Remodeling** Phase  
The remodeling phase, during which collagen is synthesized, degraded and dramatically reorganized (as it is stabilized via molecular crosslinking into a scar), is also cytokine-mediated. Although repaired tissue seldom achieves its original strength, it provides an acceptable alternative. Degradation of fibrillar collagen and other matrix proteins is driven by serine proteases and MMPs under the control of the cytokine network. MMPs not only degrade matrix components, but also function as regulatory molecules by driving enzyme cascades and processing cytokines, matrix and adhesion molecules to generate biologically active fragments. TIMPs provide a natural counterbalance to the MMPs and disruption of this orderly balance can lead to excess or insufficient matrix degradation and ensuing tissue pathology.49 Similarly, there exists a naturally occurring inhibitor of elastase and other serine proteases (i.e. SLPI).26,27 The coordinated regulation of enzymes and their inhibitors ensures tight control of local proteolytic activity. In physiologic circumstances, these molecular brakes limit tissue degradation and facilitate accumulation of matrix and repair.  
Aberrant Healing  
Rapid clearance of the inciting agent and resolution of inflammation during healing minimizes scar formation, whereas persistence of the primary insult results in continued inflammation and chronic attempts at healing. Prolonged inflammation and proteolytic activity prevent healing as evident in ulcerative lesions. On the other hand, continued fibrosis in the skin leads to scarring and potentially, disfigurement, whereas progressive deposition of matrix in internal organs such as lungs, liver, kidney or brain compromises not only their structure, but also function, causing disease and death. Inhibitors of TGF-beta (e.g. antibodies, decorin, Smad 7, antisense oligonucleotides) reduce scarring, as does local administration of exogenous TGF-beta[336](tel:336) or systemic delivery of TGF-beta[1.53](tel:1.53) IFN-? is a natural antagonist of fibrogenesis through its ability to inhibit fibroblast proliferation and matrix production and has been shown to have clinical efficacy.54,55 IL-10 may be considered anti-fibrotic via its anti-inflammatory activities,56 as are inhibitors of TNF-a.57  
Wound healing is a complex process encompassing a number of overlapping phases, including inflammation, epithelialization, angiogenesis and matrix deposition. Ultimately these processes are resolved or dampened leading to a mature wound and macroscopic scar formation. Although inflammation and repair mostly occur along a proscribed course, the sensitivity of the process is underscored by the consequences of disruption of the balance of regulatory cytokines. Consequently, cytokines, which are central to this constellation of events, have become targets for therapeutic intervention to modulate the wound healing process. Depending on the cytokine and its role, it may be appropriate to either enhance (recombinant cytokine, gene transfer) or inhibit (cytokine or receptor antibodies, soluble receptors, signal transduction inhibitors, antisense) the cytokine to achieve the desired outcome.

**2. why is wound healing referred to as impaired and why?**In a way, history of wound care is the history of humankind. Well before any written historical record, chronic wounds of all shapes and sizes have plagued patients and created a significant burden on their caretakers. It has long been noticed that some patient factors are more likely to be associated with better wound healing. Likewise, certain wound types have been noted to be associated with a better prognosis than others. Until recently, there has been little scientific evidence regarding the risk factors and characteristics, both positive and negative, responsible for wound healing behaviours. This article will review factors that lead to poor wound healing and the latest advances in their care.  
**Function**At times difficult to appreciate, the wound healing process (WHP) is a highly structured and well-organized biological process. Wound healing can be divided into 4 phases:

* Hemostasis
* Inflammation
* Proliferation
* Tissue
* remodelling

When a wound form, whether due to trauma or surgery, immediate vasoconstriction occurs via the action of thromboxane A2 and prostaglandin. Parallel to this process, the initiation of the clotting cascade takes place. Platelets arrive first to provide hemostasis and release cytokines and growth factors. These chemoattractants, including vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and fibroblast growth factor (FGF), as well as cytokines, promote the migration of inflammatory cells to the wound. After approximately 24 to 48 hours, vasodilation occurs, allowing for inflammatory cells such as neutrophils, monocytes, macrophages, and lymphocytes to arrive at the injured tissue and perform a host of different functions. Neutrophils are the first of the inflammatory cells to arrive, peaking at 24 hours. They phagocytize bacteria, clear microbial and other cellular debris. Also, polymorphonuclear leukocytes (PMNs) release reactive oxygen species that potentiate this.  
The next major step in wound healing involves the accumulation of macrophages, usually around 48 to 72 hours. Macrophages help initiate the proliferation phase of the WHP. These cells also perform a variety of diverse functions, including promoting the inflammatory healing process through the release of cytokines, clearance of cellular debris, and attracting blast cells to the area of the wounding. T-lymphocytes also play a critical but still poorly understood role, as their absence in the wound or delayed arrival has been associated with WHP impairment. As the proliferation phase gives way to remodeling, fibroblasts lay down the extracellular matrix (ECM) and allow for re-epithelialization of the wound. Fibroblasts produce components of the ECM, including collagen-glycosaminoglycan scaffolds and proteoglycans. Furthermore, endothelial cells promote angiogenesis and formation of a new capillary bed to allow for continued remodeling . Myofibroblasts promote wound contracture via actin filaments. Over time, the wound will regain up to 70% to 80% of its original tensile strength.  
Issues of Concern  
Factors Affecting Wound Healing  
The WHP is very complex and involves high levels of coordination between multiple tissues and cell types. Consequently, impairment in the process can occur at any step along the sequence that leads to process completion. Many known factors can affect or modulate wound healing. In the subsequent sections, we will discuss major modulators (both positive and negative) of the WHP, including a summary of some of the methods and techniques devised to promote wound healing.  
  
