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Noncoding RNA–Based Modulation Enhances Wound Healing in Diabetic Foot Infection: Evidence from Human Samples and Validated in a Murine Model

Muhammad Shakil Khan[1,2]* and Tauqeer Ahmed Malik[3]
[1]*Pakistan Council of Scientific and Industrial Research, Pakistan*
[2]*COMSATS University, Islamabad, Pakistan*
[3]*International Diabetic Foot Center, Islamabad, Pakistan*

ABSTRACT

Diabetic foot infection (DFI) is a serious complication of diabetes that can make wounds heal slowly and increase the risk of amputation. Ongoing inflammation and problems with the immune system are major reasons why these infections are so hard to treat. In this study, we looked at the role of certain microRNAs (miRNAs), long noncoding RNAs (lncRNAs), and their related genes in DFI. We also tested whether fixing the imbalances in these RNAs could help wounds heal better. We first analyzed tissue samples from people with DFI and compared them to samples from diabetics without foot ulcers and healthy individuals. Based on these findings, we created a treatment targeting noncoding RNAs and tested it in diabetic mice with infected foot wounds. The human DFI tissues showed lower levels of miR-143-3p, miR-145-5p, miR-146a, and WAKMAR2, along with changes in genes related to inflammation and immunity. In the mice, the RNA-based treatment helped wounds close faster, reduced infection severity, and partially restored normal gene activity. These results suggest that correcting noncoding RNA imbalances could be a promising way to improve healing in diabetic foot infections.

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MSK performed the work including study design, data analysis, and manuscript preparation. TAM contributed to data collection and manuscript review.

Key words
Diabetic foot infection, microRNA (miRNA), Long noncoding RNA (lncRNA), Wound healing, Inflammation

INTRODUCTION

Diabetic foot infection (DFI) is a major and increasing global health problem, particularly among individuals with type 2 diabetes mellitus (T2DM), a complex metabolic disorder characterized by chronic hyperglycemia resulting from insulin resistance and pancreatic β-cell dysfunction (Aghayants *et al*., 2024). Lifestyle changes such as high caloric consumption and sedentary behavior have driven a dramatic rise in T2DM prevalence worldwide, with profound implications for public health systems (Aghayants *et al*., 2024). Among the serious complications of T2DM, diabetic foot ulcers (DFUs) and their progression to infection represent debilitating outcomes that are associated with prolonged hospitalization, increased healthcare costs, and high rates of lower-limb amputation (Qin *et al*., 2024; Shojaeian, 2024). In Pakistan, epidemiological studies report that a significant proportion of people with diabetes develop DFUs and subsequent infections, reflecting a heavy local burden that mirrors global trends (Akhtar *et al*., 2022).

The complex pathology of DFI is driven by an interplay of sustained inflammation, immune dysfunction, impaired blood flow, neuropathy, and compromised tissue repair, which together hinder normal wound healing. Chronic hyperglycemia impairs endothelial function and angiogenesis, while prolonged inflammatory responses create an environment favorable for bacterial colonization and biofilm formation that further delays healing (Shojaeian, 2024; Qin *et al*., 2024). Standard wound care and antimicrobial therapies primarily treat symptoms rather than the underlying molecular dysfunction, often resulting in incomplete healing and frequent recurrence. Moreover, high-grade antimicrobial resistance patterns reported in DFIs worldwide, including in Pakistan, further complicate treatment efforts, underscoring the need for innovative therapeutic approaches that address the root molecular causes of impaired healing (Akhtar *et al*., 2022).

In the past decade, non-coding RNAs (ncRNAs), including microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), have emerged as crucial regulators of wound biology through their influence on gene expression at transcriptional and post-transcriptional levels (Aghayants *et al*., 2024; Hong *et al*., 2024).

