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THESIS

Expectations & Therapy Adherence for Alternative Drug Administration in Diabetic Foot Ulcer Patients

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Abbreviations

Abbreviation	Definition
DFU	Diabetic Foot Ulcer(s)
DM	Diabetes Mellitus
TA	Therapy Adherence
TDD	Topical Drug Delivery
TDDS	Transdermal Drug Delivery Systems
LIT	Localized Injectable Therapies
OMD	Oral Mucosal Delivery
RCT	Randomized Controlled Trial
PAD	Peripheral Arterial Disease
NPWT	Negative Pressure Wound Therapy
MSCs	Mesenchymal Stem Cells
PRP	Platelet-Rich Plasma

1. Introduction

The success of treatment for diabetic foot ulcers (DFUs) is still significantly hampered by adherence, even with the development of several medication administration techniques. The psychological facets of patient behavior are overlooked in favor of clinical outcomes and cost-effectiveness in current research (Prompers et al. 2008). There is a significant knowledge gap about how patients' expectations—influenced by cultural narratives, healthcare professional communication, and prior experiences—affect their decision to start and continue using alternative medicines.

The presence of comorbidities, the complexity of the treatment plan, and patient education are some of the variables that might affect therapeutic adherence. Effective therapy necessitates a multidisciplinary approach, which includes patient education on foot care and routine follow-ups (Andrews et al, 2015).

Practical barriers to adherence have been found by previous studies, including financial constraints, treatment complexity, and physical limitations (e.g., low dexterity for self-applying dressings) (Aalaa et al., 2012).

DFUs are a major global health issue that worsens patient quality of life, raises morbidity, and increases healthcare costs. Both patient adherence to prescribed medications and medical advancements are necessary for effective therapy. Other options for enhancing wound healing and lowering complications include topical, transdermal, and nanotechnology-based treatments. However, patient expectations, acceptability, and adherence are critical to its efficacy. This study is essential for identifying the factors that affect adherence to these alternative medicines, providing lawmakers, pharmaceutical companies, and healthcare professionals with relevant information. The project aims to improve patient outcomes and DFU management methods by tackling these problems.

2. Background

Diabetes affects around 400 million persons globally (Jodheea-Jutton et al, 2022). DFUs are a crippling consequence of diabetes mellitus that affects 15-25% of diabetics during their lifetime and accounts for 80% of non-traumatic lower-limb amputations (Boulton et al., 2020; Armstrong et al., 2017). DFUs require a multidisciplinary strategy that includes glucose control, wound debridement, unloading, and infection prevention. Even with excellent treatment, up to 50% of DFUs recur within a year, with 20% requiring amputation (Jeffcoate et al., 2018). This poor prognosis is exacerbated by non-adherence

to prescribed therapy, which is complicated by the chronic nature of care, treatment complexity, and patient-specific psychosocial variables (Hinchliffe et al., 2008).

Few research, meanwhile, have looked at the significance of cognitive-emotional traits including resignation due to chronic illness, unbelief in non-traditional therapy, or fear of negative consequences (Paton et al., 2020). Despite evidence of its safety, patients may avoid bioengineered skin replacements because to misconceptions about "artificial" tissues (Primous et al., 2024). Similarly, even if biochemical markers indicate healing, growth factor therapy may be stopped if patients are dissatisfied with the delayed visual progress (Lantis et al., 2018).

Depending on standard procedures rather than individualized patient education, healthcare professionals can lack the expertise necessary to meet these expectations (Dorresteijn et al., 2012). Time constraints make it impossible to have in-depth discussions about treatment alternatives, which exacerbates this mismatch in low-resource settings (Swaminathan et al., 2024). Because of this, efforts to improve adherence continue to be dispersed, and behavioral science concepts are not fully included into DFU treatment plans (Valk et al., 2002).

DFU is a distressing and severe symptom of uncontrolled and protracted diabetes that appears as an ulcer on the plantar portion of the foot (Raja et al, 2023).

The findings of several research show that in order to accomplish a successful preventative program and a comprehensive treatment plan, patients' presence, sentiments, and comprehension of their health situations are critical. When implementing a holistic approach to diabetes treatment, we must include all elements, including the patients' feelings, anxieties, fears, and expectations (Aalaa et al, 2021).

Alternative drug administration techniques, such as topical antimicrobials, growth factor therapies, bioengineered skin substitutes, and localized drug delivery systems (e.g., hydrogels, nanoparticles), are increasingly being used in conjunction with traditional DFU therapies, such as systemic antibiotics and conventional wound dressings (Edmonds et al., 2018). Enhancing medication absorption, lowering systemic toxicity, and increasing patient convenience are the goals of these substitutes. In contrast to saline gauze, topical platelet-derived growth factor (PDGF) has demonstrated effectiveness in speeding wound closure (Driver et al., 2015). Bioengineered tissues, such as bilayered live cellular constructions, also shorten healing times by 20–30% (Marston et al., 2016). According to research, between 30 to 60 percent of patients discontinue utilizing

alternative medications after the first three months of treatment, suggesting that adherence to these regimens is still subpar (Armstrong et al., 2023).

In the context of DFU therapy, patient expectations—which are defined as beliefs about treatment outcomes, perceived advantages, and anticipated burdens—remain understudied despite being crucial predictors of adherence (Horne et al., 2013). For instance, underestimating the need for self-care might result in uneven topical agent administration, while excessive expectations of quick recovery can cause dissatisfaction and early therapy discontinuation (Vedhara et al., 2010). Perceptions of alternative medicines are also influenced by cultural and socioeconomic characteristics; among disadvantaged communities, decreased adherence is associated with mistrust of innovative therapies and worse health literacy (Gary et al., 2008). The need to look at how cognitive and emotional aspects influence participation in alternative DFU therapy is highlighted by the discrepancy between patient expectations and clinical realities.

3. Aim of the thesis

Examining the expectations and treatment compliance of DFU patients using different medication delivery modalities is the goal of this thesis. DFUs are a serious side effect of diabetes that frequently results in serious consequences such infections, amputations, and a lower standard of living. Alternative medication delivery techniques, such as topical, transdermal, or nanotechnology-based methods, are becoming more and more popular as potential ways to enhance patient outcomes and healing rates, even when conventional therapies are still available. Optimizing therapy efficacy and long-term illness management requires a thorough understanding of patient expectations and adherence to these medications. The desire to close the gap between cutting-edge treatment alternatives and actual patient compliance is what drives this study, which will ultimately lead to more patient-centered and successful DFU management techniques. The objectives are as below:

Primary Objective:

To examine the relationship between patient expectations and adherence to alternative drug administration therapies in DFU management.

Research Questions:

1. How do patients' pre-treatment expectations influence their adherence to alternative DFU therapies?

2. What psychosocial factors (e.g., health literacy, trust in providers) mediate the expectation-adherence relationship?
3. How do healthcare providers perceive and address patient expectations during therapy selection?
4. What educational or behavioral interventions could bridge gaps between patient expectations and clinical recommendations?

4. Diabetic Foot Ulcers: An Overview

4.1. Pathophysiology and Epidemiology

Patients with chronic diabetes mellitus frequently develop DFUs, which are caused by a number of interconnected pathophysiological mechanisms. Chronic hyperglycemia causes peripheral neuropathy, which is the first and crucial occurrence. Chronically high blood sugar levels harm peripheral nerves, impairing sensory awareness and making patients oblivious to pressure points or small foot injuries (Armstrong et al, 1998). Together with motor neuropathy, this loss of protective feeling leads to aberrant walking patterns and foot abnormalities, which increase the risk of ulcers (Rebolledo et al, 2011). Vascular impairment is a significant factor in the development of DFU in addition to neuropathy. Peripheral artery disease (PAD), which reduces blood flow to the lower limbs, is caused by diabetes's acceleration of atherosclerosis (Jeffcoate & Harding, 2003). The ischemia that results restricts the flow of nutrients and oxygen required for tissue repair, which impedes the healing of wounds. Furthermore, because decreased perfusion also restricts immune cells' access to the site of damage, diabetic individuals are more susceptible to infections due to their weakened vascular condition (Lipsky, 2016).

Another significant consequence in the setting of DFUs is infection. Diabetic wounds are particularly vulnerable to microbial invasion because of compromised circulation and weakened immune responses. If an infection is not treated promptly, it can spread to deeper tissues and bone, resulting in osteomyelitis and, eventually, limb amputation (Armstrong et al, 2017). These ulcers are characterized by chronic inflammation, which further interferes with the body's natural healing mechanisms. The high recurrence rates seen in DFU patients are a result of persistent inflammation, which also hinders efficient tissue regeneration (Prompers et al., 2008).

Epidemiologically, DFUs pose a serious threat to public health. According to research, diabetic people may have a 25% lifetime chance of having a diabetic foot ulcer (Jeffcoate & Harding, 2003). This risk is further increased by variables including the length of

diabetes, inadequate glycemic management, and the existence of concomitant illnesses (Singh et al, 2005). Furthermore, older patients and those with more severe diabetes problems are more likely to experience DFUs, highlighting the significance of early identification and preventative strategies (Lavery et al., 2020).