**Diabetes**There is no doubt that diabetes plays a detrimental role in wound healing. It does so by affecting the WHP at multiple steps. Wound hypoxia, through a combination of impaired angiogenesis, inadequate tissue perfusion, and pressure-related ischemia, is a major driver of chronic diabetic wounds [10]. Ischemia can lead to prolonged inflammation, which increases the levels of oxygen radicals, leading to further tissue injury. Elevated levels of matrix metalloproteases in chronic diabetic wounds, sometimes up to [50-100](tel:50-100) times higher than acute wounds, cause tissue destruction and prevent normal repair processes from taking place. Furthermore, diabetes is associated with impaired immunity, with critical defects occurring at multiple points within the immune system cascade of the WHP. For example, neutrophils show impaired chemotaxis and phagocytosis. As a result, diabetic wounds are prone to chronic infection due to inadequate bacterial clearance. To further complicate matters, these wounds have defects in angiogenesis and neovascularization. Normally, wound hypoxia stimulates mobilization of endothelial progenitor cells via vascular endothelial growth factor (VEGF). In diabetic wounds, there are aberrant levels of VEGF and other angiogenic factors such as angiopoietin-1 and angiopoietin-2 that lead to dysangiogenesis. Diabetic neuropathy may also play a role in poor wound healing. Lower levels of neuropeptides, as well as reduced leukocyte infiltration as a result of sensory denervation, have been shown to impair wound healing. When combined, all these diverse factors play a role in the formation and propagation of chronic, debilitating wounds in patients with diabetes.  
  
**TobaccoAbuse**  
Cigarette smoking leads to numerous adverse health consequences, including various types of cancer, primary lung disease, and cardiovascular disease, among others. However, in addition to those, smoking has severe ill-effects on the WHP. This occurs through multiple pathways, but most have the common theme of inducing wound ischemia. For example, nicotine in smoke acts as a vasoconstrictor. Also, tobacco use stimulates the release of catecholamines such as epinephrine, leading to further reductions in tissue blood flow and hypoxia. Relative wound ischemia can also result from the development of chronic obstructive pulmonary disease, which can lead to the permanent lowering of oxygen tension in the blood. Furthermore, nicotine reduces fibrinolysis, causing blood to become more viscous, leading to decreased tissue/regional blood flow. Carbon monoxide (CO) in cigarette smoke binds to hemoglobin with [200](tel:200) times greater affinity than oxygen, so even small amounts of carbon monoxide can profoundly reduce the oxygen carrying capacity of hemoglobin. CO binding to hemoglobin will cause a leftward shift of the oxyhemoglobin dissociation curve, leading to less oxygen unloading at the tissue level. In addition to the induction of ischemia, smoking leads to immunopathy of the wound via impaired PMN migration into the wound. Fibroblast migration and proliferation are also hindered, leading to decreased production of ECM and ultimately weaker scar formation. Not surprisingly, patients who stop smoking show improvement in wound healing.  
  
**Malnutrition**The nutritional needs of the healing wound are very complex. Wounds require a myriad of different micro and macronutrients to heal properly. Regarding macronutrients, proteins are the key building blocks of our tissues, highlighting the importance of ample supply of protein/amino acid-rich nutrition to ensure adequate wound healing. Among amino acids of importance to the WHP, arginine, and glutamine play a critical in the overall process. Arginine improves immune function, supports collagen deposition (as a precursor to proline), and plays a role in neovascularization. Arginine supplementation also has a positive effect on wound healing. Glutamine is a critical energy source in proliferating cells (e.g., connective tissue including immune and progenitor blast cells). This amino acid is thought to improve the overall wound strength by increasing levels of mature collagen. The 2 other major macronutrients, fatty acids and carbohydrates, are also critical to wound healing. Carbohydrates, primarily glucose, act as the primary fuel for cells as it becomes broken down to form adenosine triphosphate (ATP). Polyunsaturated fatty acids, such as omega-3 and omega-6 fatty acids, both of which are essential fatty acids, may enhance the WHP by having an overall positive effect on host immune function .  
  
