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Advances in gangrene management: A comprehensive review

Khushi A. Agrahari *, Supriya S. Barewar, Dr. Ravindra L. Bakal and Pooja R. Hatwar

Department of Pharmacology, Shri Swami Samarth Institute of Pharmacy, At Parsodi, Dhamangaon Rly, Dist. -Amravati (444709) Maharashtra, India.

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Abstract

Gangrene is a disease that is life-threatening for anybody and has that potential to cause morbidity and mortality to individuals suffering from it, and this disease is not easy to cure. Gangrene is broadly classified as wet, dry in this article. For many years, people have been diagnosed with gangrene, because of many factors like diabetes mellitus, peripheral artery disease, poor blood supply and infection and treatment for gangrene includes insulin and antibiotics which is effective to some extent. But this review is highlight for gangrene and demonstrating the treatment for it, which is most likely to cure, these treatment approaches help in personalized medicines for individuals with respect to their health condition to achieve a remarkable progress with good outcomes. This review has explained the ways to cure and prevent this deadly condition and also covered the possible comorbidity of it.

Keywords: Gangrene; Wet Gangrene; Dry Gangrene; Raynaud's Disease; Burger's Disease; Stem Cells

1. Introduction

Gangrene is a clinical disease characterized by ischemia and necrotic tissue that commonly surrounds a digit or extremity. It is distinguished by darkened or black tissue and accompanying sloughing of normal tissue planes. Gangrene most usually affects the arms and legs, including the toes and fingers. It can also affect muscles and organs within the body, such as the gallbladder. Pre-gangrene is the penultimate stage of vascular insufficiency before gangrene develops; the phrase is commonly used to describe lower-limb ischemia. Clinically, it manifests numbness, tingling, acute pain, and discoloration in the affected area [1]. Gangrene is a condition that causes the degeneration or loss of an organ or tissue, typically caused by a lack of blood supply in the body. This could be due to infectious or inflammatory processes as a result of injury or wounds on bodily parts or to progressive alterations induced by chronic diseases such as diabetes mellitus [2]. Gangrene is described as focal or widespread necrosis ++ of the skin and underlying tissue. However, this term is difficult to apply. Gangrene has various causes, just like foot ulcers [3]. Debridement and intravenous antibiotics are frequently employed in the early stages of gangrene therapy, and both are generally effective in treating the disease. If treatment is not received, gangrene can progress and become fatal. Gangrene has become a global health concern, affecting morbidity and mortality rates among numerous ethnic groups. According to a study, the prevalence of gangrene in India ranges from 0% to 5% of the population, with the majority of affected individuals aged 20 to 40 [4]. This is a serious and potentially fatal complication caused by bodily tissue death because of insufficient blood flow and oxygen levels. Gangrene frequently affects diabetics' lower extremities, where poor circulation and neuropathy enhance the risk. There are two varieties of gangrene: dry gangrene, which is characterized by tissue dryness, shriveling, and blackening, and moist gangrene, which involves tissue infection and liquefaction. Gangrene requires rapid medical attention since it can cause systemic infection and sepsis if left untreated [5].

* Corresponding author: Khushi A. Agrahari

2. Aetiology of Gangrene

Blood is extremely vital in preserving health. When blood does not circulate freely throughout the body, cells cannot live, infection develops, and tissue dies from gangrene. Any disease that alters blood flow raises the risk of gangrene, including [6]:

2.1. Atherosclerosis

Atherosclerosis is caused by hyperlipidemia and lipid oxidation, and it has long been a leading cause of death. It is a vascular intima illness that affects the entire vascular system, from the aorta to the coronary arteries, and is characterized by intimal plaques. The term atherosclerosis is derived from Greek and refers to thickening of the intimal layer of arteries and fat accumulation. The plaque's center core contains fatty material that is covered by a fibrous covering. The term atherosclerosis is divided into two parts: Atherosis (fat buildup accompanied by numerous macrophages) and sclerosis (fibrosis layer including smooth muscle cells [SMC], leukocytes, and connective tissue). The plaques then develop with the expansion of fibrous tissues and surrounding smooth muscle, bulging inside the arteries and reducing blood flow. Fibroblasts produce connective tissue and deposit calcium in the lesion, resulting in arterial sclerosis, or stiffening. Finally, the uneven surface of the arteries promotes clot formation and thrombosis, resulting in an abrupt restriction of blood flow [7].