Clinicians may now more accurately evaluate vascular impairment in the diabetic foot because to recent developments in noninvasive diagnostic techniques like duplex ultrasonography and transcutaneous oxygen monitoring (Richard et al., 2011). These methods provide more precise risk assessment and direct focused therapies meant to increase wound healing and perfusion.

DFUs still place a significant strain on healthcare systems across the world in spite of these technical advancements. Management of DFUs is particularly difficult because to their multifactorial nature, which includes neuropathy, vascular insufficiency, infection, and chronic inflammation (Bandyk, 2018). To treat the several facets of the illness, patients frequently need multidisciplinary therapy from endocrinologists, vascular surgeons, podiatrists, and wound care experts (Sheehan, 2004). Additionally, the necessity for context-specific investigations is highlighted by differences in the epidemiology of DFUs among various groups, particularly in areas with limited access to specialist treatment (Zhang et al., 2017).

Recent studies have started to shed light on the genetic and metabolic elements that contribute to DFUs' poor wound healing at the molecular level. The chronic nature of these wounds has been linked to changes in growth factor signaling, poor extracellular matrix remodeling, and dysregulation of cytokine profiles (Game et al., 2012). These discoveries provide the groundwork for the creation of focused treatments that might eventually enhance the recovery results for diabetes patients.

In conclusion, a combination of neuropathic, vascular, and immunologic dysfunctions that impede wound healing characterize the pathogenesis of diabetic foot ulcers. According to epidemiology, DFUs have a major impact on morbidity, quality of life, and healthcare expenses, and they impact a sizable fraction of the diabetic community. Developing more effective treatment and preventative methods to address this difficult problem requires a complete knowledge of these pathways.

4.2. Conventional Treatment Strategies

DFUs have historically been managed using a multimodal strategy intended to address the underlying pathophysiology and facilitate efficient wound healing. Offloading,

debridement, infection control, vascular evaluation, and glycemic management are some of the fundamental therapies included in conventional therapy techniques.

The foundation of DFU management is thought to be offloading. To promote healing, it entails lowering or dispersing mechanical pressure from the ulcerated region. To accomplish this, unique orthotic devices, total contact casts, and specialized footwear are frequently used (Armstrong et al., 2017). By easing the strain on high-pressure locations, these devices lower the chance of further tissue injury and foster a healing environment (Singh et al., 2005).

Debridement of the wound is another essential part of DFU therapy. To reduce the bacterial burden, reduce inflammation, and promote the growth of healthy granulation tissue, necrotic and nonviable tissue must be removed from the ulcer (Jeffcoate & Harding, 2003). Surgical, enzymatic, and autolytic debridement techniques are chosen according to the state of the wound and the patient's general health. To keep the wound bed clean and get the ulcer ready for additional therapeutic measures, regular debridement procedures are required (Game et al., 2012).

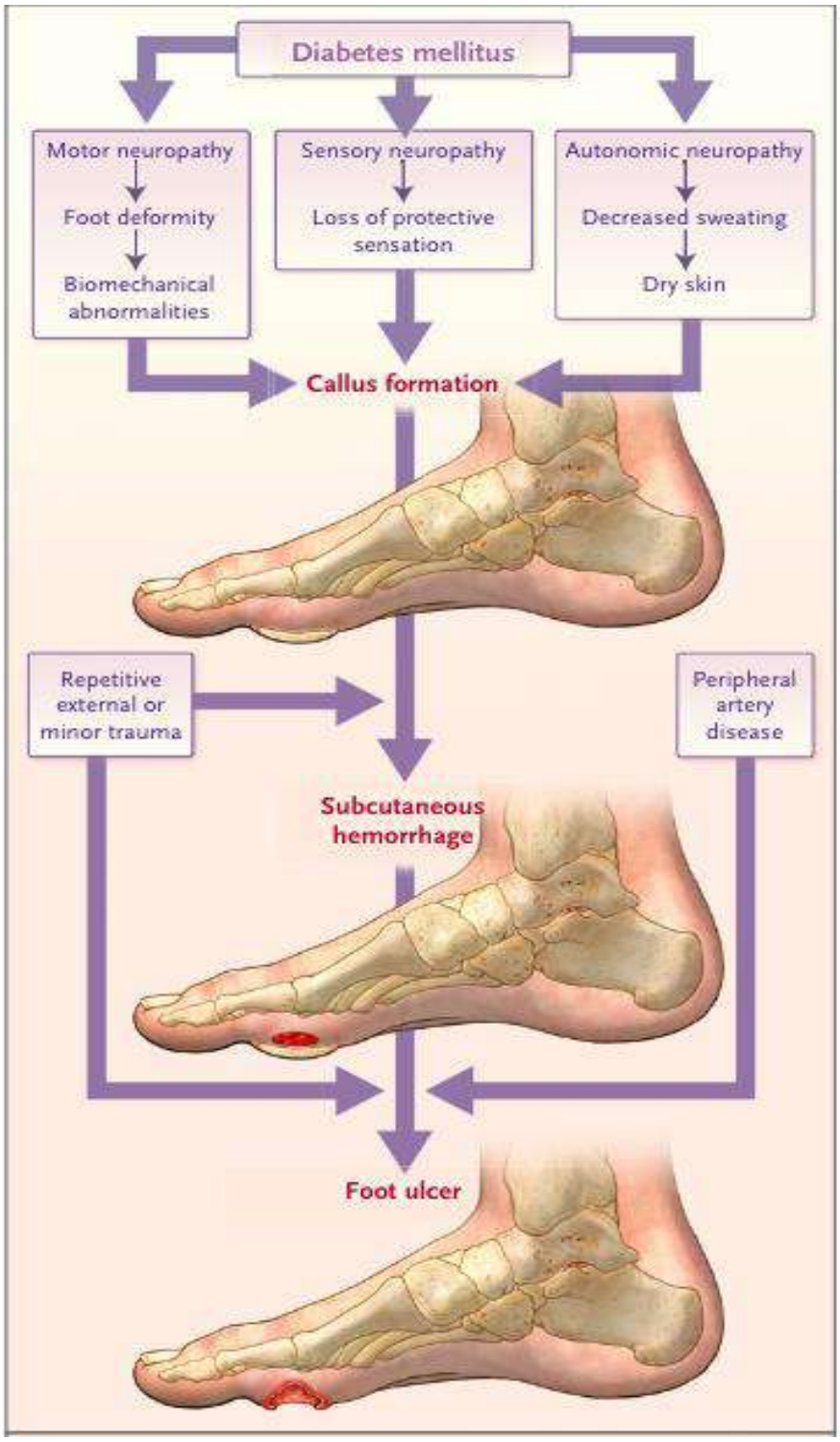

Figure 1: Common Pathway of Diabetic Foot Ulcer Occurrence and Recurrence (Armstrong et al, 2017)

Because diabetic patients have a higher risk of developing serious infections, infection control is crucial to the management of DFUs. Systemic antibiotics that are suited to the suspected infections and local resistance patterns must frequently be used early and aggressively due to the compromised immune response and decreased vascular supply

(Lipsky, 2016). Local wound care, including the use of antiseptic dressings and cutting-edge wound care products, is essential for controlling and preventing infections in addition to systemic therapy (Everett & Mathioudakis, 2018).

When there is substantial peripheral arterial disease (PAD), revascularization operations are recommended. Interventions like angioplasty, bypass surgery, or endovascular therapies are used to restore appropriate perfusion in patients with impaired blood flow, which is essential for successful wound healing (Braun et al., 2004). To choose the best course of action, a thorough vascular evaluation is essential, particularly when traditional wound care has not produced the desired results (Chowdhury et al., 2024).

Another essential component of DFU therapy is maintaining ideal glycemic control. Numerous elements of the wound-healing process, such as collagen formation and immunological function, are hampered by hyperglycemia. According to Lavery et al. (2020), strict glycemic control lowers the risk of infection and promotes tissue regeneration by fostering a positive biochemical environment. A multidisciplinary team strategy comprising endocrinologists, dietitians, and diabetes educators is usually used to handle this management issue.

Advanced wound treatment techniques have been included with traditional approaches in recent years. One such invention that has proven effective in encouraging wound closure is negative pressure wound treatment (NPWT), which lowers edema and promotes the production of granulation tissue (Game et al., 2012). Furthermore, topical growth factors and bioengineered skin replacements have demonstrated potential, especially for ulcers that do not respond to conventional therapies (Kumar et al., 2023).

Even with the advancements brought about by these traditional therapies, problems still exist. Many individuals have recurrence even after initial healing due to the chronic nature of DFUs. The chronic underlying diabetic neuropathy and vascular insufficiency that contribute to the development of new ulcers are partially to blame for this high recurrence incidence (Armstrong et al., 2017). Management might be made more difficult by the fact that patients may not always follow treatment guidelines, which include unloading, frequent debridement, and stringent glucose control (Singh et al., 2005).

