



Biofilm-Associated Infections in Diabetes: Microbial Virulence, Oxidative Stress, and Impaired Wound Healing

Ndu Ijeoma Festa and Nnodim Johnkennedy

¹Faculty of Medical Laboratory Science, Department of Medical Microbiology, Parasitology and Immunology. Federal University Otuoke, Bayelsa State, Nigeria.

²Department of Medical Laboratory Science, Imo State University, Owerri, Nigeria.

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*Corresponding Author: **Ndu Ijeoma Festa**

Faculty of Medical Laboratory Science, Department of Medical Microbiology, Parasitology and Immunology. Federal University Otuoke, Bayelsa State, Nigeria.

Abstract

Diabetes mellitus increases the risk for chronic and recurrent infections, including diabetic foot infections and nonhealing wounds. Biofilms are complex microbial communities encased in extracellular polymeric substances that they manufacture themselves, and that favour infection persistence, antimicrobial tolerance, immunological evasion, and delayed tissue repair. The diabetic wound environment, which favours biofilm formation, is characterised by hyperglycaemia, poor peripheral circulation, neuropathy, immunological dysfunction and protracted inflammation. Important microbial infections include Staphylococcus aureus, Pseudomonas aeruginosa, enterococci and a number of Gram-negative bacilli. Polymicrobial communities are sometimes encountered. Microbial virulence elements comprising adhesins, toxins, quorum-sensing systems, extracellular enzymes and matrix components linked with biofilm formation allow colonisation and tissue injury. Simultaneously, oxidative stress, mitochondrial dysfunction, advanced glycation end-product production and poor antioxidant defences generated by hyperglycaemia impede cellular signalling, angiogenesis, collagen deposition and epithelial regeneration. Microbial biofilms interacting with oxidative stress produce a self-perpetuating inflammatory milieu which hinders normal wound progression. This study discusses the microbiological mechanisms involved in biofilm infections in diabetes, the biochemical pathways linking oxidative stress and impaired wound healing and the clinical consequences in terms of diagnosis and management. It stresses the necessity of appropriate microbiological assessment, glycaemic control, wound debridement, pressure off-loading, vascular assessment and antimicrobial stewardship. Novel treatment techniques with potential benefits include antibiofilm agents, targeted medication delivery, quorum-sensing inhibition, and molecular diagnostics, however these require further clinical confirmation.

Keywords: Diabetes mellitus; biofilm; diabetic foot ulcer; microbiological virulence; oxidative stress; chronic inflammation; wound healing; antimicrobial resistance.

Introduction

Diabetes mellitus is a chronic metabolic condition with hyperglycemia, either due to a defect in insulin secretion, insulin action or both. In addition to the metabolic effects, diabetes causes profound changes in immunological function, vascular integrity, peripheral nerve function and tissue repair. These anomalies enhance the risk of skin and soft tissue infections and contribute to the development of chronic diabetic wounds, notably foot ulcers. [1]

Diabetic foot ulcers are an important source of morbidity, hospitalisation and lower-extremity amputation. These lesions are frequently associated with peripheral neuropathy, peripheral artery disease, recurrent mechanical stress, and poor tissue regeneration. Once the protective skin barrier is breached, bacteria can colonise the wound and under favourable conditions develop biofilms that encourage persistent infection. [2]

Biofilm is a population of microorganisms adhered to a biological or non-biological surface and embedded in a matrix of extracellular polymeric substances (EPS) made up of polysaccharides, proteins, extracellular DNA and other biomolecules. Physiological properties of biofilm-associated bacteria are markedly different from free living planktonic cells. These changes can lead to increased tolerance to antimicrobial drugs, reduced vulnerability to host immunological responses and promote persistent infection. [3]

Biofilm persistence in diabetic wounds mixes with metabolic inefficiency and oxidative stress to create a pathological state where inflammation persists without efficient tissue healing. Reactive oxygen species are a crucial component of normal antimicrobial defence and wound signalling. However, excessive or prolonged synthesis of reactive oxygen species can harm host tissues and hinder cellular regeneration [4]. Therefore, understanding the association between microbial virulence, oxidative stress, and poor wound healing is crucial to develop efficient ways to prevent and treat biofilm-associated infections in diabetic persons.