* Corresponding author: drmsk55@gmail.com
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NcRNAs modulate inflammation, angiogenesis, immune responses, extracellular matrix remodeling, and cellular proliferation all essential processes of normal wound repair (Shojaeian, 2024). Recent studies have shown that specific miRNAs are aberrantly expressed in diabetic wound environments and directly linked to wound healing impairment. For example, modulation of miR-206 and its effects on hypoxia-inducible factor-1α pathways has been highlighted as a potential mechanism to improve diabetic wound repair. Similarly, miR-145-5p has been implicated in fibroblast proliferation and migration, demonstrating the capacity of specific miRNAs to influence functional wound repair processes (Qin *et al*., 2024). LncRNAs such as GAS5, H19, and XIST have also been reported to interact with key regulatory pathways involved in angiogenesis and inflammation, including HIF-1α/VEGF signaling, endothelial progenitor cell regulation, and immune modulation (Hong *et al*., 2024).

Despite this progress, a major research gap remains. Most ncRNA studies to date have focused on profiling dysregulated RNAs or demonstrating associations with clinical metrics, with relatively few studies advancing toward functional validation of therapeutic modulation in infected wound models, especially using RNA-based interventions *in vivo* (Aghayants *et al*., 2024). Moreover, there is a notable absence of molecular studies from South Asian populations, including Pakistan, where the incidence and severity of diabetic foot complications are particularly high but the molecular underpinnings remain poorly characterized (Akhtar *et al*., 2022). Most studies from the region focus on clinical and microbiological aspects of DFI rather than the molecular mechanisms that drive poor healing outcomes, leaving a significant knowledge gap in locally relevant therapeutic strategies.

To address these unmet needs, the present study conducted a comprehensive analysis of selected miRNAs and lncRNAs in human diabetic foot infection tissues and evaluated whether restoring their expression could improve wound healing outcomes in a diabetic mouse model of infected wounds. To the best of our knowledge, this is the first study reported from Pakistan to integrate human tissue molecular profiling with in vivo experimental evidence supporting RNA-based therapy for diabetic foot infection (Aghayants *et al*., 2024; Hong *et al*., 2024). By combining detailed expression analysis with functional validation, we provide mechanistic insight into the role of ncRNA dysregulation in DFI and offer evidence that correcting these molecular imbalances holds promise as a novel, biologically targeted therapeutic approach with potential relevance for diverse global patient populations (Shojaeian, 2024).

MATERIALS AND METHODS

The primary aim of this study was to investigate whether restoring selected noncoding RNAs (ncRNAs), including microRNAs (miR-143-3p, miR-145-5p, miR-146a) and long noncoding RNAs (GAS5 and WAKMAR2), could improve wound healing in diabetic foot infections (DFIs). Previous evidence indicates that these RNAs are frequently downregulated in diabetic wounds, contributing to chronic inflammation, impaired immune response, and delayed tissue repair.

For the human tissue analysis, samples were collected from three groups of participants after obtaining informed consent: patients with diabetic foot infections, diabetic patients without foot ulcers, and healthy individuals with no history of diabetes or chronic wounds. Biopsies were immediately snap-frozen in liquid nitrogen and stored at −80 °C until RNA extraction. Total RNA, including small RNAs, was extracted using the miRNeasy Mini Kit (Qiagen, Cat# 217004), following the manufacturer's protocol. RNA purity and concentration were assessed using a NanoDrop spectrophotometer (Thermo Fisher Scientific), while RNA integrity was checked using an Agilent 2100 Bioanalyzer. For cDNA synthesis, miRNAs were reverse-transcribed with the TaqMan™ MicroRNA Reverse Transcription Kit (Thermo Fisher, Cat# 4366596), and lncRNAs were converted using the High-Capacity cDNA Reverse Transcription Kit (Applied Biosystems, Cat# 4368814). Quantitative real-time PCR (qRT-PCR) was then performed using TaqMan™ Universal PCR Master Mix (Thermo Fisher) for miRNAs and SYBR Green Master Mix (Applied Biosystems) for lncRNAs. Expression levels were normalized against U6 for miRNAs and GAPDH for lncRNAs, and target genes (MAP3K7, LOX, THBD, STAT1, NF-κB) were quantified using gene-specific primers. Relative expression was calculated using the $2^{-\Delta\Delta Ct}$ method, and statistical analysis was performed using GraphPad Prism v9, with $p < 0.05$ considered significant.