Moreover, traditional therapies are not always successful, even if they have proven helpful in lowering the rate of amputations and enhancing overall results. A one-size-fits-all strategy is unsatisfactory due to individual diversity in response to therapy, which is impacted by variables including genetic predisposition and the existence of comorbid

illnesses (Ramirez-Acuña et al, 2019). As a result, individualized treatment approaches that take into account variables unique to each patient in order to maximize therapy are gaining popularity.

In summary, a wide range of traditional therapeutic approaches that focus on unloading, debridement, infection control, revascularization, and glycemic management are used to treat diabetic foot ulcers. Despite the fact that these tactics have significantly improved patient outcomes, problems such high recurrence rates, patient non-adherence, and individual variability highlight the necessity for continued study and development. Incorporating individualized treatment plans and cutting-edge wound care devices should improve healing outcomes even further for this difficult patient group.

4.3. Challenges in Diabetic Foot Ulcer Management

Effective management of DFUs is still hampered by a number of variables, including biological complexity, patient-related problems, and systemic healthcare concerns, despite tremendous advancements in both understanding and therapy. DFUs are particularly challenging to treat due to their multifactorial nature, which frequently results in persistent, recurring wounds that are unresponsive to standard treatments.

The chronic and complex pathophysiology that underlies DFUs is a major treatment problem. As was covered in earlier sections, neuropathy, vascular insufficiency, and defective wound healing interact to provide a hostile environment for tissue repair, which leads to DFUs (Armstrong et al, 1998; Chauhan et al, 2023). Patients are still at a significant risk of ulcer recurrence even after successful first treatment because these underlying problems continue. The inflammatory environment that defines DFUs exacerbates this chronicity by persistently impeding the healing process (Prompers et al., 2008).

Another significant obstacle is infection control. Due to vascular impairment and compromised immunological responses, diabetic individuals are naturally more vulnerable to infections (Lipsky, 2016). If DFU infections are not immediately and adequately controlled, they can quickly worsen, developing into osteomyelitis and perhaps requiring amputation. The selection of appropriate antimicrobial therapy is made more difficult by the growing incidence of organisms resistant to antibiotics (Nather et al., 2004). Early infection identification and prompt treatment are typically essential, but they are frequently challenging to do in standard clinical practice.

Another issue that has a big impact on DFU results is patient adherence to recommended treatment plans. Strict adherence to intricate treatment regimens, including as offloading, routine wound care, and careful glucose control, is necessary for the effective management of DFUs (Singh et al, 2005; Pouget et al, 2021). However, a number of patients find it difficult to follow these regimens because of things like a lack of knowledge, financial limitations, and the psychological toll that comes with having chronic wounds (Lavery et al., 2020). This non-adherence prolongs the cycle of chronicity and re-injury by impeding healing and raising the risk of ulcer recurrence.

The difficulties in managing DFU are exacerbated by the healthcare system itself. One significant drawback is the fragmentation of care, which results in uneven and subpar management due to a lack of integrated multidisciplinary teams. Endocrinologists, vascular surgeons, podiatrists, infectious disease experts, and wound care nurses should ideally work together to provide DFU treatment. However, due to logistical difficulties and resource limitations, such integrated care models are not often used in many contexts, especially in low- and middle-income nations (Tuglo et al., 2022). This disarray may lead to insufficient therapy, delayed diagnosis, and ultimately worse patient outcomes.

Financial limitations make administering DFUs even more challenging. Long-term rehabilitation, surgical procedures, and sophisticated wound care products can be prohibitively expensive, especially for people with no insurance. In addition to having an impact on individual patients, the financial burden of DFUs puts a great deal of strain on healthcare systems, which have to spend a lot of money to treat these complicated wounds (Shahi et al., 2012). The literature continuously highlights the significant economic impact of DFU management, despite the fact that this review does not provide precise financial numbers.

Alternative medication delivery methods are one of the emerging therapy modalities that provide a viable way to get over some of these obstacles. Targeted therapy with few systemic adverse effects is the goal of novel drug delivery methods, which include transdermal patches, topical formulations, and localized drug-release devices (Kandregula et al., 2022; Kandregula et al., 2022). Regulatory approval, a lack of long-term data, and patient response variability are some of the challenges that come with clinically implementing these sophisticated systems (El Hage et al., 2022). Therefore, even when novel treatments have promise, thorough clinical studies are necessary to confirm their acceptance into standard clinical practice.

Furthermore, another difficulty is the variation among DFU patients. According to Van Netten et al. (2016), differences in ulcer size, depth, infection status, and patient comorbidities call for customized treatment plans as opposed to a one-size-fits-all strategy. It is challenging to standardize treatment methods and create accurate result predictions because of this diversity. Future studies on prediction models and biomarkers might aid in better customizing therapies to each patient's unique profile (Armstrong et al., 2023). Last but not least, persistent monitoring and follow-up are important but difficult aspects of DFU care. Because of underlying neuropathy and vascular problems, individuals are still susceptible to recurrence even after an ulcer has healed (Armstrong et al., 2017). Preventing re-ulceration requires establishing uniform follow-up procedures and strengthening patient education regarding self-care techniques. However, a major gap that prevents long-term improvements in patient outcomes is the lack of such guidelines in many healthcare settings (Alexiadou & Doupis, 2012).

5. Alternative Drug Administration in Diabetic Foot Ulcer Management

5.1. Overview of Alternative Administration Routes for Diabetic Foot Ulcer Therapy

Chronic lesions that are prone to infection and poor healing are the hallmark of DFUs, a crippling consequence of diabetes mellitus. Conventional systemic treatments, including injectables or oral antibiotics, frequently struggle with systemic adverse effects, patient non-adherence, and insufficient drug concentration at the wound site (Boulton et al., 2005). Alternative medication delivery methods, including as topical, transdermal, and localized delivery systems, have become more popular in DFU therapy in order to overcome these drawbacks. These pathways, their workings, and their uses in therapeutic settings are examined in this section.

Topical Drug Delivery

By applying therapeutic drugs directly to the ulcer site, topical administration allows for localized medication activity while reducing systemic exposure. Creams, gels, ointments, and hydrogels containing antimicrobials, growth hormones, or anti-inflammatory compounds are examples of common formulations (Yang et al, 2022). For example, because of their broad-spectrum antibacterial action, silver sulfadiazine creams are frequently utilized, especially in infected DFUs (Edmonds et al., 2018). In order to encourage tissue regeneration, hydrogels improve the transport of substances like

platelet-derived growth factor (PDGF) by keeping the wound environment wet (Driver et al., 2015).

Topical distribution has been significantly improved by recent developments in nanotechnology. The solubility and stability of hydrophobic medications, such curcumin, which has anti-inflammatory and antioxidant qualities, are enhanced by nanoemulsions and lipid-based carriers (Yao et al., 2013). Furthermore, continuous release of antibiotics like vancomycin is provided by bioengineered dressings that incorporate collagen or hyaluronic acid scaffolds, guaranteeing extended therapeutic levels at the wound bed (Hotkar et al., 2015).

The capacity to establish a regulated microenvironment at the ulcer site is one of the main benefits of topical medication administration. For instance, hydrogels offer a moist wound environment that promotes the production of granulation tissue and can improve re-epithelialization (Zhao et al, 2024). Furthermore, medications like growth hormones, antibiotics, or anti-inflammatory compounds can be added to hydrogel formulations and released gradually. According to Chijcheapaza-Flores et al. (2023), this local release maximizes the drug's bioavailability at the target location while reducing the possibility of systemic adverse effects.

Nanoparticle-based advanced formulations have also been studied for topical DFU management applications. For example, gold nanoparticles have been investigated for their antibacterial qualities and capacity to improve wound healing through cellular response modulation (Xu et al., 2023). A potential platform for topical therapeutics is provided by nanoemulsion-based devices, which also increase the stability and penetration of encapsulated medications. Additionally, using their natural antibacterial and healing-promoting qualities, natural ingredients like honey have been included into topical therapies (Manjit et al, 2024).