2.2. Diabetes

Diabetes mellitus (DM) is the most common endocrine condition. It is caused by a deficit or inadequate insulin synthesis by the pancreas, resulting in a rise or decrease in blood glucose levels. It has been discovered to harm several body systems, including the blood vessels, eyes, kidneys, heart, and nerves. Diabetes increases the risk of a variety of consequences, including cardiovascular and peripheral vascular disorders, stroke, neuropathy, renal failure, retinopathy, blindness, and amputations [8].

2.3. Peripheral arterial disease

Peripheral artery disease (PAD), characterized by partial or full occlusion of the arteries in the lower extremities, is one of the most prevalent symptoms of atherosclerosis. Inflammation plays an essential role in the initiation and progression of PAD, and the inflammatory mediators involved are comparable to those that contribute to the development of coronary artery disease. Cigarette smoking and diabetes mellitus, the two biggest predictors of PAD, increase oxidative stress, which directly and indirectly stimulates inflammatory pathways [9].

2.4. Peripheral Arterial Embolism

Blue thrombophlebitis, especially when combined with severe pain and arteriospasm may closely resemble embolic blockage [10].

2.5. Trauma

Coagulation is an essential component of inflammation, and extensive activation of coagulation causes the systemic inflammatory response syndrome and an increased susceptibility to sepsis [11]. Burn injuries cause cardiogenic, hypovolemic, and distributive shock. The primary cause of intravascular volume depletion is increased capillary permeability and fluid changes [12]. Frostbite is a local tissue damage produced by cold exposure and freezing. When tissue reaches subfreezing temperatures, intra- and extracellular ice production causes electrolyte and pH alterations, as well as cell membrane breakage, which results in cell death and tissue damage. Reperfusion injury during tissue rewarming can result in inflammation, vasoconstriction, thrombus formation, endothelial damage, edema, and ischemia, all of which can cause more tissue damage. Frostbite can cause a wide range of injuries, from negligible tissue loss to significant necrosis requiring amputations [13].

2.6. Raynaud's phenomenon

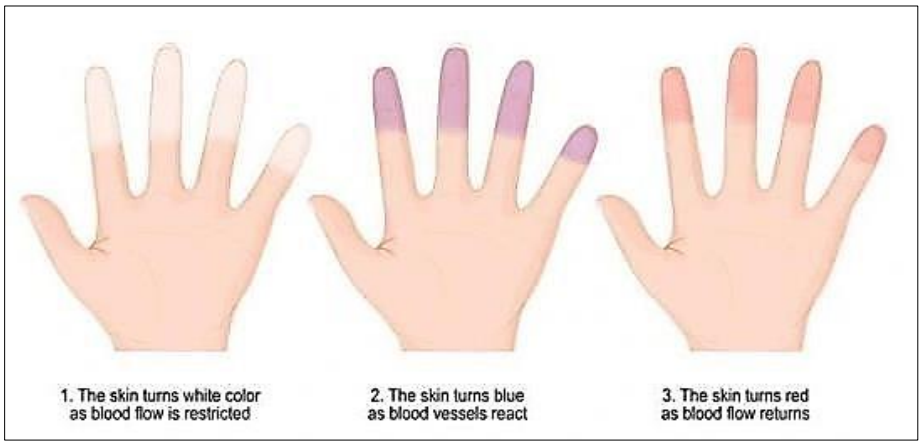

Figure 1 Raynaud's disease [14]