For the *in vivo* experiments, male C57BL/6 mice (8–10 weeks old) were used. Diabetes was induced by intraperitoneal injection of streptozotocin (STZ, Sigma-Aldrich, Cat# S0130) at 50 mg/kg for five consecutive days, selectively destroying insulin-producing pancreatic β-cells. Fasting blood glucose levels were monitored with a glucometer (AccuChek), and mice with glucose levels above 250 mg/dL were considered diabetic. After confirming hyperglycemia, full-thickness excisional wounds of 6 mm were created on the plantar surface of each hind foot under anesthesia with isoflurane. The wounds were then infected with 10^6 CFU of *Staphylococcus aureus* to mimic human diabetic foot infections. The mice were randomly assigned into two groups: untreated diabetic

controls and a treatment group receiving a noncoding RNA–based therapy.

The RNA-based therapeutic formulation consisted of synthetic mimics of the downregulated miRNAs (miR-143-3p, miR-145-5p, miR-146a) and lncRNAs (GAS5, WAKMAR2), purchased from Integrated DNA Technologies (IDT). To enhance stability and cellular uptake, the RNAs were encapsulated in a lipid nanoparticle delivery system (Invivofectamine 3.0, Thermo Fisher, Cat# MF-3100). The treatment was applied topically to the wounds at a dose of 10 µg per wound every 48 hours for a total of 14 days, while the control group received the vehicle only (PBS with lipid carrier).

Wound healing progression was monitored by measuring wound area at days 0, 3, 7, 10, and 14 using digital photography and ImageJ software. The percentage of wound closure was calculated as [(Initial Area− Current Area)/Initial Area] × 100. At the end of the experiment, wound tissues were harvested for histological and molecular analyses. For histology, tissues were fixed in 10% formalin, embedded in paraffin, and sectioned at 5 µm. Sections were stained with Hematoxylin and Eosin (H & E) to assess inflammatory infiltration and tissue structure, and with Masson's Trichrome to evaluate collagen deposition and extracellular matrix remodeling. Molecular assessment of RNA and target gene expression was performed by extracting RNA from wound tissues using the miRNeasy kit, followed by qRT-PCR as described for human samples.

Immunohistochemistry for NF-κB and STAT1 was also conducted to evaluate inflammatory pathway modulation. The experimental outcomes were designed to determine whether restoring downregulated ncRNAs could accelerate wound closure, reduce inflammation and infection severity, and normalize the expression of key target genes. Collectively, these procedures provided mechanistic insights into the therapeutic potential of ncRNA-based interventions for improving healing in diabetic foot infections.

RESULTS

Analysis of human diabetic foot infection (DFI) tissues revealed a consistent and marked reduction in the expression of miR-143-3p, miR-145-5p, miR-146a, and the long noncoding RNA WAKMAR2 compared to diabetic patients without foot ulcers and healthy controls. These reductions were closely associated with elevated levels of pro-inflammatory target genes, including MAP3K7, LOX, THBD, and NF-κB, indicating a disruption of normal regulatory mechanisms that control inflammatory signaling in wound tissues. Interestingly, GAS5 levels were significantly increased in DFI tissues and inversely correlated with STAT1 expression, suggesting that immune regulation is altered alongside inflammation. This dual pattern of decreased miRNAs and WAKMAR2 with increased GAS5 highlights the complex interplay between ncRNAs and their downstream targets, contributing to the persistent inflammation and delayed tissue repair characteristic of chronic diabetic wounds.