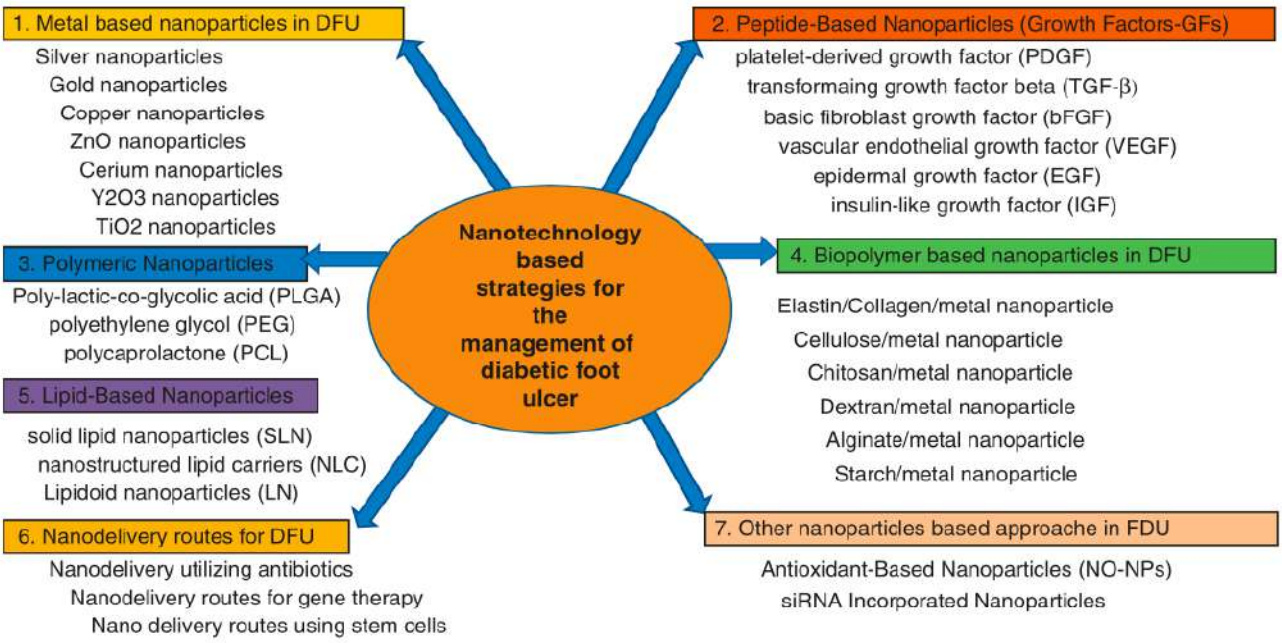

Figure 2: Nanotechnology-based strategies for treatment of DFU (Ansari et al, 2021)

Poor local vascularity is one of the key problems in DFU therapy that topical preparations are intended to address. Systemic medications sometimes do not reach the ulcerated tissue in sufficient amounts because of peripheral artery disease, which is frequently linked to diabetes. By delivering active ingredients straight to the wound bed, topical treatments get over this restriction and increase the effectiveness of their effects (Jeffcoate et al., 2020). Additionally, to improve the healing process even more, topical administration methods can be used in conjunction with physical therapies like debridement or negative pressure wound therapy (Lebrun et al., 2010).

Despite these benefits, topical medication administration for DFUs still faces a number of difficulties. The varying permeability of diabetic skin, which can be affected by age, the chronicity of the lesion, and the existence of calluses or scar tissue, is one significant drawback. These elements may have an impact on the drug's ability to penetrate the wound and distribute evenly. In order to increase skin permeability and drug release kinetics, formulation scientists have optimized the formulation's physicochemical characteristics, such as particle size, viscosity, and pH (Godavarty et al., 2023).

Making sure the formulation stays in touch with the wound for an adequate amount of time is another issue with topical medication administration. In DFUs, where frequent dressing changes may disrupt the therapeutic effect, this is particularly important. In response, scientists have created bioadhesive formulations that may cling firmly to the surface of the wound, extending medication exposure and promoting better healing

results. Furthermore, topical formulations that contain stimuli-responsive components, such pH-sensitive or temperature-sensitive polymers, enable a "smart" release of the medication in reaction to the wound environment (Zhao et al., 2024).

Transdermal Delivery Systems

Transdermal delivery uses patches or microneedles to administer medications via the skin barrier, avoiding the gastrointestinal tract. Advances in microneedle technology enable accurate medication administration to deeper tissue layers without harming nearby healthy skin, however this procedure is less prevalent in DFU treatment because of reduced skin integrity (Prausnitz & Langer, 2008). For instance, by modifying local glucose metabolism, insulin-loaded microneedles have shown promise in improving wound healing (Wu et al., 2025). Transdermal drug delivery systems (TDDS) are a non-invasive way to get drugs into the bloodstream through the skin. By skipping the gastrointestinal system and first-pass metabolism and offering a consistent release of therapeutic drugs, TDDS provide special benefits in the setting of DFUs. When inadequate local vascularity, a prevalent problem in diabetic patients, limits systemic treatment, this approach is especially appealing (Wu et al, 2025).

TDDS includes a range of methods, including as iontophoresis systems, microneedle arrays, and patches. Conventional patches are made to deliver medications over a certain time period at a regulated pace. However, the skin's barrier qualities may restrict their efficacy, especially in diabetic individuals who may have compromised skin integrity (Ataei et al., 2023). Research has concentrated on improving skin permeability using physical techniques like microneedles or chemical enhancers in order to get beyond these obstacles.

Transdermal delivery has seen a revolution thanks to microneedle arrays. Drugs may be directly delivered into the epidermis or even the dermis with these devices, which are made up of microscopic needles that gently pierce the stratum corneum. The danger of needle breakage or material residue in the skin can be reduced by designing microneedles to dissolve after medication delivery using a variety of materials, including silicon, metals, and polymers. Because they combine the benefits of systemic and local administration, they are especially promising for use in DFU patients, guaranteeing that therapeutic doses are reached even in regions with impaired circulation (Jarrar, 2025).

Iontophoresis is another cutting-edge method in TDDS that uses a low electrical current to push charged drug molecules through the skin. In order to provide targeted therapy

without systemic damage, iontophoresis has been investigated as a way to administer antibiotics and anti-inflammatory medicines directly to infected or inflammatory DFU sites (Langoni Cassettari et al, 2014). Iontophoretic devices are promising, but further clinical validation is needed before they can be widely used, especially in diabetic patients.

By using nanotechnology, formulation scientists have improved the design of transdermal patches in addition to these physical techniques. To improve medication solubility and penetration, for instance, lipid-based nanoparticles and nanoemulsions have been used into patch formulations. These formulations are ideal for long-term illnesses like DFUs because they can enhance absorption and offer sustained release patterns. By lowering the frequency of administration, the deployment of such sophisticated systems may also improve patient adherence (Kandregula et al, 2022).

Making sure the medication reaches the target site in therapeutic concentrations is one of the difficulties in applying TDDS for DFUs. Because of glycation and other metabolic alterations, diabetic skin frequently shows decreased permeability (Izquierdo et al., 2015). Thus, enhancing the efficiency of transdermal systems requires optimizing their design, such as by choosing suitable penetration enhancers or by adjusting the microneedle size. Clinical research has started to show that TDDS can greatly enhance outcomes for patients with chronic wounds when these variables are properly managed.

Localized Injectable Therapies

Deeper ulcer layers are the focus of injectable treatments such growth factors or intralesional corticosteroids. In chronic wounds, injections of platelet-rich plasma (PRP), which concentrate autologous growth factors, speed up collagen production and angiogenesis (Mulder et al., 2014). In a similar vein, stem cell injections from bone marrow or adipose tissue exhibit potential for paracrine signaling-based tissue regeneration (Lopes et al., 2018). Another possible targeted injectable strategy is stem cell treatment. The ability to develop into diverse cell types, including those involved in tissue repair, is possessed by mesenchymal stem cells (MSCs). It is believed that stem cells' therapeutic benefits are mediated by both their capacity to regenerate damaged tissues and their production of paracrine substances that alter the wound microenvironment. Research is still ongoing, though, on topics like integration, cell survival, and the ideal dose. Another localized injectable treatment that has demonstrated significant promise in the treatment of DFU is platelet-rich plasma (PRP). PRP is made

from the patient's own blood and includes a potent blend of cytokines and growth factors. PRP can promote tissue regeneration and hasten healing when applied to or injected into the wound bed (Villela & Santos, 2010). Although standardization of preparation techniques and injection procedures is still required, clinical usage of PRP has been linked to faster healing periods and better overall results (Edmonds et al., 2018).

Innovative biomaterials are also a part of localized injectable therapy. For instance, injectable hydrogels that function as a scaffold for cell development and a controlled-release delivery system for medicinal medicines have been investigated by researchers. By imitating the extracellular matrix, these hydrogels can offer structural support and a healing-friendly environment (Edmonds et al., 2020). One benefit of injectable hydrogels is their ability to adapt to the uneven forms of chronic wounds, guaranteeing that the therapeutic payload is distributed evenly. To increase their effectiveness even further, they might be used with bioactive substances or nanoparticles.

The ability of targeted injectable therapy to lessen systemic adverse effects is a major advantage. The danger of negative effects that are frequently connected to systemic administration is reduced by administering the therapeutic drug directly to the wound. For individuals who may be more susceptible to systemic toxicity, such as the elderly or those with several comorbidities, this focused administration is especially beneficial. Additionally, localized injections can be administered again as necessary to keep the therapeutic concentration at the wound site at its ideal level. This is crucial for chronic wounds that need to be managed over an extended period of time.

Emerging Routes: Inhalational and Oral Mucosal Delivery

Although it has not been well investigated, inhaling vasodilators (such as prostacyclin analogs) may enhance peripheral blood flow in diabetic patients, hence aiding in the indirect healing of ulcers (Lim et al., 2017). For systemic immunomodulators like metformin, which may lessen inflammation in chronic wounds, oral mucosal administration is being investigated despite its unusual nature (An et al., 2021).