Raynaud's syndrome is typically described as a triphasic color shift in the digits, first with white or pallor (ischemic phase), then blue or cyanosis (deoxygenation phase), and finally red or erythema (reperfusion phase). It is usually found in the hands, although it can also affect the toes, nose, earlobes, and nipples. It may start in one finger and spread symmetrically to the other digits, usually sparing the thumb. Primary Raynaud's attacks are more likely to be symmetrical, episodic, and free of peripheral vascular disease. Primary Raynaud's should show no signs of tissue gangrene, digital pitting, or tissue damage. Patients with secondary Raynaud's describes attacks that are more frequent, painful, and often asymmetric.

Leads to digital ulcers. These ulcerations can heal to form scars or digital pits, or they can develop into more severe digital necrosis, gangrene, or auto-amputation. Digital ulcers can become secondary infections, resulting in osteomyelitis and requiring surgical surgery. Secondary Raynaud's may be indicated by an age of onset more than 40, male gender, digital ulcerations, asymmetric attacks, ischemia symptoms proximal to the fingers and toes, and aberrant nailfold capillaroscopy [15].

2.7. Buerger's disease

Buerger's disease is distinguished by periodic increasing inflammation and clotting in the small and medium arteries and veins of the hands and feet [16]. Clinically, BD appears as peripheral ischemia, which causes acute pain and discomfort, most usually in the arch of the foot or the calf of the leg. Symptoms may also include chest pain and distinctive skin abnormalities such as asymmetric coldness, skin atrophy, and irregular nail growth. The condition can develop into gangrene and amputation, drastically reducing patients' quality of life [17].

3. Types of Gangrene

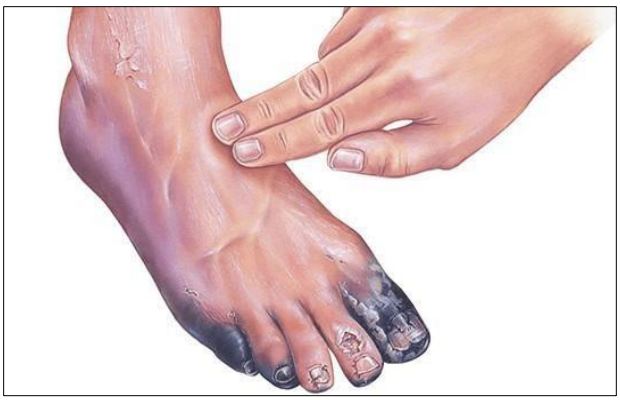

Figure 2 Dry Gangrene [18]

3.1. Dry gangrene

It occurs at the distal region of the leg due to ischemia (limited blood flow) and frequently arises in the toes and feet of older individuals due to arteriosclerosis, hence the name "senile gangrene." Dry gangrene is most commonly caused by arterial occlusions [19]. Dry gangrene is more likely to develop in persons who have hypercholesterolemia, diabetes, or arteriosclerosis. The delayed oxidation process of ischemia, as well as the inability of germs to survive, generates dryness and a shrunken, reddish-black appearance. These symptoms are induced by the ischemic part's limited oxygen supply. It may fall off if the damaged (gangrenous) part is not surgically removed. The patient may occasionally experience burning in the area being treated. The majority of the time, dry gangrene poses no threat to life. If adequate measures are taken and medication is continued, the patient will feel better [20]. Dry gangrene can be treated pharmacologically with opioid analgesics, anticoagulants, antiplatelets, and fibrinolytics. Intravenous antibiotics and improved vascular circulation Antibiotics alone are ineffective because they do not adequately enter affected tissue. The primary treatment for gangrene is surgical removal of all dead tissue, and if conservative and mild debridement fails, the last choice is amputation of the diseased region [21]. Dry gangrene of the glans penis is typically caused by vascular disease. The femoral artery, followed by the superficial external pudendal arteries, supplies blood to the penile skin. The deeper components of the penis are supplied by three branches of the internal pudendal artery: the bulbourethral, dorsal, and cavernosal arteries. The terminal branches of the dorsal artery supply the glans penis [22].