Several micronutrients are worth mentioning because they play a particularly important role in wound healing. These include ascorbic acid, or vitamin C, vitamin A, vitamin E, as well as magnesium, zinc, and iron. Vitamin C supports the hydroxylation of proline to hydroxyproline, which is essential for proper collagen formation. Vitamin A similarly supports collagen formation, as well as immune modulation, and decreased metalloprotease ECM degradation. As an antioxidant, vitamin E helps protect against oxidative tissue destruction, as well as may decrease excess scar formation. Magnesium is a cofactor in enzymes involved in collagen synthesis. Zinc, on the other hand, is a cofactor for DNA and RNA polymerase, playing a vital role in cell division. Finally, iron deficiency has been shown to result in impaired collagen synthesis. Further discussion of the most critical among the above micronutrients is provided at the end of this manuscript.  
  
**Obesity**Obesity is a significant factor in surgical wound healing. Abdominal obesity is correlated with oxidative stress, a phenomenon associated with deficiency of adiponectin (e.g., adipose-derived cytokine with antioxidant and anti-inflammatory properties). Adiponectin-deficient state leads to impaired perfusion and reepithelialization of the wound. Moreover, hypovolemia combined with relative hypoperfusion and reduction in oxygen delivery lead to further tissue injury. Consequently, wound complications, including surgical site infections and fat necrosis are more prevalent in obese patients. Various combinations of the same factors may be associated with impaired secondary healing following primary wound-related morbidity .  
  
Pressure ulcers are more likely to develop in obese patients through pressure-related ischemia and hypovascularity, as well as decreased mobility. Contact between the skin and various hospital surfaces (e.g., stretchers, operating room tables) may result in friction, leading to ulceration and wound formation. Systemic effects of obesity, such as hypertension, hyperglycemia, and upregulation of the stress hormones in response to the physiologic burden of surgery and acute illness, all work to impair further wound healing. Additional factors involved in this complex process include blunting of the immune and inflammatory responses. Interestingly, these ill-effects of obesity are largely reversible through weight loss .  
  
**Stress**  
Stress has been demonstrated to be a major contributor to a broad range of health conditions and illnesses, including cardiovascular disease, cancer, and obesity. Stress states lead to upregulation of stress hormones via the hypothalamic-pituitary axis and the release of adrenocortical hormones. Resultant changes include elevated levels of cortisol, glucocorticoids, and catecholamines. Cortisol works to blunt the immune response by blocking the production of important cytokines such as IL-1beta, IL-6, and TNF-alpha. The impairment of immune response ultimately leads to deficient wound healing.  
Vitamins, Trace Elements, and Growth Factors  
  
Although a detailed discussion of the role of vitamins and trace elements in the WHP is well beyond the scope of the current review/synopsis of this topic, the authors feel strongly that a brief overview of this topic is fully warranted. It has long been known that Vitamin A may have beneficial effects on wound healing in the setting of previous systemic exposure to corticosteroids. More specifically, Vitamin A has been shown to overcome the inhibitory effects of cortisone (and related corticosteroids) on the rate of gain in tensile strength of the wound. This may be especially pronounced in early stages of the WHP. At the same time, Vitamin A by itself does not seem to be a significant modulator of the WHP, suggesting that its beneficial action in the setting of prior corticosteroid use is related to the interaction(s) specific to corticosteroid-specific pathway(s).  
Vitamin C and zinc have both been found to improve wound healing characteristics, although clinical adoption and implementation of this therapeutic combination is less than universal. Mechanistically, vitamin C has several favorable effects on the WHP. First, it is a powerful antioxidant and free radical scavenger. Second, it is important to systemic immunity, and along with Zinc helps boost the immune system when taken in the postoperative period. Together with Arginine and Zinc, Vitamin C is important for collagen synthesis. The evidence is strongest for supplementing vitamin C and zinc during the immediate postoperative period.  
Among other interesting (and important) developments in wound care, there is evidence that vitamin-D supplementation may help positively modulate impaired wound healing, although further research toward mechanistic understanding is required in this area. More specifically, the role of vitamin D in the WHP may be indirect, through beneficial effects on closely related physiological processes, such asglucosehomeostasis.  
Finally, another vast topic area that is worth mentioning (but too extensive to fully discuss in this review) is the use of growth factors in the modulation of the WHP.  It has been demonstrated that delivery of various specific growth factors (e.g., basic fibroblast growth factor, epidermal growth factor, keratinocyte growth factor) may produce beneficial effects on chronic wounds, with many experimental and clinical applications highlighting promise in the area of diabetic wound care. Further research is required to better define mechanisms of action, potential side effects, and the overall risk-benefit of human application of such therapies.  
  