Biofilm Formation and Sustenance in Diabetic Wounds

Biofilm generation is one of the key mechanisms that leads to microbial persistence and delayed healing in diabetic wounds. The process usually includes initial microbial adhesion, microcolony creation, extracellular matrix production, maturation, and eventual dispersal. The stages are controlled by the microbial type, nutritional availability, wound wetness, oxygen tension, tissue injury and interactions between bacteria and host cells. Poor circulation, high blood sugar, nerve damage and a weakened immune system might create a good environment for microbes to colonise and cause persistent infection in diabetes. [5]

The first step of biofilm formation is the adhesion of microorganisms to exposed extracellular matrix proteins, damaged tissues, necrotic material and wound surfaces. Bacterial adhesins mediate adhesion and subsequent colonisation. Surface proteins of *Staphylococcus aureus* mediate adherence to host tissues and proteins. *Pseudomonas aeruginosa* utilises flagella, pili, and other surface features in attachment and early biofilm formation. Diabetic wounds commonly have devitalised tissue, increased exudate and altered extracellular matrix components that can support persistence of microbes. Also, recurrent tissue injury, poor perfusion and delayed wound closure increase the exposure of sensitive tissues to bacteria, which makes biofilm creation more likely. [6]

Attached microbial cells secrete an extracellular polymeric substance (EPS) matrix that provides structural stability and allows interactions with the forming biofilm. This matrix includes polysaccharides, proteins, extracellular DNA, lipids and host generated compounds. It enhances cellular adhesion and cohesiveness, alters the local chemical environment and may impair the efficacy of some antimicrobial medicines. However, limited drug penetration is not the main factor for antimicrobial tolerance in biofilms. Other important factors are slow microbial growth, decreased metabolic activity, stress-response systems, persister cells and gradients of oxygen and nutrients. Biofilm-associated antimicrobial tolerance is different from hereditary antimicrobial resistance, yet biofilms can contribute to persistence and selection of resistant organisms. [7]

Older biofilms have heterogenous microbial communities due to differences in oxygen availability, nutrition supply, pH and waste accumulation. Some cells are metabolically active and some are in slow-growing or dormant phases, which can allow them to withstand antimicrobial treatment and potentially re-establish the wound. Microbial cells or aggregates are released from the biofilm during dispersal and can be disseminated to surrounding tissue or other areas of the wound. Thus, repeated rounds of attachment, maturation and dissemination can maintain infection, even in the face of temporary improvement of superficial wound symptoms. [8]

Diabetic wound biofilms are generally multi-species bacterial communities, and may include fungus. Microbial interactions can be cooperative, competitive or neutral and depend on the species involved and the wound environment. Some organisms can change the oxygen levels locally, create protective extracellular chemicals, or affect the availability of nutrients and antibacterial action. Such interactions complicate treatment since the behaviour of microbial communities may differ from that of individual pathogens investigated in isolation. The presence of several organisms, however, does not always imply that each organism is playing a role in a clinically important infection. Therefore, proper clinical assessment and microbiological interpretation is crucial to direct efficient management. [9]

Major microbial pathogens and how they cause disease

The microbiological makeup of diabetic wound infections differs according to the chronicity and severity of the lesion, past antibiotic exposure, geographic location and local healthcare practices. Commonly implicated species are *S. aureus*, beta-haemolytic streptococci, *P. aeruginosa*, enterococci and members of the Enterobacterales. Anaerobic microbes may also be involved, especially in severe necrotic or ischaemic wounds.

Staphylococcus aureus is a major cause of skin and soft tissue infections. Its pathogenicity repertoire comprises of adhesins, cytotoxins, extracellular enzymes, immune-evasion factors and biofilm-associated proteins. These variables increase attachment to the tissue, disturbance of host defences and persistence.

The bacterium is able to create biofilms on injured tissue and on implanted items. Biofilm-associated growth may lower resistance to antimicrobials and cause chronic inflammation. Methicillin-resistant *S. aureus* can further complicate therapy when suitable antimicrobial agents are limited.

Pseudomonas aeruginosa is an opportunistic gram-negative bacterium with great metabolic plasticity and potential for biofilm formation. It creates extracellular polysaccharides such as alginate under particular strains and circumstances, and utilises quorum-sensing mechanisms to coordinate aspects of microbial behavior. [10]

Virulence factors include elastases, proteases, rhamnolipids and other released products that can damage host tissues or interfere with immune responses. The organism can also create pyocyanin, a redox-active pigment which can perturb cellular redox equilibrium and contribute to oxidative damage.

Intrinsic and acquired resistance mechanisms, and biofilm-associated tolerance may complicate therapy. However, the clinical relevance of *P. aeruginosa* in each chronic diabetic wound should not be taken for granted and should be determined by adequate examination.