Another new method that gets over the restrictions of first-pass metabolism and gastrointestinal degradation is oral mucosal administration. This method makes use of the oral mucosa's abundant vascular supply, especially in the buccal and sublingual regions, to promote quick medication absorption. Drugs that promote systemic healing responses, such as growth factors or anti-inflammatory medications, might be

administered by oral mucosal delivery in the context of DFU therapy while preserving a non-invasive profile that promotes patient adherence.

There are a number of benefits to both oral mucosal and inhalational routes. They provide non-invasive substitutes for injections and may be more palatable to patients, especially those who need frequent doses or are needle averse. Furthermore, these pathways promote fast absorption, which may result in more immediate therapeutic benefits. The lung's wide surface area and weak alveolar-capillary barrier, for example, allow for quick absorption of aerosolized medications when employing inhalational administration, which may be crucial in cases of rapid exacerbations of DFUs. Likewise, oral mucosal administration can avoid the harsh gastrointestinal tract environment, improving bioavailability and protecting delicate therapeutic molecules (Saini et al, 2010).

Notwithstanding their potential, a number of obstacles need to be overcome before these new avenues may be regularly used to DFU administration. Particle size and formulation stability are important factors for inhalational administration. It is necessary to design the aerosolized medication to get the best possible lung deposition without irritating the lungs or having negative respiratory effects. Furthermore, the effectiveness of medication administration may be impacted by patient-specific variables such breathing patterns and lung function (Boulbou et al, 2003). In order to enhance therapeutic advantages and minimize potential negatives, research is being conducted to improve aerosol compositions and delivery systems.

The primary obstacle to oral mucosal administration is getting beyond the mucosal epithelium's barrier characteristics. The mucosa is highly vascularized, but it also serves as a barrier to keep extraneous substances out of the underlying tissues. Drug formulations must thus be especially made to increase permeability, frequently by adding absorption enhancers or by cutting-edge delivery methods such dissolving microneedles. Furthermore, because of swallowing and salivary flow, the drug's residence duration in the oral cavity is usually brief, which calls for the creation of mucoadhesive formulations that can extend contact with the mucosal surface.

5.2. Advantages and Limitations of Alternative Approaches

Alternative drug administration routes offer distinct benefits over systemic therapies but are not without challenges. This section evaluates their clinical utility, patient acceptability, and practical limitations.

Transdermal and topical medication delivery techniques have a number of unique benefits that can greatly improve patient results. Topical treatments successfully reduce systemic toxicity by offering localized medication action, which is a crucial advantage for patients with hepatic or renal comorbidities (Everett & Mathioudakis, 2018). It has been demonstrated, for example, that topical metronidazole reduces anaerobic infections without causing gastrointestinal adverse effects (Lipsky, 2016). Furthermore, transdermal patches are made to make dosage schedules easier, which is especially helpful for older patients who are taking several drugs (Alenazi & Khan, 2025). Another noteworthy advantage is that hydrogels and films help to maintain a moist wound environment, which encourages autolytic debridement and reduces discomfort while changing dressings (Everett & Mathioudakis, 2018).

Despite these advantages, topical administration has a number of drawbacks. One significant difficulty is the inadequate medication penetration in necrotic tissue; in chronic diabetic foot ulcers (DFUs), biofilms and necrotic debris can impede drug absorption, frequently requiring supplementary debridement (Koreyba et al., 2022). Furthermore, the long-term use of certain topical antibiotics, including neomycin, is complicated by the possibility of hypersensitivity responses (Jimenez et al., 2017).

Injectable and transdermal systems may provide difficulties. The absorption of medications delivered transdermally can be severely restricted in diabetic patients due to skin barrier failure, which is typified by epidermal thinning and decreased vascularity (Ena et al., 2021). Furthermore, modern medicines like platelet-rich plasma (PRP) treatments and bioengineered dressings are still too expensive and difficult to get in low-resource environments (Moore et al., 2021). These difficulties show that in order to balance patient accessibility, safety, and efficacy, medication delivery methods must be continuously innovated and optimized.

Patient-Centered Considerations

Cultural beliefs and self-care capabilities influence adherence to alternative therapies. For instance, elderly patients may struggle with microneedle self-application, while others may distrust novel biologics (Aalaa et al., 2012).

5.3. Current Evidence and Emerging Trends

With the introduction of customized medicine and revolutionary advancements in biomaterials, the body of data supporting alternate delivery routes for DFUs is growing quickly. The clinical effectiveness of topical therapies has been shown in recent randomized trials; topical PDGF (becaplermin) has shown encouraging results in treating neuropathic ulcers, but high costs and strict regulations are preventing its widespread use (López-Moral et al., 2024). Furthermore, it has been discovered that honey-based dressings have antibacterial and anti-inflammatory properties that are on par with those of traditional iodine solutions, suggesting that they might be a good substitute for traditional wound care methods (Zhao et al., 2023).

This subject has been further advanced by advances in nanotechnology, which have made it possible to create novel delivery methods. The targeted delivery of siRNA to suppress pro-inflammatory cytokines, like TNF-α, in chronic wounds is now possible with nanoparticle-loaded hydrogels (Pandey et al., 2024), and gold nanoparticles conjugated with antibiotics improve biofilm penetration, effectively treating infections that are resistant to multiple drugs (Ansari et al., 2021). Meanwhile, stem cell and gene therapies have demonstrated promise; gene-activated matrices delivering HIF-1α plasmids are currently being studied for their potential to modulate hypoxia (Huang et al., 2023), and mesenchymal stem cell (MSC) dressings promote angiogenesis through VEGF secretion, with phase II trials reporting improved healing rates (Yu et al., 2022). Additionally, the incorporation of digital health solutions, such smart dressings with wireless connectivity and pH sensors, makes it easier to monitor wound biomarkers in real time, which improves the timing of therapy (Lazarus et al., 2023). In order to further customize therapy and improve patient outcomes, complementary mobile applications for adherence tracking have been developed (Matijevich et al., 2024).

6. Patient Expectations in Therapy

6.1. The Role of Patient Expectations in Treatment Outcomes

In a variety of therapeutic settings, patient expectations have become a crucial factor in deciding treatment success. Researchers have stressed for decades that patients' expectations about their care may have a big impact on both their subjective experiences and actual clinical outcomes. The Common-Sense Model of Self-Regulation, which holds that patients create cognitive representations of their disease and treatment that direct coping and adherence, is at the center of this conversation (Leventhal, Meyer, & Nerenz,

1980; Leventhal, Brissette, & Leventhal, 2003). These expectations-shaped cognitive representations influence how patients interact with and react to recommended therapy, claim Horne and Weinman (1999). For example, the "expectancy effect" (Robbins et al., 2008) describes how a patient's expectation that a therapy would be very helpful can promote more involvement and perhaps improve the biological response to treatment.

Expectations function on several levels. Patients' expectations about treatment results are influenced by their own beliefs, cultural background, and past experiences (Petrie & Weinman, 2012). Patients are more likely to report better results and stick to treatment plans when they anticipate improvement (Horne et al., 2013). On the other hand, pessimism can contribute to worse results in a self-fulfilling prophesy caused by low expectations or unfavorable views about the effectiveness of therapy (Bandura, 1997). Research showing that greater patient expectations are linked to better clinical indicators, less symptom load, and even improved quality of life in chronic illnesses lends credence to this interaction between cognition and outcome (DiMatteo, 2004).

Because DFUs are chronic and recurrent, expectations become even more important while managing the illness. Patients with DFU are more vulnerable to the impact of their expectations on their emotional health and treatment results since they frequently undergo repeated treatments and deal with long-term management issues (Armstrong et al, 2017). According to Leventhal et al. (2012), patients are more likely to stick with a therapy when they have reasonable yet hopeful expectations about its possible advantages. Better wound healing and general condition management may result from this constructive involvement.

Furthermore, studies indicate that the placebo response may be influenced by patient expectations, which might alter the therapies' true therapeutic impact (Horne & Weinman, 1999). This is especially important when it comes to alternative medication administration, since new delivery systems may be greeted with skepticism or optimism at first. For example, research has demonstrated that patients are more likely to adhere to the treatment plan and report favorable results when they expect less side effects and better local healing outcomes from different delivery methods (Ryan & Deci, 2000). The design of therapies targeted at enhancing drug adherence in chronic illnesses like DFUs and clinical practice are both impacted by this dynamic.

The interaction between patient expectations and communication with healthcare practitioners is another factor to take into account. It has been demonstrated that good doctor-patient communication helps patients match their expectations with practical

treatment results, which enhances adherence and satisfaction (Street et al., 2009; Epstein & Street, 2011). Patients are more likely to develop balanced expectations that promote improved treatment engagement when doctors provide them clear, evidence-based information regarding the advantages and disadvantages of a particular therapy (Kaplan et al., 1989). According to Conner and Norman (2005), patient expectations are so dynamic and constantly molded by their interactions with peers, family, and medical professionals.