**MaggotDebridement**While considered by many as archaic, maggot debridement therapy (MDT) has been shown unequivocally to be of benefit in wound healing. MDT is based on the observation that fly larvae only debride dead, devitalized, and necrotic tissue. Healthy, viable tissue is not threatened during the MDT, making this therapy uniquely suited for debridement of devitalized tissues with truly surgical precision. In fact, MDT is considered a form of "biosurgery." While feeding on non-viable tissue, maggots secrete proteolytic enzymes that liquefy necrotic tissue within the wound. This liquefied material is then ingested, resulting in effective debridement of the tissue of interest. It has been shown that MDT can help debride large wounds in as little as 72 hours, resulting in a viable granulation bed that is suitable for conventional wound management. In addition to chemical debridement, larval secretions are also characterized by significant antimicrobial activity, active against a wide range of pathogenic (and often antibiotic-resistant) bacteria, mostly gram-positive species. Maggots work best on moist environments with sufficient oxygen supply. They are approved for use in non-healing necrotic skin and soft tissue wounds, pressure and venous stasis ulcers, neuropathic foot ulcers, and non-healing traumatic or surgical wounds [50]. Most recent developments in this area include the introduction of transgenic maggots that secrete human growth factors in their saliva. Clinical applications of this therapy are continually expanding. Of interest, application of MDT can be accomplished through direct exposure of the maggots to the wound bed (using a specialized "housing") or through indirect exposure (using larvae contained within a sealed, semi-permeable bag).  
  
**HyperbaricOxygen**  
Hyperbaric oxygen therapy (HBOT) is another treatment modality that has been around for quite some time, but only recently saw a resurgence in interest due to promising effects on the WHP, especially in the setting of chronic and complicated wounds. Chronic wounds, often seen as a consequence of diabetes, arterial or venous disease, are increasingly common and result in significant impact on the affected patients, their caretakers, and the healthcare system in general. The beneficial action of HBOT on wound healing is predicated on the increased supply of oxygen to wounds that are refractory to other, more conventional treatment approaches. In practice, HBOT involves the patient being temporarily enclosed in a special chamber that in many ways approximates conditions used for deep sea divers and involves gradual "dive" followed by a pre-defined time interval at a certain "oxygen pressure level," and subsequent gradual "resurfacing" process. While in the chamber, the patient is exposed to markedly elevated concentrations of pure oxygen, leading to elevation of systemic and tissue oxygen levels. Effectively, the patient is receiving [100](tel:100)% oxygen at 2 to 3 times the atmospheric pressure at the sea level (see below regarding potential dangers of this therapy).  
It has been demonstrated that HBOT is effective in improving the course of chronic diabetes-related extremity wounds, potentially reducing the need for major (but not necessarily minor) amputations. Available evidence suggests beneficial effects of HBOT on wounds are usually apparent within approximately 6 weeks of therapy, but long-term beneficial effects continue to be questionable. Another area where HBOT can be beneficial is the management of necrotizing soft tissue infections (e.g., necrotizing fasciitis), with evidence showing potential mortality benefit, lower amputation rates, and an overall reduction in surgical debridements. Additional difficult-to-treat types of wounds that have been speculated to benefit from HBOT are the chronic pressure ulcers (due to its inherently "ischemic" nature) and venous ulcers; however, there is no solid evidence to support HBOT for either of these indications at this time.   
Despite its potential benefits, there are significant potential dangers of HBOT, including the risk of oxygen fire/explosion, the risk of pneumothorax, as well as the possibility of damage to eardrums during repeated "dives." Consequently, appropriate provider is credentialing and patient/staff safety procedures must be strictly followed to reduce any undue risks of harm.  
Enhancing Healthcare Team Outcomes  
The best management of wounds is taken care of by an interprofessional team of a nurse specializing wound care and a clinician with significant wound experience. Caring for wounds not only involves regular follow-ups but patient education. A coordinated team approach has been shown to be most effective in wound management.

**3. Examine the role of oxidative stress in the development and progression of impaired wound healing**

Recently oxidative stress has been proposed as the cause of hypertension. An imbalance in superoxide and nitric oxide production may account for reduced vasodilation, which in turn can favor the development of hypertension. In vitro and in human studies support this hypothesis. The supplementation of antioxidants, particularly in the form of fresh fruit and vegetables, reduces blood pressure, supporting a role for free radicals in hypertension.  
  
DASH, Dietary Approaches to Stop HypertensionROS, reactive oxygen speciesRVD, renovascular disease  
It is estimated that 30% of the adult population may have arterial hypertension and that 30–60% of diabetic patients have associated hypertension.  
Hypertension is often associated with metabolic abnormalities such as dyslipidemia, impaired glucose tolerance, insulin resistance, and obesity. This is known as the “metabolic syndrome.” A series of observations has provoked much speculation and interest in the phenomenon of insulin resistance as a common factor underlying the link between obesity, diabetes, and hypertension (3). Epidemiological data linking hyperinsulinemia, obesity, and hypertension seem to be associative rather than causal, but this is inconsistent (4). It has become increasingly evident that the relationship between insulin, insulin resistance, and blood pressure varies according to racial group (5). On the other hand, chronic and marked hyperinsulinism in patients with insulinomas is not associated with elevated blood pressure values (6). Although the causal relationship between insulin and blood pressure is still inconclusive, evidence suggests that a reduced hepatic insulin clearance may contribute to increased insulin levels in hypertension (7, 8). To summarize, current experimental findings linking hyperinsulinemia or insulin resistance to hypertension have been provocative: many inconsistencies remain and causal relationships have not been established. A recent hypothesis pointed out the possible role of oxidative stress as a key player in the pathogenesis of insulin resistance, β-cell dysfunction, and hypertension.  
  