3.2 Wet Gangrene

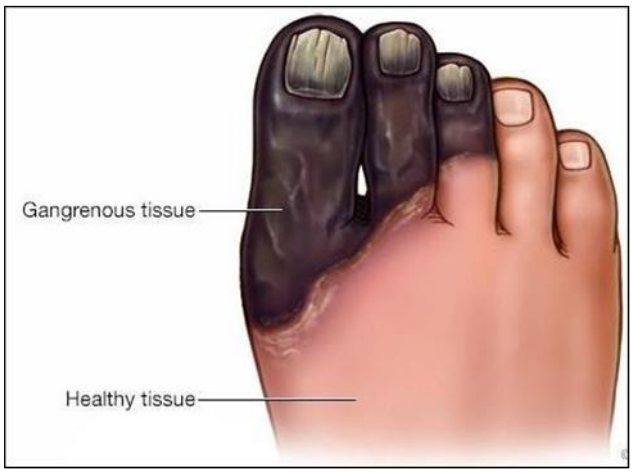

Figure 3 Wet Gangrene [23]

It occurs in moist tissues and organs such as the mouth, bowel, lungs, cervix, and vulva. Bedsores occurring on body parts such as the sacrum, buttocks, and heels are also classified as wet gangrene infections. Wet gangrene is characterized by numerous bacteria and generally has a poor prognosis (compared to dry gangrene) due to septicemia [24]. Spraying hydrogen peroxide, which is a bactericide and helps in providing oxygen, is also recommended on the affected part [25]. Saprogenic bacteria cause wet gangrene to occur. Frequent infections causing microorganisms are Clostridium perfringens, Klebsiella, Staphylococcal sp., and Streptococcus sp., and likewise Bacillus fusiformis. There is less supply in this scenario. A blockage of blood arteries results in a lack of oxygen and blood. Blood accumulates on the wounded area, promoting bacterial growth. Swelling occurs as a result of a bacterial infection in both the stinking and afflicted areas. The invading bacteria produce harmful compounds, which cause septic illness. Skin is occasionally removed, and the cells begin to disintegrate. As a result, the liquids from the cells spread, making the area surrounding them wet [20]