Furthermore, expectations have an impact on quantifiable physiological changes in addition to psychological results. Positive expectancies may increase immune function and reduce stress, which might indirectly lead to better clinical results, according to research in psychoneuroimmunology (Bandura, 1997; Ryan & Deci, 2000). These results highlight the possibility of using patient expectations to enhance treatment outcomes through a holistic therapy strategy that integrates psychological treatments with both traditional and alternative therapies.

In conclusion, patient expectations have a complex and wide-ranging impact on treatment results. Patients' perceptions about the nature and effectiveness of a therapy can have a substantial impact on how they stick to it, how their bodies react to it, and how well the therapeutic intervention works as a whole. Research continuously shows that encouraging reasonable but optimistic expectations through supportive treatment and good communication can result in better outcomes for a number of chronic illnesses, including diabetic foot ulcers (Horne & Weinman, 1999; Petrie & Weinman, 2012). More investigation into the systematic use of expectations to improve treatment results is necessary in light of the increasing focus on patient-centered care (Horne et al., 2013).

6.2. Factors Influencing Patient Expectations

Patient expectations are the result of a complex interaction between environmental, societal, and individual elements rather than being developed in a vacuum. The formation of expectancies has been explained by a number of theoretical frameworks, such as the Common-Sense Model of Self-Regulation (Leventhal et al., 1980) and the Health Belief Model (Rosenstock, 1974). According to these models, patients' expectations are impacted by their own views about sickness, their experiences receiving treatment in the past, and their perceptions of the severity and vulnerability of their condition (Conner & Norman, 2005).

The quality of information patients get about their ailment and available treatments is a major factor in determining their expectations. Patients' perceptions of the anticipated results of a therapy can be greatly influenced by healthcare practitioners' effective communication (Epstein & Street, 2011). For instance, patients are more likely to form realistic expectations that support adherence and favorable results when therapists fully describe the workings, advantages, and possible hazards of a medication. On the other hand, inaccurate or too optimistic information might create irrational expectations, which could eventually compromise treatment satisfaction and adherence (Ashmore et al, 2018). Patient expectations are also greatly influenced by social and cultural variables. What individuals anticipate from their healthcare experiences can be influenced by cultural views on disease and recovery as well as societal conventions around medical procedures. For example, patients may have higher expectations for alternative medication delivery techniques than for standard therapies in societies that place a high value on traditional cures. By offering common experiences and reaffirming certain views on the effectiveness of therapy, social support networks—such as peer and family influences—further modify these expectations (Costa et al, 2024).

Personal psychological aspects are also important. More positive treatment expectations have been associated with personal characteristics including optimism, self-efficacy, and health locus of control (Bandura, 1997). High self-efficacy patients typically have optimistic expectations regarding the efficacy of their treatments because they feel that they have control over their own health outcomes (Horne & Weinman, 1999). Furthermore, expectations for the future are shaped by both positive and bad previous events. Patients are likely to anticipate similar advantages in the future if they have previously had positive results from similar therapies (Hanlon et al, 2024).

It is impossible to ignore how the media and public health initiatives affect patient expectations. As digital media has emerged, people are increasingly using the internet to obtain health-related information, which has the potential to greatly influence their expectations. However, there is a significant range in the quality and dependability of this type of information, and inaccurate information might result in inflated expectations that negatively impact treatment choices (Abrar et al, 2020).

Patient expectations are also shaped by systemic and economic issues. Depending on their prior experiences with the healthcare system, people may form expectations that are either too cautious or too hopeful in systems where treatment quality and availability vary widely. Furthermore, the availability of contemporary therapeutic modalities and

sophisticated technology interventions might raise patient expectations, perhaps above what is clinically feasible (Driver et al, 2010). The psychological condition of the patient at the time of diagnosis also matters. According to Morrison and Maddock (2007), anxiety, sadness, and stress are known to affect cognitive processing and might cause people to have negative expectations for the results of therapy. On the other hand, proactive treatment and adherence have been linked to favorable mental states (Ryan & Deci, 2000). According to research, patients' physiological reaction to therapy can be improved when they feel that a treatment is effective. This phenomenon has been noted in a variety of medical specialties (Horne et al., 2013).

The role of the therapeutic alliance must also be taken into account. It has been demonstrated that more reasonable and constructive expectations are shaped by a solid, trustworthy connection between patients and healthcare professionals (Epstein & Street, 2011). These kinds of connections encourage candid conversation, which makes it possible to modify expectations in light of continuing treatment experiences. By ensuring that patient expectations and clinical reality are in line, this dynamic engagement can result in more successful shared decision-making (Roter & Hall, 2006).

In conclusion, a wide range of elements, including personal psychological characteristics, past experiences, and systemic, social, and cultural influences, all play a role in the development of patient expectations. Designing treatments that not only educate patients but also match their expectations with attainable treatment outcomes requires a thorough grasp of these aspects. According to the literature, enhancing adherence and, eventually, treatment results requires maximizing patient expectations through supportive healthcare settings, culturally sensitive care, and effective communication. In order to create all-encompassing solutions that address the various factors that impact patient expectations, future research should keep examining these multifaceted aspects.

6.3. Impact of Expectations on Therapy Adherence

A key factor in treatment effectiveness is still therapy adherence, especially for chronic illnesses that call for long-term care. Adherence behaviors are significantly impacted by patient expectations, which affect whether or not patients regularly adhere to treatment plans. A increasing body of data demonstrates that optimistic expectations might act as a trigger for increased adherence, whereas negative or inaccurate expectations can contribute to inferior compliance (Rodrigues et al, 2024). Patients' conviction that the therapy is essential is one way that expectations affect adherence. According to the

Necessity-Concerns Framework, patients are more likely to follow a treatment plan when they believe it is very necessary and are less concerned about any negative side effects (Horne et al., 2013). This approach is being used more and more to evaluate adherence in patients with DFUs after being validated across a variety of chronic disorders, such as diabetes and cardiovascular diseases (DiMatteo, 2004). A thorough grasp of the treatment's mechanism and its advantages will help patients receiving alternative drug administration for DFUs feel more obligated to take their medication, which will increase adherence.

Self-efficacy, or the conviction that one can carry out the actions necessary for effective therapy, is another crucial component. According to Bandura's (1997) theory of self-efficacy, those who have a high level of self-efficacy are more likely to stick with demanding routines despite setbacks. Patients frequently show more confidence in controlling their condition when they have optimistic expectations about the results of an alternate drug delivery strategy, which leads to better adherence (Ryan & Deci, 2000). When patients get ongoing feedback from healthcare professionals, this self-regulation process is further strengthened and their expectations are kept in line with their treatment experiences (Osterberg & Blaschke, 2005).

Additionally, adherence habits are significantly shaped by the connection between the patient and the practitioner. Negative expectations can be reduced and a supportive atmosphere can be created for patients and physicians via effective communication and trust. Research has shown that patients are more likely to follow treatment plans when medical professionals actively participate in shared decision-making and give succinct, understandable explanations of the recommended course of action. When it comes to alternative medicine administration, where new delivery techniques could first be viewed with suspicion, this cooperative dynamic is especially crucial (López-Moral et al, 2024).

Adherence is also influenced by outside factors and social support. Peer groups, community networks, and family members can support continuous adherence practices and promote good expectations. Patients' expectations of the effectiveness of therapy rise when they witness others' favorable results or when they have support from their social networks, which improves compliance. Such support networks are crucial for long-term, complicated treatment plans for chronic illnesses like DFUs (Laopoulou et al, 2020).

Furthermore, expectations and adherence may be impacted by the characteristics of the alternate drug delivery technique itself. Patients are more likely to have positive expectations when innovative delivery technologies minimize adverse effects or

streamline the administration procedure. Patients are more likely to stick with a treatment when they have fewer side effects and think it's more convenient. This link emphasizes how crucial it is to create treatment modalities that are easy to use and satisfy patients' expectations for both effectiveness and usability (Gulcan, 2009). Adherence is made even more difficult by the psychological effects of chronic disease. Emotional burdens like anxiety and sadness are common in chronic diseases, and they can have a detrimental impact on patients' expectations and willingness to follow their treatment plans. Realigning expectations and enhancing adherence might be achieved by addressing these psychological aspects through supportive treatments or psychotherapy. It has been demonstrated that include psychological support in treatment programs improves patients' opinions of the effectiveness of their care and raises adherence rates overall (Vas & Chockalingam, 2023).

In conclusion, a significant factor influencing therapeutic adherence is patient expectations. Adherence may be greatly improved by having positive expectations that are supported by a strong feeling of treatment necessity, high self-efficacy, good communication with healthcare professionals, and supportive social networks. On the other hand, unfavorable or unreasonable expectations might result in treatment termination and worse results. Therefore, methods for matching patient expectations with practical treatment objectives are crucial for maximizing adherence, especially in complicated situations like diabetic foot ulcers that are managed with alternate medication delivery. These linkages should be further investigated in future studies, and customized therapies that address the complex drivers of adherence should be developed.