OXIDATIVESTRESS   
Regarding hypertension, endothelial cells play a major role in arterial relaxation. Nitric oxide is the factor released by the endothelium that causes vascular relaxation (10). The half-life of nitric oxide is only a few seconds, since it is rapidly degraded by the oxygen-derived free radical superoxide anion. Superoxide anion is a major determinant of nitric oxide (NO) biosynthesis and bioavailability and can thus modify endothelial function. It can also act as a vasoconstrictor. In addition, nitric oxide synthase (NOS), and in particular the endothelial isoform of NOS (eNOS), is now recognized as an important source of superoxide. The finding that eNOS can generate superoxide rather than NO in response to atherogenic stimuli has led to the concept of “NOS uncoupling,” where the activity of the enzyme for NO production is decreased, in association with an increase in NOS-dependent superoxide production. As a result, eNOS may become a peroxynitrite generator, leading to a dramatic increase in oxidative stress, since peroxynitrite formed by the NO-superoxide reaction has additional detrimental effects on vascular function by oxidation of cellular proteins and lipids.  
  
A decrease in NO bioavailability and an increase in oxidative stress are present in human hypertension. These findings are based, in general, on increased levels of biomarkers of lipid peroxidation and oxidative stress. Decreased antioxidant activity (superoxide dismutase and catalase) and reduced levels of reactive oxygen species (ROS) scavengers (vitamins E and C and glutathione) may also contribute to oxidative stress. Furthermore, l-arginine, a NO precursor that augments endothelium-dependent vasodilation, acutely improves endothelium-dependent flow-mediated dilation of the brachial artery in patients with essential hypertension.  
  
Growing evidence indicates that NADPH-driven generation of ROS and activation of reduction-oxidation (redox)-dependent signaling cascades are critically and centrally involved in the role of Ang II-induced hypertension (21). Ang II elicits its actions via two distinct receptors: the AT1 and Ang II type 2 receptors (AT2). Although the AT2 receptor is usually expressed at low density in adults, it is upregulated in pathological states such as vascular injury, salt depletion, heart failure, or cardiac hypertrophy. Pharmacological studies indicate that there is crosstalk between AT1 and AT2 receptors and stimulation of the AT2 receptor opposes the effect of the AT1. Whereas stimulation of the AT1 receptor leads to cellular growth, angiogenesis, and vasoconstriction, AT2 receptor stimulation causes opposite effects, anti-proliferation, anti-angiogenesis, and vasodilation. Thus, AT1 and AT2 receptors are ideal candidates for maintaining a proper balance between the vasodilator agent NO and ROS. Recent data demonstrate that Ang II, acting through the AT1 receptor, stimulates nonphagocytic NADPH oxidase, causing the accumulation of superoxide, hydrogen peroxide, and peroxynitrite. Thus, in pathological states, the stimulation of the AT1 receptor by increased circulating or tissue levels of Ang II will produce an inflammatory response. In contrast, blockade of the AT1 receptor, which is accompanied by increased circulating Ang II levels, will stimulate the AT2 receptor and oppose the effect of AT1 receptor activation, a mechanism that appears to be involved in the beneficial effects of the angiotensin receptor blockers. These beneficial effects may be exerted at various levels, as Cipollone et al. demonstrated that the AT1 receptor antagonist irbesartan decreases inflammation and inhibits cyclooxygenase (COX) and prostaglandin (PG)E2-dependent synthase (COX-2/mPGES-1) expression in plaque macrophages, and this effect may in turn contribute to plaque stabilization by inhibition of metalloproteinase-induced plaque rupture.  
  
Human studies seem to support a role of oxidative stress in the development of hypertension. In diabetes and obesity, which are commonly associated with hypertension, chronic oxidative stress is present. Conversely, caloric restriction in the obese and fasting in normal subjects leads to a marked reduction in ROS generation and other indexes of oxidative stress. Studies using nonspecific markers of oxidative damage have observed higher superoxide and hydrogen peroxide production in hypertensive subjects, which returned to levels observed for control subjects after blood pressure reduction. A reduction in superoxide dismutase and glutathione peroxidase activity have been observed in newly diagnosed and untreated hypertensive subjects, compared with control subjects, with superoxide dismutase activity being inversely correlated with blood pressure within the hypertensive group, but not the control group. Higher production of hydrogen peroxide has also been observed in treated and untreated hypertensive subjects compared with normotensive subjects, with a significant correlation between hydrogen peroxide levels and systolic blood pressure. In addition, both malignant and nonmalignant hypertensive subjects had higher lipid hydroperoxide production, as measured by the ferrous oxidation–xylenol (FOX) assay, compared with control subjects.