3.2. Pathophysiology

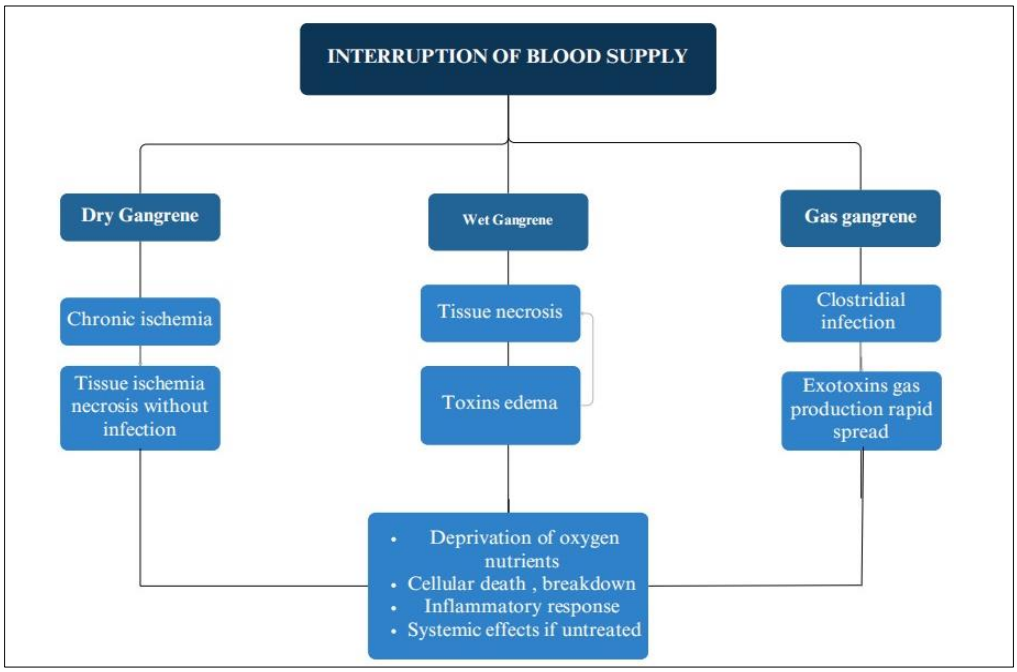

Figure 4 Pathophysiology of gangrene [26]

Pathophysiology involves alternating narrowing and expansion of the limb's arteries. Initially, the injured limb feels chilly and numb. Infection, lymphangitis, and gangrene can make injuries worse [26].

3.2.1. Risk Factors

- Diabetes mellitus
- Alcohol misuse disorder
- Obesity
- Immune-compromised state
- Hypertension
- Peripheral vascular disease
- HIV infection
- Tobacco use
- Chronic renal failure
- Hematologic disorders
- Congestive heart failure
- Chronic liver disease
- Malignancy
- Recent surgery [27].

Delays in identification and treatment could lead to severe complications. Complications include septic shock, necrotizing fasciitis, limb amputation, and even death. Although early antibiotic treatment was commenced, patients with risk characteristics should exercise caution [28].

3.3. Clinical manifestations

- Infection spreads fast.
- Sweating and having high blood pressure.
- Skin that is cold or numb.
- Pain is possible but not certain.
- Infection-related swelling and pain
- Skin color changes from red to brown to black.

- Symptoms may include blisters or sores with foul-smelling discharge (pus), fever, and a crackling sound when pressed [6].

3.4. Comorbidities

Table 1 Comorbidity and their contribution to gangrene

Comorbidity	How it contributes to Gangrene	References
Diabetes Mellitus	Compromised immunological response Impaired wound healing capacity increased the chance of developing gangrene.	[29]
Peripheral Arterial Disease	Severely impaired arterial blood supply, indicating wound failure.	[30]
Atherosclerosis	Insufficient blood supply to the tissues causes them to shrink and charred and become disconnected.	[31]
Obesity	These conditions led to the development of synergistic gangrene from an obliterative endarteritis caused by the spread of microbes, which produced secondary ischemia vascular thrombosis, facilitating anaerobic bacteria proliferation.	[32]
Chronic Kidney Disease	Gangrene of the penis in a patient with chronic kidney disease (CKD or ESRD) is a rare occurrence, usually as Dystrophic calcification of the arteries causes substantial luminal blockage.	[33]
Severe infections (Clostridium perfringens)	Two conditions are required for the onset Gas gangrene is defined by (i) the presence of clostridial spores and (ii) a region of tissue hypoperfusion produced by circulatory failure in a specific location or significant soft tissue injury and necrotic muscle tissue. Clostridial species are common in feces, with several identified in normal human feces.	[34]

3.5. Diagnosis Magnetic Resonance Imaging (MRI)

Magnetic resonance imaging (MRI) can assist in discovering infections and gases. MRI is more sensitive in detecting soft tissue infections in their early stages. T2-weighted MRIs are beneficial in detecting wet gangrene since the area of concern will have a higher signal intensity. Gradient-echo MRI has been shown to be the most effective at identifying gas within soft tissue. Gas gangrene will appear as blooming artifacts on gradient-echo MRI [35].

3.6. Computed Tomography CT

The diagnosis is primarily clinical, relying on complementary analytical, microbiological, and radiological testing, with computed tomography (CT) being the most sensitive and specific imaging test for this condition. Computerized Tomography (CT) is the most sensitive and precise method. CT can detect subcutaneous collections and the extent of fascial damage that other modalities cannot [36].