Enterococci can survive adverse environmental conditions and participate in polymicrobial infection. Moderate to severe infections may include Enterobacterales, including *Escherichia coli*, *Klebsiella* species, and *Proteus* species, especially when there has been past drug exposure or healthcare contact. [11]

Anaerobes may be involved in infections of necrotic tissue with inadequate perfusion. *Candida* spp. may be isolated from some chronic wounds but their presence alone does not necessarily imply invasive fungal illness.

Antimicrobial-resistant organisms complicate treatment and highlight the need for acquiring adequate specimens and using susceptibility results to guide therapy.

Quorum sensing is a cell-density-dependent communication method that enables bacteria to coordinate the expression of chosen genes. In organisms such as *P. aeruginosa* quorum-sensing networks control aspects of pathogenicity, extracellular enzyme production, biofilm growth and community behaviour.

Quorum sensing interference has been gained interest as a potential antibiofilm method since it may diminish specific virulence functions without outright killing the microorganisms. However, quorum sensing inhibition is still a developing method and not a substitute for well-established infection management. [12]

Diabetes and Oxidative Stress

Oxidative stress happens when the formation of reactive oxygen species (ROS) is higher than the antioxidant systems' capacity to control these species and repair the oxidative damage. Reactive substances include the superoxide anion, hydrogen peroxide and extremely reactive derivatives such as hydroxyl radicals.

Not all ROS are bad. They are involved in intracellular signaling, immunological defence, angiogenesis, and wound repair at regulated concentrations. However, continued overproduction of these can cause harm to proteins, lipids, nucleic acids and cell membranes. [13]

Chronic hyperglycaemia changes intracellular glucose metabolism and can increase mitochondrial and non-mitochondrial ROS generation. Oxidative damage results from excessive substrate availability, mitochondrial malfunction and changes in cellular redox equilibrium.

Hyperglycaemia also stimulates a number of interlinked metabolic processes, including increased production of advanced glycation end products, protein kinase C signaling and the polyol pathway. These mechanisms can compromise endothelial function, interfere with cellular communication and upregulate inflammatory responses [14]

Advanced glycation end products (AGEs) are generated by non-enzymatic interactions of reducing sugars or reactive carbonyl chemicals with proteins, lipids or nucleic acids. Accumulation of these molecules can alter the extracellular matrix proteins and affect the normal tissue characteristics.

AGEs can also bind to the receptor for advanced glycation end products (RAGE) which induces inflammatory signals and increases ROS production. These effects may interfere with endothelial function, collagen organization, fibroblast activity, and normal tissue regeneration. [15]

Thus, AGE buildup in chronic diabetes wounds may foster an environment where inflammatory damage persists and extracellular matrix remodelling becomes less efficient.

The antioxidant defence system of the body comprises of enzymatic components like superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidases and non-enzymatic antioxidants like glutathione.

SOD catalyses the conversion of superoxide anion to hydrogen peroxide. Catalase and glutathione peroxidases are involved in the elimination of hydrogen peroxide. It is also involved in detoxification and intracellular redox control. In diabetes, chronic oxidative stress, metabolic dysfunction and tissue-specific responses may change the activity of antioxidant enzymes and availability of glutathione. These alterations differ in kind and extent depending on illness severity, tissue type, infection status and date of testing. So, the oxidative stress in diabetic wounds should not be only ascribed to the decreased activity of antioxidant enzymes, but the overproduction of ROS, compromised antioxidant capacity, and insufficient resolution of inflammation may be concurrent.

ROS interact with inflammatory pathways, like nuclear factor kappa B (NF- κ B), and may induce the development of inflammatory mediators. Continued activation of these pathways can lead to increased tissue-damaging enzymes and prolong the inflammatory phase of wound healing.

Neutrophils and macrophages create ROS as part of their antimicrobial defence. However, overproduction or unregulated production can damage adjacent host tissue. This leads to a contradiction in chronic wounds where antimicrobial defence is active yet effective tissue healing is impaired. [16]

Interaction With Biofilm and Oxidative Stress

Biofilm-associated infections and oxidative stress are related processes, not distinct clinical occurrences. Biofilms contribute to microbial survival and promote long-lasting host inflammatory responses, and the diabetes metabolic milieu negatively affects tissue repair and changes immunological function.