Accordingly, Minuz et al. recently demonstrated that oxidant stress is markedly increased in hypertensive patients with renovascular disease (RVD) compared with either patients with essential hypertension and comparable levels of blood pressure or healthy normotensive subjects and suggested that increased oxidative stress might be related to renal artery stenosis and activation of Ras. These authors found a significant positive correlation between the urinary excretion of 8-iso-prostaglandin F2α (a reliable marker of in vivo lipid peroxidation) and renal vein renin ratio (a highly specific functional test for the detection of renal artery stenosis, renal hypoperfusion, and activation of Ras). Moreover, Minuz et al. found a significant correlation between the reduction in 8-iso-prostaglandin F2α excretion after successful angioplasty in RVD hypertensive patients with baseline Ang II ratio and renal vein renin ratio. All these findings provide additional evidence for a causal link between renin activation and enhanced oxidative stress and may suggest that Ang II is a stimulus for oxidant stress in RVD.

**REFERENCES**

1. Progress in molecular biology and translational science,2015
2. Douglas B. Stairs, ... John P. Lynch, in Progress in Molecular Biology and Translational Science, 2010
3. Singer, A.J. & R.A. Clark ([1999](tel:1999)) New Engl. J. Med. [341](tel:341):[738](tel:738).
4. Liekens, S. et al. ([2001](tel:2001)) Biochem. Pharmacol. 61:[253](tel:253).
5. Khalil, N. ([1999](tel:1999)) Microbes Infect. 1:[1255](tel:1255).
6. Wahl, S.M. (1999) “Transforming growth factor beta.” in Inflammation: Basic Principles and Clinical Correlates, Third Edition, J. Gallin and R. Snyderman, eds., Lippincott-Raven Publishers, Philadelphia, pp. 883-892.
7. Wahl, S.M. et al. (1987) Proc. Natl. Acad. Sci. USA 84:5788.
8. Ashcroft, G.S. et al. (1999) Nat. Cell Biol. 1:260.
9. McCartney-Francis, N.L. & S.M. Wahl (2001) “TGF-beta and macrophages in the rise and fall of inflammation.” in TGF-beta and Related Cytokines in Inflammation, Breit, S.N. and S.M. Wahl, ed., Birkhauser, Basel, pp. 65-90.
10. Heldin, C.H. et al. (2001) “Signal transduction mechanisms for members of the TGF-beta family.” in TGF-beta and Related Cytokines in Inflammation, Breit, S.N. and S.M. Wahl ed., Birkhauser, Basel, pp. 11-40.
11. Braddock, M. (2001) Ann. Med. 33:313.
12. Wahl, S.M. (1994) J. Exp. Med. 180:1587.
13. Chen, W. & S.M. Wahl (1999) Microbes Infect. 1:1367.
14. Sundy, J.S. & B.F. Haynes (2000) Curr. Rheumatol. Rep. 2:402.
15. Gillitzer, R. & M. Goebeler (2001) J. Leukoc. Biol. 69:513.
16. Cacalano, G. et al. (1994) Science 265:682.
17. Morales, J. et al. (1999) Proc. Natl. Acad. Sci. USA 96:14470.
18. Leibovich, S.J. & R. Ross (1975) Am. J. Pathol. 78:71.
19. Clarke, R.A.F. (1996) “Wound repair: overview and general considerations” in The Molecular and Cellular Biology of Wound Repair, Clark, R.A.F. ed., Plenum, New York, pp. 3-50.
20. Huttunen, M. et al. (2000) Exp. Dermatol. 4:258.
21. Hebda, P.A. (1998) J. Invest. Derm. 91:440.
22. Wikner, N.E. et al. (1998) J. Invest. Derm. 91:207.
23. Barrandon, Y. & H. Green (1987) Cell 50:1131.
24. Higashiyama, S. et al. (1991) Science 251:936.
25. Werner, S. et al. (1994) J. Invest. Derm. 103:469.
26. Coffey, Jr., R.J. et al. (1987) Nature 328:817.
27. Werner, S. et al. (1992) Proc. Natl. Acad. Sci. USA 89:6896.
28. Ashcroft, G.S. et al. (2000) Nat. Med. 6:1147.
29. Song, X.Y. et al. (1999) J. Exp. Med. 190:535.
30. Conway, E.M. et al. (2001) Cardiovascul. Res. 49:507.
31. Belperio, J.A. et al. (2000) J. Leukoc. Biol. 68:1.
32. Brown, L.F. et al. (1992) J. Exp. Med. 176:1375.