3.7. X-ray

If gas gangrene is present, an X-ray of the diseased area will reveal minute dots that are gas bubbles within the tissue [25].

3.8. Duplex ultrasound

Duplex ultrasonography is used to determine blood flow status in blood arteries. This approach allows vascular surgeons to easily detect the presence of any blockage or clot and arrange therapy [37].

3.9. Carotid duplex test

This test is done to determine the rate of blood flow through the carotid arteries. It aids in the detection of any plaques that could cause carotid artery disease [37].

3.10. Ankle–brachial index test

This test is useful in assessing arterial blood circulation and blood pressure in the lower limbs [37].

4. Treatment and Management

It has been demonstrated that tissue gangrene can move at dizzying speeds of up to 2-3 cm/h; therefore, prompt diagnosis and surgical treatment are critical [36]. Blood transfusions have also been used in the treatment of some patients [38]. Patients were monitored by an endocrinologist to regulate their blood sugar and given antibiotics to treat infections. Each patient received an oral dose of 100 mg aspirin and 75 mg clopidogrel (Plavix). Outpatient wound dressings were done with normal saline, followed by wrapping the toe with betadine gauze, primarily along the line of demarcation. To ensure routine follow-up, each patient was scheduled for a daily dressing appointment. In addition, appointments were scheduled once per week at the vascular surgery clinic and once every four weeks at the endocrinology and infectious disease medicine clinic. Patients who developed active infection in the form of clinical cellulitis, pus discharge, edema, or wet gangrene with septicemia were surgically amputated [39].

4.1. Fluid resuscitation

Fluid resuscitation can be attempted with a colloid or crystalloid solution. Intravenous fluid resuscitation is an essential part of critical care practice. The goal is to raise intravascular volume to improve cardiac output and organ perfusion. Failure to resuscitate patients effectively can result in multi-organ malfunction syndrome and, ultimately, death [40].

4.2. Surgical Debridement

Surgical debridement is regarded as the cornerstone of treatment for gas gangrene. When gas gangrene is suspected, vigorous debridement of all tissues implicated should be performed. Seek medical attention right away to ensure proper diagnosis and treatment [41]. It has been demonstrated that the degree of internal necrosis involvement is frequently much more than indicated by outward symptoms, necessitating recurrent debridement in order to prevent mortality [36].

4.3. Broad spectrum antibiotics

The most often used broad-spectrum agents are carbapenems or B-lactam/B-lactamase inhibitor combos such as piperacillin/tazobactam, ampicillin/sulbactam, and ticarcillin/clavulanic acid. Clindamycin or metronidazole combined with a quinolone (such as levofloxacin) provides adequate empiric coverage. Early therapy with broad-spectrum antibiotics is critical for treating acute diabetic foot infections. Any chronic deep infection in bone requires antimicrobial therapy as well as surgical treatment or debridement [42]. A broad-spectrum penicillin or third-generation cephalosporin, gentamicin and metronidazole, or clindamycin are recommended antibiotics; however, they should be changed and directed based on microbiological culture results [36].

4.4. Hemodynamic resuscitation and patient optimization.

Hemodynamic resuscitation and adjustment of the patient's comorbidities are critical components of ED FG management. The Surviving Sepsis Campaign recommendations indicate that patients with sepsis or septic shock and indications of hypoperfusion get intravenous crystalloid fluid during the first 3 hours. These fluids should ideally be balanced crystalloids, such as lactated Ringer solution or PLASMA-LYTE A (Baxter Healthcare Corporation, Deerfield, Illinois). Fluid resuscitation should be guided by hemodynamic measures (heart rate, blood pressure, urine output, and lactate clearance), and patients should be regularly observed utilizing dynamic indices (passive leg lift) to gauge responsiveness to fluid treatment [27].