Microbial compounds can activate pattern-recognition receptors on keratinocytes, macrophages, neutrophils and endothelial cells. This triggers cytokines, attracts leukocytes and signals for inflammation. These responses are needed to manage infection but prolonged activation may promote oxidative damage and breakdown of extracellular matrix. Biofilm-associated bacteria can also resist immune attack by matrix protection, changing states of growth and immune-evasion pathways. Poor microbial clearance leading to prolonged exposure to microbial antigens and inflammatory stimuli.

At the same time, the wound's capacity to recover tissue integrity is compromised by hyperglycaemia, compromised perfusion and altered cellular metabolism. Further impairment of oxygen supply occurs with ischaemia and inflammatory ROS can damage cellular membranes and components of the extracellular matrix.

This interaction creates a self-reinforcing pathological cycle: microbial persistence drives inflammation, chronic inflammation drives increased oxidative and proteolytic damage, tissue injury creates opportunities for microbial persistence, and metabolic dysfunction constrains effective wound repair.

But the relationship is complicated. Healing requires some inflammation and ROS can contribute to microbial death. The pathogenic problem is not the total removal of ROS or immunological activity, but the excessive, persistent, or spatially dysregulated inflammatory response [17]

Impaired healing in diabetes: mechanisms

Normal wound healing follows overlapping phases of haemostasis, inflammation, proliferation and tissue remodelling. Successful healing involves the coordinated interactions of immune cells, keratinocytes, fibroblasts, endothelial cells, platelets, extracellular matrix components and growth factors.

Diabetes impairs several of these systems

Typically, acute wounds go to resolution of inflammation after control of microbial contamination and injured tissue. Persistent infection, metabolic problems and dysregulated immune signalling may prolong inflammatory activity in diabetic wounds.

Neutrophil-derived proteases and matrix metalloproteinases in excess can destroy extracellular matrix proteins and growth factors. This diminishes the pool of structural and signalling molecules essential for tissue healing. Macrophage dysfunction may also hinder the transition from mostly inflammatory to reparative functions. The end outcome is a physiologically active but inefficient wound environment that fails to progress to closure.

Angiogenesis is required to restore blood supply to damaged tissue. Hyperglycaemia, endothelial dysfunction, oxidative stress, and poor growth-factor signalling may limit efficient neovascularisation.

Delivery of oxygen and nutrients may also be limited in peripheral arterial dysfunction. Leukocyte function, tissue metabolism, collagen production, and efficiency of systemic antimicrobial therapy are compromised at the site of infection by insufficient perfusion. The combined consequences of microvascular dysfunction and large-vessel disease are of particular importance in persistent diabetic foot ulcers.

Fibroblasts produce collagen and other extracellular matrix components that offer the structural support for healed tissue. Diabetic wounds may be impaired in fibroblast proliferation and collagen formation due to oxidative stress, inflammatory mediators, and altered growth-factor signalling. At the same time, increased proteolytic activity may increase matrix breakdown. Degradation surpasses synthesis, resulting in insufficient granulation tissue development, and the wound remains susceptible to recurrent damage and microbial invasion.

Keratinocytes move and proliferate to reinstate the epidermis barrier. Impairment of processes such as hyperglycemia, oxidative damage, chronic inflammation, and microbial products. Biofilm persistence may impede efficient epithelial migration by sustaining inflammatory activation and degrading the wound bed. Increased risk of recurrent colonisation is associated with delayed re-epithelialisation and a longer period of exposure of underlying tissues to the external environment.

Diabetic peripheral neuropathy impairs protective feeling and may change foot biomechanics. Consequently, patients may be unaware of pressure injury, slight trauma, or early wound worsening. New tissue breaks down with repeated mechanical stress, keeping the wound in a condition of chronic damage. Thus, off-loading pressure and preventive foot care are important aspects of treatment in addition to infection control and metabolic management. [18]

Microbiological Evaluation and Clinical Diagnosis

Routine clinical findings alone are insufficient for biofilm related infection diagnosis. Chronic wounds are frequently colonised with microorganisms and positive culture results do not always correlate with tissue invasion or clinically relevant infection.

The 2023 International Working Group on the Diabetic Foot/Infectious Diseases Society of America (IWGDF/IDSA) guideline suggests that diabetes-related soft-tissue infection should be diagnosed mainly by clinical examination and its severity should be assessed by an established classification system. If infection is suspected a sample of tissue obtained by curettage or biopsy is preferred to a superficial swab for microbiological examination. [18]

Traditional culture and antibiotic susceptibility testing remain useful for the identification of clinically relevant infections and directing therapy. Molecular techniques, sequencing and sophisticated imaging may offer information in particular conditions, but their role depends on the clinical question, availability and proven interpretation.