33. Ferrara, N. (1999) Curr. Top. Microbiol. Immunol. 237:1.
34. Ferrara, N. et al. (1996) Nature 380:439.
35. Shibuya, M. (2001) Int. J. Biochem. Cell Biol. 33:409.
36. Ornitz, D.M. et al. (1996) J. Biol. Chem. 271:15292.
37. Branton, M.H. & J.B. Kopp (1999) Microbes Infect. 1:1349.
38. Niesler, C.U. & M.W.J. Ferguson. (2001) “TGF-beta superfamily cytokines in wound healing” in TGF-beta and Related Cytokines in Inflammation (Breit, S.N. and S.M. Wahl, ed., Birkhauser, Basel, pp. 173-198.
39. Munz, B. et al. (1999) EMBO J. 18:5205.
40. Blessing, M. et al. (1996) J. Cell Biol. 135:227.
41. Ross, R. et al. (1990) Philos. Trans. R. Soc. Lond. B. Biol. Sci. 327:155.
42. Claesson-Welsh, L. (1996) Int. J. Biochem. Cell Biol. 28:373.
43. Circolo, A. et al. (1991) J. Biol. Chem. 266:12283.
44. Laiho, M. et al. (1987) J. Biol. Chem. 262:17467.
45. Powers, C.J. et al. (2000) Endocr. Relat. Cancer 7:165.
46. Payne, W.G. et al. (2001) Am. J. Surg. 181:81.
47. Ortega, S. et al. (1998) Proc. Natl. Acad. Sci. USA 95:5672.
48. Andresen, J.L. & N. Ehlers (1998) Curr. Eye Res. 17:79.
49. Gallucci, R.M. et al. (2000) FASEB J. 14:2525.
50. Grinnell, F. (1994) J. Cell Biol. 124:401.
51. Birkedal-Hansen, H. (1995) Curr. Opin. Cell Biol. 7:728.
52. Wahl, S.M. et al. (1993) J. Exp. Med. 177:225.
53. Border, W.A. & N.A. Noble (1998) Kidney Int. 54:1390.
54. Nakao, A. et al. (1999) J. Clin. Invest. 104:5.
55. Song, X. et al. (1999) J. Immunol. 163:4020.
56. Ghosh, A.K. et al. (2001) J. Biol. Chem. 276(14):11041.
57. Duncan, M.R. et al. (1985) J. Exp. Med. 162(2):516.
58. Akdis, C.A. (2001) Immunology 103(2):131.
59. Lumbers M. Challenges in wound care for community nurses: a case review. Br J Community Nurs. 2019 Mar 01;24(Sup3):S25-S27. [PubMed]
60. Everett E, Mathioudakis N. Update on management of diabetic foot ulcers. Ann. N. Y. Acad. Sci. 2018 Jan;1411(1):153-165. [PMC free article] [PubMed]
61. Sen CK. Human Wounds and Its Burden: An Updated Compendium of Estimates. Adv Wound Care (New Rochelle). 2019 Feb 01;8(2):39-48. [PMC free article] [PubMed]
62. Boyko TV, Longaker MT, Yang GP. Laboratory Models for the Study of Normal and Pathologic Wound Healing. Plast. Reconstr. Surg. 2017 Mar;139(3):654-662. [PubMed]
63. Nuutila K, Katayama S, Vuola J, Kankuri E. Human Wound-Healing Research: Issues and Perspectives for Studies Using Wide-Scale Analytic Platforms. Adv Wound Care (New Rochelle). 2014 Mar 01;3(3):264-271. [PMC free article] [PubMed]
64. Heughan C, Hunt TK. Some aspects of wound healing research: a review. Can J Surg. 1975 Mar;18(2):118-26. [PubMed]
65. Hunt TK. Recent advances in wound healing. Surg Annu. 1970;2(0):1-9. [PubMed]
66. Rodrigues M, Kosaric N, Bonham CA, Gurtner GC. Wound Healing: A Cellular Perspective. Physiol. Rev. 2019 Jan 01;99(1):665-706. [PMC free article] [PubMed]
67. Avishai E, Yeghiazaryan K, Golubnitschaja O. Impaired wound healing: facts and hypotheses for multi-professional considerations in predictive, preventive and personalised medicine. EPMA J. 2017 Mar;8(1):23-33. [PMC free article] [PubMed]
68. Davis FM, Kimball A, Boniakowski A, Gallagher K. Dysfunctional Wound Healing in Diabetic Foot Ulcers: New Crossroads. Curr. Diab. Rep. 2018 Jan 23;18(1):2. [PubMed]
69. Lim HS, Lip GY, Blann AD. Angiopoietin-1 and angiopoietin-2 in diabetes mellitus: relationship to VEGF, glycaemic control, endothelial damage/dysfunction and atherosclerosis. Atherosclerosis. 2005 May;180(1):113-8. [PubMed]
70. Goniewicz ML, Smith DM, Edwards KC, Blount BC, Caldwell KL, Feng J, Wang L, Christensen C, Ambrose B, Borek N, van Bemmel D, Konkel K, Erives G, Stanton CA, Lambert E, Kimmel HL, Hatsukami D, Hecht SS, Niaura RS, Travers M, Lawrence C, Hyland AJ. Comparison of Nicotine and Toxicant Exposure in Users of Electronic Cigarettes and Combustible Cigarettes. JAMA Netw Open. 2018 Dec 07;1(8):e185937. [PMC free article] [PubMed]