4.5. Amputation

Amputation, an old surgical operation, is still used to save lives today. Despite advances in medical care and diagnosis, patients in low- and middle-income countries (LMICs) continue to present with preventable indications for amputation. This has become a healthcare burden, particularly in the senior age group, as these patients are more likely to have comorbidities that either result in or increase the indication for amputation or complicate their management.

Peripheral artery disease (PAD) appears to be the most prevalent.

Most older patients have cardiovascular and metabolic risk factors, leading to the need for amputation. The most prevalent type of amputation occurred below the knee [43]. People with critical limb ischemia caused by severe vascular disease or diabetic foot infection (sepsis) may require below-knee amputation if no other therapeutic options exist. Keeping the knee joint increases the likelihood of walking with an artificial leg or prosthesis and maintains social independence following amputation [44].

4.6. Preoperative Physiotherapy Management:

The patient was taught wound care and pain management techniques. These therapies were critical in healing and maintaining the outcome measure parameters, such as keeping the wound clean and dry, monitoring for infection, practicing personal hygiene, and performing preoperative range of motion exercises. To help our patients achieve a better outcome, we added strength training and breathing exercises to our normal therapy regimen [45].

4.7. Postoperative Physiotherapy Management:

After surgery, patient education is critical to reducing postoperative problems. Cleaning and treating wounds, as well as providing adequate support, are all part of amputee care. Good nourishment, comfortable sleep, correct placement, and the use of anti-inflammatory medications as needed all help to prevent postoperative problems. Once the patient is stable, we concentrate on ROM (range of motion) by performing exercises suggested by a physical therapist to strengthen the afflicted muscles. Finally, patients are taught how to walk using a walker under constant supervision [45].

4.8. Insulin therapy

Insulin therapy for glycemic management has been recommended in critically sick patients with a target blood glucose level of 140 to 200 mg/dL, which is appropriate for patients with hyperglycemia [27]. Insulin therapy should strive to replicate nature, which is extraordinarily effective at minimizing postprandial hyperglycemia and preventing hypoglycemia between meals. The site of administration of insulin injection is equally critical for better and safer insulin activity, which can be administered intramuscularly or intravenously. Different insulin formulations are available, including human insulin, cow insulin, and pork insulin [8]. In addition to boosting cellular glucose absorption, insulin has other immunomodulatory actions. Insulin has a trophic effect on mucosal and epidermal barriers, limiting bacterial invasion and translocation, improving wound matrix development, and inhibiting proinflammatory mediators [12].

5. Prevention

To prevent gangrene,

- Avoid tobacco usage and external trauma (e.g., frostbite).
- Patients with diabetes should keep sugar levels under control and keep an eye on their feet for any signs of wounds, infection, or redness.
- Patients with diabetic neuropathy (numbness in the arms, legs, fingers, and toes) should do this every day.
- Any wound or burn should be treated right away, especially in diabetics.
- Anyone who notices coldness and redness in a specific place (e.g., toes, fingers) should see a doctor promptly.
- Dry gangrene can be avoided if a blood vessel obstruction is detected early [46]. These strategies include timely skin therapy and deep tissue infections/foot ulcers, regional blood supply optimization, fall and stump injury prevention, routine self-foot care, appropriate foot unloading, and blood pressure, cholesterol, and glucose optimization, as well as smoking cessation [43].

5.1. Recent Advances Nanotechnology in Wound Healing

Recent advances in nanotechnology have opened up new avenues for medication delivery applications, allowing the transfer of biomolecules such as DNA/RNA or GFs, which can be used in chronic wound healing. requirements.

Nanoparticles, nanofibers, and self-assembled nanocarriers are employed to treat chronic wounds, particularly those that have shown promising outcomes in diabetic wound healing. NPs with wound-healing capabilities and NPs used as drug delivery systems. Their key advantages include regulated and sustained release, increased medication half-life, and bioavailability [47].