For study, biofilm detection methods such as microscopy and molecular characterisation can be useful. However, at now there is no conventional diagnostic test that is universally approved and reliably identifies clinically significant biofilm infection in any diabetic wound. The IWGDF recommendation admits that more research is required on the definition and clinical assessment in practice of persistent biofilm infection. [19]

Assessment should also include depth of ulcer, necrosis, systemic symptoms, peripheral perfusion, neuropathy and potential osteomyelitis. Inflammatory biomarkers such as C-reactive protein, erythrocyte sedimentation rate and procalcitonin may aid decision-making in the setting of equivocal clinical results, but none should be used to replace a full clinical evaluation.

Therapeutic approaches

Management is only effective when infection, wound mechanics, perfusion and metabolic regulation are addressed simultaneously. Antimicrobial-only treatment without attention to devitalised tissue, ischaemia or repetitive pressure is unlikely to reliably resolve biofilm-associated infection.

Effective debridement removes dead tissue and decreases wound matter that supports microbial colonies. Biofilm formations can be disrupted and access to the wound bed improved. However, biofilms may re-form after therapy. The choice of debridement should depend on the wound condition, vascular status and clinical indication. Severe ischaemia, presumed deep infection and widespread necrosis necessitate specialised examination and suitable surgical or vascular intervention.

Local wound treatment includes wound washing, proper dressings, moisture management and periodical reassessment.[20]

Systemic antibiotics are appropriate for wounds that are clinically infected and not just for the presence of bacteria in a culture. The drug should be selected based on severity of infection, probable microorganisms, previous antimicrobial exposure, local resistance trends, culture results, renal function, allergies, and other patient-specific considerations. Choice and duration of antimicrobials should be guided by clinical judgement and current guidelines. Unnecessary antibiotic exposure in untreated ulcers with no demonstrated benefit leads to increased antimicrobial resistance and harmful consequences.

Antibiotics alone may not be enough in the presence of significant necrotic tissue, an undrained collection, severe ischaemia or infected bone needing further intervention.

Optimising glycaemic management can help boost immune function and tissue regeneration, but it will not eradicate existing biofilms on its own. Management should also include hydration, nutrition, comorbidities, and other variables impacting recovery.

Assessment for peripheral arterial disease is recommended with input from a vascular specialist and revascularisation considered if necessary. Pressure off-loading, proper footwear and preventive foot care are important in reducing repetitive injury and improving healing.

These measures are an integral part of multidisciplinary diabetic foot care. [21]

Given the role of oxidative stress in the pathogenesis of diabetic wounds, antioxidants have been studied as a potential supplementary therapy. Experimental strategies are based on chemicals designed to boost natural antioxidant defences and/or decrease excessive ROS production and/or improve redox signalling.

But ROS also contribute to antibacterial defence and regular wound regeneration. Thus, excessive suppression of ROS may hamper beneficial host responses. Antioxidant therapies should be explored for their impact on microbial clearance, inflammation, tissue regeneration, and clinically relevant healing outcomes. [22]

At this time, antioxidant therapy should not substitute standard wound care, proper antibiotic therapy, glucose control, and vascular assessment.

Conclusion

Biofilm-related infections have a large role in the duration and complexity of some diabetic wound infections. Their effects are due to interactions among microbial adherence, formation of extracellular matrix, virulence-factor activity, antimicrobial tolerance, and host immunological responses. The healing potential of diabetic wounds is further compromised by hyperglycaemia, oxidative stress, endothelial dysfunction, neuropathy and decreased remodelling of the extracellular matrix.

This cycle of microbial persistence, inflammation, oxidative stress, and tissue damage can lead to delayed wound closure and an increased risk of catastrophic consequences. Thus, management of such infections involves more than just antibiotic medication. Appropriate infection identification, wound debridement where appropriate, culture-guided antibiotics, glycaemic optimisation, vascular evaluation, pressure off-loading and coordinated multidisciplinary care remain crucial.

Emerging antibiofilm and redox-modulating medicines are interesting research avenues, but their clinical relevance needs to be validated in thorough investigations. The integration of microbiology, clinical biochemistry, immunology and wound physiology provides a valuable foundation for better understanding and management of chronic diabetic wounds.

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