71. McDaniel JC, Browning KK. Smoking, chronic wound healing, and implications for evidence-based practice. J Wound Ostomy Continence Nurs. 2014 Sep-Oct;41(5):415-23; quiz E1-2. [PMC free article] [PubMed]
72. Garg A. Pathophysiology of tobacco use and wound healing. Dent Implantol Update. 2010 Jan;21(1):1-4. [PubMed]
73. Balaji SM. Tobacco smoking and surgical healing of oral tissues: a review. Indian J Dent Res. 2008 Oct-Dec;19(4):344-8. [PubMed]
74. Lassig AAD, Bechtold JE, Lindgren BR, Pisansky A, Itabiyi A, Yueh B, Joseph AM. Tobacco exposure and wound healing in head and neck surgical wounds. Laryngoscope. 2018 Mar;128(3):618-625. [PMC free article] [PubMed]
75. Whiteford L. Nicotine, CO and HCN: the detrimental effects of smoking on wound healing. Br J Community Nurs. 2003 Dec;8(12):S22-6. [PubMed]
76. Campos AC, Groth AK, Branco AB. Assessment and nutritional aspects of wound healing. Curr Opin Clin Nutr Metab Care. 2008 May;11(3):281-8. [PubMed]
77. Saghaleini SH, Dehghan K, Shadvar K, Sanaie S, Mahmoodpoor A, Ostadi Z. Pressure Ulcer and Nutrition. Indian J Crit Care Med. 2018 Apr;22(4):283-289. [PMC free article] [PubMed]
78. Barchitta M, Maugeri A, Favara G, Magnano San Lio R, Evola G, Agodi A, Basile G. Nutrition and Wound Healing: An Overview Focusing on the Beneficial Effects of Curcumin. Int J Mol Sci. 2019 Mar 05;20(5) [PMC free article] [PubMed]
79. Chen LR, Yang BS, Chang CN, Yu CM, Chen KH. Additional Vitamin and Mineral Support for Patients with Severe Burns: A Nationwide Experience from a Catastrophic Color-Dust Explosion Event in Taiwan. Nutrients. 2018 Nov 16;10(11) [PMC free article] [PubMed]
80. Molnar JA, Vlad LG, Gumus T. Nutrition and Chronic Wounds: Improving Clinical Outcomes. Plast. Reconstr. Surg. 2016 Sep;138(3 Suppl):71S-81S. [PubMed]
81. Houdek MT, Griffin AM, Ferguson PC, Wunder JS. Morbid Obesity Increases the Risk of Postoperative Wound Complications, Infection, and Repeat Surgical Procedures Following Upper Extremity Limb Salvage Surgery for Soft Tissue Sarcoma. Hand (N Y). 2019 Jan;14(1):114-120. [PMC free article] [PubMed]
82. Pierpont YN, Dinh TP, Salas RE, Johnson EL, Wright TG, Robson MC, Payne WG. Obesity and surgical wound healing: a current review. ISRN Obes. 2014;2014:638936. [PMC free article] [PubMed]
83. Broadbent E, Kahokehr A, Booth RJ, Thomas J, Windsor JA, Buchanan CM, Wheeler BR, Sammour T, Hill AG. A brief relaxation intervention reduces stress and improves surgical wound healing response: a randomised trial. Brain Behav. Immun. 2012 Feb;26(2):212-7. [PubMed]
84. Broadbent E, Petrie KJ, Alley PG, Booth RJ. Psychological stress impairs early wound repair following surgery. Psychosom Med. 2003 Sep-Oct;65(5):865-9. [PubMed]
85. Kantak NA, Mistry R, Varon DE, Halvorson EG. Negative Pressure Wound Therapy for Burns. Clin Plast Surg. 2017 Jul;44(3):671-677. [PubMed]
86. de Jesus LE, Martins AB, Oliveira PB, Gomes F, Leve T, Dekermacher S. Negative pressure wound therapy in pediatric surgery: How and when to use. J. Pediatr. Surg. 2018 Apr;53(4):585-591. [PubMed]
87. Garcia-Ruano A, Deleyto E, Garcia-Fernandez S. VAC-instillation therapy in abdominal mesh exposure: a novel indication. J. Surg. Res. 2016 Dec;206(2):292-297. [PubMed]
88. Barbera F, Lorenzetti F, Marsili R, Lisa A, Guido G, Pantaloni M. The Impact of Preoperative Negative-Pressure Wound Therapy on Pectoralis Major Muscle Flap Reconstruction for Deep Sternal Wound Infections. Ann Plast Surg. 2019 Aug;83(2):195-200. [PubMed]