Nanofibers are ideal wound dressings because they mirror the ECM of the skin and allow for oxygen/nutrient exchange. Furthermore, they can load biomolecules into their matrix or even nanoparticles. Encapsulating biomolecules allows for varied release profiles that can be tailored to the needs of wound physiopathology. They are also capable of encapsulating Nanocarriers encapsulate them, allowing for topical administration with associated benefits (lower dose and fewer adverse effects). In contrast, nanofiber meshes have been used as artificial skin. When MSCs are employed, they can develop into endothelial cells or produce GFs to initiate the wound-healing process [47].

6. Hyperbaric oxygen therapy (HBOT)

HBOT is the medicinal application of oxygen at pressures greater than atmospheric pressure. It significantly increases the partial pressure of oxygen in bodily tissues, inhibiting the growth of anaerobic microorganisms. Another key function of HBOT is to reduce the hypoxic (oxygen-deficient) environment of surrounding ischemic tissue, hence limiting the extent of necrosis [41]. Many clinical studies have found that elevated pressure and oxygen bioavailability during HBOT affect a variety of activities, including angiogenesis, immunological activation, and tissue regeneration. HBOT has been employed in a variety of therapeutic applications, including necrotic injuries, thermal and radiation burns, and tissue regeneration and repair. HBOT's physiological effects indicate that it has a role in stem cell dynamics and other tissue regeneration processes such as angiogenesis and vascularization. HBOT induces hyperoxia, which activates a number of signaling pathways and results in the release of signaling molecules and growth factors. HBOT treatment often consists of several sessions, putting the patient through a cycle of high and normal oxygen levels. The transition from a hyperoxic to a hypoxic state activates a feedback loop, allowing secondary effects to be triggered. Because of the variety of treatment protocols and a lack of understanding of pressure effects on human physiology, the mechanism of HBOT therapeutic outcomes remains unknown. HBOT, on the other hand, has been demonstrated to improve healing and regeneration rates [48].

6.1. Stem cell therapy for diabetic wounds

MSCs can now be utilized to treat delayed or disrupted wounds, and multiple studies have shown that they can treat diabetic wound healing (DW). Muscle transplants have provided the most successful results. There are several factors that influence the healing process of a wound. Regeneration necessitates interactions between dermal and epidermal cells, as well as interactions between cells and cytokines; it has been demonstrated that umbilical cord (UC)MSCs increase the levels of VEGF, basic fibroblast growth factor (bFGF), and hepatocyte growth factor (HGF) in DFUs when administered alongside them. HGF, a downstream PI3K pathway, impacts VEGF synthesis via the c-MET signaling cascade [49]. Prolonged inflammation can cause a low oxygen environment, resulting in aberrant angiogenic signaling. The anti-inflammatory and immunomodulatory actions of transplanted stem cells have been identified as potential reasons for stem cell therapy's restorative benefits. Mild inflammation regulates the immune system, helping to eliminate pathogens, accelerate tissue repair, and maintain homeostasis. Stem cell therapy can be classified into two types: local and systemic delivery [50]. In a three-year Phase I clinical trial, Zhang et al. demonstrated that local and intravenous injections of human umbilical cord-derived mesenchymal stem cells can induce vascular regeneration in the lower limbs and effectively restore blood supply to the legs. Furthermore, the study found that injecting mesenchymal stem cells directly into injured muscle boosts the immune response, which promotes tissue healing. As a result, this patient swiftly restored blood circulation to the lower limbs, creating an optimal environment for wound healing [51].

7. Conclusion

Gangrene is a severe condition that requires prompt medical attention to prevent complications. Understanding its causes, types, and treatment options is crucial for effective management. Recent advances in nanotechnology, hyperbaric oxygen therapy, and stem cell therapy offer promising avenues for improving wound healing and tissue regeneration. Early diagnosis, surgical debridement, broad-spectrum antibiotics, and hemodynamic resuscitation are essential components of gangrene management. Preventive measures, such as controlling blood sugar levels and avoiding tobacco use, can help mitigate the risk of gangrene. A multidisciplinary approach is vital for optimizing patient outcomes.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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