7. Therapy Adherence in Diabetic Foot Ulcer Patients

7.1. Definition and Importance of Therapy Adherence

A key factor in treatment effectiveness is therapy adherence, particularly for chronic illnesses where ongoing therapy is necessary to avoid consequences. The degree to which patients comply to recommended regimens, such as medication usage, wound care procedures, and lifestyle changes, is referred to as adherence in the context of managing DFUs, especially when using alternate drug delivery techniques. According to Horne and Weinman (1999), adherence encompasses a wide range of actions that are consistent with the treatment plan and goes beyond simply taking medicine. Additionally, Osterberg and Blaschke (2005) stress that if patients do not follow their treatment plans consistently, even the most effective therapies will not work.

Therapy adherence is crucial for both clinical results and the financial viability of healthcare. Non-adherence in DFU patients may result in greater rates of infection, delayed wound healing, and eventually hospitalization or limb amputation. According to DiMatteo (2004), a large percentage of treatment failures in chronic illnesses can be attributed to non-adherence. Furthermore, patients who adhere to their treatment programs consistently see quantifiable improvements in their health, which lowers total healthcare expenses (Sabaté, 2003). This is especially important for DFUs, where the necessity of excellent adherence is highlighted by the high expense of addressing problems.

Another important factor in improving the effectiveness of alternate medication delivery techniques is therapy adherence. Alternative methods, such topical formulations or localized drug-delivery systems, are intended to optimize therapeutic results while reducing adverse effects, in contrast to traditional systemic medicines. According to Kandregula et al. (2022), patients who follow these innovative techniques might greatly accelerate wound healing due to the local medication concentration attained. However, the willingness and capacity of the patient to regularly adhere to the new protocols—which are frequently more complicated than normal regimens—is crucial to the effectiveness of these treatments.

The psychological effect of adherence on treatment results is another aspect of it. The Common-Sense Model of Self-Regulation states that patients' expectations and beliefs regarding their condition and its management have a significant impact on how they behave. Patients are more inclined to stick with a therapy if they have high expectations about its advantages. This creates a positive feedback loop that improves both subjective well-being and objective clinical outcomes. According to this phenomenon, which is also known as the "expectancy effect," encouraging reasonable but hopeful expectations is essential to encouraging adherence (Connell et al, 2021).

Additionally, the patient's involvement in the treatment process acts as a mediator in the link between therapy adherence and treatment results. Better overall disease management, increased self-efficacy, and a stronger sense of control over one's health are all linked to effective adherence (Bandura, 1997). These psychological aspects are especially important for long-term, complex treatments for chronic illnesses like DFUs. Research has repeatedly demonstrated that patients who feel empowered and well-informed are more likely to stick with their treatment plans over time, which eventually leads to improved clinical results (McIntosh et al, 2019).

The integration of digital health tools has also emerged as a promising strategy to enhance therapy adherence. Vrijens et al. (2012) indicate that mobile applications and electronic reminder systems can help patients manage their dosing schedules and adhere to complex treatment regimens. In the specific context of alternative drug administration for DFUs, these technologies provide real-time feedback and facilitate timely interventions, thereby overcoming common barriers such as forgetfulness or miscommunication. This digital support not only boosts adherence but also offers healthcare providers a mechanism for monitoring patient compliance and tailoring interventions accordingly.

In conclusion, therapy adherence is a complex concept that is critical to attaining the best possible treatment results, especially when using alternate medication delivery to treat diabetic foot ulcers. Its significance extends to better use of cutting-edge therapy modalities, better clinical results, lower healthcare costs, and more patient self-efficacy. In light of these numerous advantages, encouraging high adherence rates ought to be a top concern for researchers, legislators, and healthcare professionals.

7.2. Determinants of Adherence: Patient-Related, Treatment-Related, and Socioeconomic Factors

A variety of variables that may be generally divided into patient-related, treatment-related, and socioeconomic determinants affect therapy adherence in patients with diabetic foot ulcers. Complex interactions between these variables influence treatment results by influencing adherence habits. Developing focused strategies to increase adherence requires a deep comprehension of these drivers.

Patient-related factors include health literacy, psychological state, and individual motivations. Studies have found that patients with limited health literacy often struggle with adhering to treatment plans due to a lack of understanding of the importance of adherence (Pourhabibi et al., 2022). Psychological factors, such as depression and anxiety, can also hinder adherence, as these conditions can reduce a patient's motivation to follow treatment recommendations (Pouwer et al., 2023).

Adherence is mostly determined by patient-related variables. Important factors include personal traits including psychological well-being, self-efficacy, past experiences, and health attitudes. A foundation for comprehending how a patient's confidence in controlling their health affects their chances of sticking to therapy is provided by Bandura's (1997) research on self-efficacy. Patients are more likely to adhere to their recommended regimens when they feel capable of managing their ailment (Ng et al,

2024). Furthermore, expectations and eventual adherence behaviors are significantly shaped by the cognitive and emotional reactions to a diagnosis, as described in the Common-Sense Model of Self-Regulation. Patients who perceive their condition as severe and believe in the efficacy of the treatment are more likely to adhere, whereas those with low perceived threat or skepticism about treatment benefits may exhibit poor adherence (Horne & Weinman, 1999).

Adherence is also significantly impacted by treatment-related variables. Adherence may be aided or hindered by the intricacy of the treatment plan, which includes the frequency, duration, and mode of administration. Although they are frequently intended to maximize local therapeutic benefits and reduce systemic adverse effects, alternative medication delivery techniques may add more complication. For instance, patients could be less likely to adhere strictly to a novel medication delivery system if it is difficult to use or causes discomfort (Zhang et al, 2021). On the other hand, adherence rates are often greater for therapies that are seen as simple to use and come with thorough, unambiguous instructions. Furthermore, side effects—or even the prospect of them—can discourage patients from sticking with their treatment. Improving adherence requires both effective management of these adverse effects and methods to streamline the regimen.

The intricacy of treatment regimens and the design and usability of offloading devices are issues associated to therapy. For instance, it has been demonstrated that the perceived weight and pain of removable cast walkers (RCWs) contribute to their low adherence rates (Ababneh et al., 2022). Likewise, patients may become disinclined to follow treatment programs due to the intricacy of wound care regimens (Netten et al., 2019).

The adherence landscape is further influenced by socioeconomic considerations. Access to healthcare services, educational attainment, and financial limitations are important indicators of adherence. Individuals from poorer socioeconomic backgrounds could find it difficult to afford ongoing therapy, have trouble getting regular medical care, or lack the health literacy necessary to comprehend complicated treatment plans. Social variables, such as a lack of social support or cultural views that may affect attitudes toward contemporary medical procedures, exacerbate these difficulties (Ha et al, 2021). There are several ways in which these factors interact. A patient's poor socioeconomic position, for example, may reduce their health literacy, which may then have an adverse effect on their comprehension of the risks and benefits of therapy, eventually resulting in a decrease in adherence (DiMatteo, 2004). Similarly, individuals with low cognitive or intellectual abilities may find treatment-related variables, including complicated

regimens, more difficult. Therefore, it is crucial to think about these characteristics holistically as opposed to separately. Interventions that tackle many facets of the adherence conundrum, including educational initiatives that enhance health literacy while streamlining treatment regimens, are probably going to be more successful (Rosenstock, 1974).

Furthermore, a key determinant of adherence is the quality of the patient-provider interaction. Patients' perceptions and management of their treatment can be greatly impacted by the trust and effective communication that exist between healthcare professionals and patients. Research indicates that patients are more likely to follow their treatment plans when they feel heard and educated (Epstein & Street, 2011). This cooperative relationship improves adherence by strengthening the patient's belief in the effectiveness of the treatment and boosting their comprehension of their therapy.

Furthermore, the expectations and actions of patients are significantly shaped by social norms and cultural factors. Different adherence patterns may result from the coexistence of contemporary medical treatments and traditional healing methods in various societies. Designing culturally responsive therapies that might close the gap between conventional wisdom and contemporary medical practice requires an understanding of these subtleties. By bringing treatment practices into line with patients' cultural values and beliefs, for instance, culturally appropriate educational programs have been demonstrated to increase adherence.

In summary, there are many different and connected factors that influence therapy adherence in the management of diabetic foot ulcers. These include socioeconomic factors that impact literacy and access, treatment-related factors like regimen complexity and side effects, and patient-related factors like self-efficacy and health beliefs. A comprehensive, integrated strategy that takes into account each patient's particular difficulties is needed to address these variables. Future studies should concentrate on creating thorough models that take these factors into account and evaluating focused interventions meant to get over the obstacles to adherence.

7.3. Strategies to Enhance Adherence

Numerous tactics have been put forth and put into practice to improve adherence since it is crucial for the best possible treatment outcomes, especially when managing DFUs with alternate medication delivery. To address the many obstacles to adherence, these tactics include behavioral, educational, technical, and systemic treatments.

Patient education is a fundamental tactic. Patients who get educational interventions are given thorough information regarding their disease, the justification for the recommended course of treatment, and the anticipated advantages. According to Horne and Weinman (1999), patients who are well-informed have a greater grasp of the need for therapy, which promotes improved adherence. Individual counseling, group seminars, and written or digital training materials are just a few of the different ways that educational programs can be delivered. When these programs are customized to the patient's cultural background and degree of health literacy, they are very successful. Regarding DFUs, education encompasses not only medication compliance but also the significance of appropriate wound care and lifestyle adjustments (Raju et al, 2022).

Another crucial tactic is to strengthen the bond between the patient and the practitioner. Higher adherence rates have been repeatedly associated with effective communication between patients and healthcare professionals. Expectations can be brought into line with practical results by healthcare professionals who participate in collaborative decision-making, listen intently, and answer patients' concerns. Patients are encouraged to stick to their treatment regimens despite obstacles because of this connection founded on trust. These connections and, thus, adherence may be further strengthened by providing healthcare personnel with training programs that prioritize patient-centered care and communication skills (Zhu et al, 2023).

Adherence tactics have also been transformed by technological interventions. Adherence has been successfully increased by the use of telemedicine services, electronic reminders, and mobile health applications (Lazarou et al, 2024). Digital solutions can help patients remember to take their prescriptions, monitor the healing process of wounds, and communicate with medical professionals more quickly. Furthermore, these technologies allow real-time monitoring and feedback, which helps clinicians to act quickly when non-adherence is identified and supports adherence behaviors (Owolabi et al., 2020). Such digital alternatives can simplify complicated regimens and lessen the cognitive strain associated with self-management for DFU patients who use alternate medication administration techniques (Lazarou et al, 2024).

One important tactic is to make the treatment plan itself simpler. It is well recognized that complicated treatment plans make it difficult for patients to follow them, especially those who have cognitive impairments or low health literacy (Osterberg & Blaschke, 2005). Adherence can be significantly increased by streamlining the regimen, such as by

lowering the frequency of doses, using combination medicines, or creating user-friendly drug delivery methods (Kandregula et al, 2022).

Community-based therapies and social support are also important factors in improving adherence. Peers, family, and community organizations can offer patients both practical and emotional support, which encourages them to follow their treatment plans. Online or in-person support groups provide patients a chance to talk about their experiences and get knowledge from others who have gone through similar struggles. Long-term motivation maintenance and the reinforcement of healthy habits can both benefit greatly from these networks. Adherence has been shown to improve with interventions that include community outreach and family education, especially in areas with limited access to healthcare (Luo et al, 2023).

Another crucial tactic is to address socioeconomic constraints. Policy-level initiatives can greatly increase adherence for people who have restricted access to healthcare or budgetary limitations. To lessen the financial burden of long-term therapy, these might include the creation of patient support programs, enhanced insurance coverage, and subsidized treatment programs (Sabaté, 2003). Furthermore, practical issues that impede adherence might be resolved by offering flexible scheduling for follow-up visits or transportation support. Healthcare systems can foster an atmosphere where patients can concentrate more on self-care and continuous adherence by lowering the external responsibilities related to treatment (Glanz, Rimer, & Viswanath, 2008).

Cognitive-behavioral therapy (CBT) and motivational interviewing are two behavioral techniques that have demonstrated potential in improving adherence. These methods investigate and resolve opposing ideas and feelings in order to alleviate patients' ambivalence regarding therapy. Specifically, motivational interviewing increases patients' intrinsic drive to stick with treatment and helps them express why they want to change (Binning et al, 2019). In order to encourage and reinforce adherence, such behavioral interventions can be included into standard clinical treatment, especially for patients with chronic diseases where sustained involvement is essential (Ryan & Deci, 2000).

Lastly, maintaining adherence over time requires ongoing observation and feedback. Healthcare professionals can see early indicators of non-adherence and take swift action by scheduling routine follow-up appointments and periodically reviewing the treatment plan. In addition to giving patients the certainty that their progress is being continuously

watched, this continuous review enables prompt treatment regimen adjustments depending on each patient's needs (Francia et al, 2019).

In conclusion, a multimodal strategy is needed to improve therapy adherence in diabetic foot ulcer patients receiving alternate medication delivery. Overcoming adherence hurdles requires a variety of tactics, including behavioral methods, technology advancements, social support, regimen simplification, patient education, enhanced patient-provider contact, and ongoing monitoring. Optimizing clinical results and enhancing general quality of life need a customized, integrated intervention approach that takes into account the particular difficulties this patient population faces.

8. Conclusion

8.1. Summary of Key Findings

Important information about the efficacy, patient adherence trends, and potential to revolutionize chronic wound care has been gleaned from research on alternate drug delivery systems for the treatment of DFUs. There is strong evidence that localized administration methods, such topical and transdermal procedures, can improve medicine absorption at the wound site and lessen systemic adverse effects. For example, compared to oral or injectable insulin, hydrogel-based insulin delivery devices have been demonstrated to give two to three times higher medicine retention in ulcer beds, therefore directly reducing inflammation brought on by hyperglycemia. Similarly, silver nanoparticle dressings deliver sustained antibacterial activity against multidrug-resistant pathogens like Pseudomonas aeruginosa without the need for significant systemic absorption, thus lowering the risk of nephrotoxicity. These findings are consistent with the broader movement toward precision medicine in diabetes treatment, which emphasizes targeted drug delivery to reduce common comorbidities.

Notwithstanding these encouraging benefits, patient adherence is still a major problem that is fueled by usability and accessibility concerns. There are both logistical and psychological obstacles to alternative treatments that lower the frequency of dose, such as weekly microneedle patches as opposed to daily oral antibiotics. A significant percentage of DFU cases include elderly patients, who frequently have difficulty administering viscous topical medicines like PDGF gels on their own, which results in inconsistent usage. Cultural views are also important; research suggests that patients in low-income areas may favor conventional treatments over innovative bioengineered dressings because they don't trust new technology. nonetheless, by providing real-time

feedback on wound development, smart dressings with embedded sensors have shown promise in improving adherence; nonetheless, their expensive cost may prevent broad use.

Additionally, the formation of biofilms that reduce the efficiency of systemic antibiotics usually complicates chronic DFUs. In preclinical models, emerging nanotechnological techniques—like topical sprays of quorum-sensing inhibitors and nitric oxide-releasing nanoparticles—have demonstrated the capacity to disrupt biofilm matrices and decrease biofilm viability by 70–80% in 48 hours, outperforming conventional debridement techniques. However, because of defined protocols and regulatory obstacles, the adoption of these improvements in clinical practice is still sluggish. Lastly, it has been demonstrated that integrating multidisciplinary treatment models—which entail cooperation between podiatrists, endocrinologists, and wound care nurses—significantly improves patient adherence. Telemedicine initiatives and nurse-led training programs have improved treatment results and decreased abuse rates, especially in remote areas with limited access to healthcare.

8.2. Recommendations for Practice and Research

While pointing up important research gaps that require immediate attention, the evidence base also supports practical measures to maximize alternate medicine delivery in DFU therapy. In DFU-specific wound clinics, multidisciplinary treatment models that unite podiatrists, pharmacists, and diabetes educators should be included into clinical practice. Such cooperative environments can offer thorough adherence support and expedite the therapy selection process. To enhance treatment results, standardized biofilm management procedures that include mechanical debridement with specific topical antibiofilm medicines such lactoferrin are also crucial. In addition, enhancing patient education through the development of visual aids and multilingual tutorials can significantly improve the correct application of transdermal patches or injectable therapies, while mobile health applications, like FootSense, can play a pivotal role in reminding patients about dressing changes and tracking their progress.

Addressing issues of equity and affordability is also crucial. Given their potential to avoid amputations and lower total treatment costs, public healthcare systems must advocate for insurance coverage of bioengineered dressings. In low-income areas, partnerships with non-governmental organizations might make it easier to provide subsidized topical antimicrobials, especially those with formulations that have a longer shelf life, such

iodine cadexomer beads. Another interesting approach is the use of tailored medication into DFU therapy. While adjusting drug release kinetics precisely based on real-time pH data can be achieved by customizing nanocarrier systems, such as pH-responsive hydrogels, to individual wound microenvironments, methods such as proteomic profiling can assist in identifying patients who may benefit from growth factor therapies.

Future studies need to fill in a number of areas. To assess the recurrence rates and late adverse effects linked to innovative nanomaterials, such as silver nanoparticle dressings, long-term safety and effectiveness studies, including 5-year longitudinal trials, are necessary. Using mixed-methods approaches, studies exploring socioeconomic and cultural factors of adherence may provide insight into how cultural perceptions affect the uptake of cutting-edge medicines like stem cell treatments. Furthermore, randomized studies will be essential for verifying predictive biomarkers (such MMP-9 levels) in order to direct the usage of matrix metalloproteinase inhibitors. Innovative drug delivery systems, including 3D-printed dressings customized to wound dimensions and inhalable nanovaccines targeting diabetic immunopathy, also merit exploration. Finally, regulatory and policy reforms are needed, calling for collaboration with agencies like the FDA to create expedited approval pathways for combination products and establishing international registries to monitor real-world outcomes of advanced therapies.

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