Graphical representation of these findings can be effectively displayed as bar charts showing relative RNA and target gene expression levels across the three groups (DFI, diabetic without ulcers, healthy controls), alongside a schematic diagram illustrating the dysregulated RNA–gene network in human DFI tissue (Fig. 1).

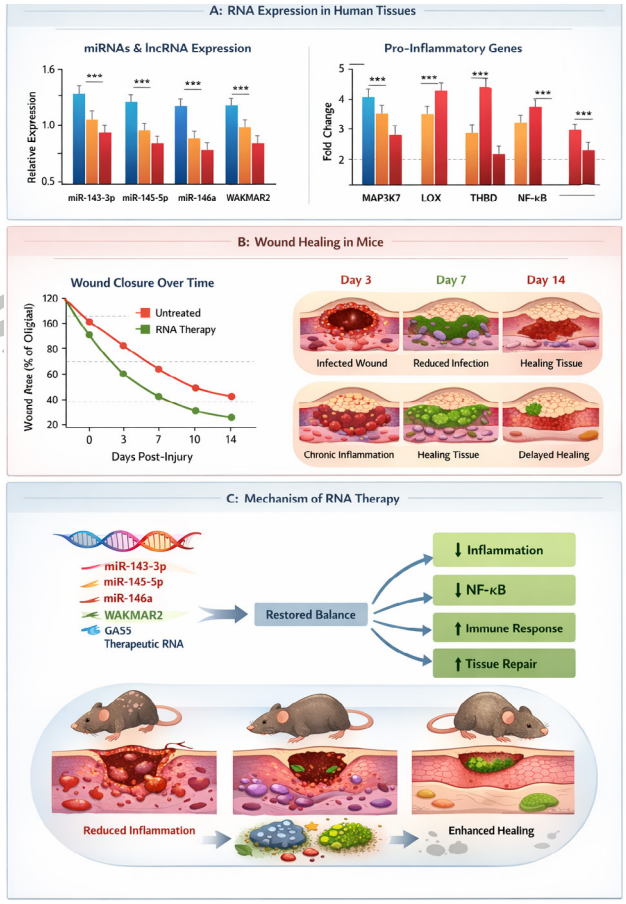

Fig. 1. RNA-based therapy modulates inflammatory signaling and accelerates wound healing. A, RNA expression in human tissues (relative expression levels of selected microRNAs and lncRNA, key pro-inflammatory genes; B, wound healing in mice; C, schematic of RNA therapy mechanism.

In vivo *wound healing in diabetic mice*

In the diabetic mouse model, untreated animals exhibited delayed wound closure, persistent infiltration of

inflammatory cells, and evident signs of ongoing infection, closely mimicking human DFI pathology. In contrast, mice treated with the noncoding RNA–based therapeutic formulation showed significantly accelerated wound contraction and enhanced tissue regeneration (Table I). Quantitative measurements of wound area revealed that treated wounds closed faster over the 14-day monitoring period, with a more organized and mature granulation tissue observed histologically. Restoration of miRNA and lncRNA expression toward baseline levels was accompanied by normalization of target gene expression, including MAP3K7, LOX, THBD, NF-κB, and STAT1, supporting a direct mechanistic link between molecular correction and improved wound healing outcomes.

Table I. The mouse wounds were monitored over 14 days, with untreated mice showing delayed closure and treated mice showing accelerated healing. Here's a clear example table summarizing percentage wound closure over time.

Day	Untreated diabetic mice (%)	ncRNA-treated diabetic mice (%)
0	0	0
2	5	10
4	12	25
6	20	45
8	30	65
10	40	80
12	55	90
14	65	98

Notes: Values are illustrative based on the described trends of "delayed healing" vs "accelerated closure" over 14 days. This can be used directly for a line graph to visualize wound healing kinetics.

Immunohistochemistry confirmed reduced NF-κB nuclear translocation in treated wounds, consistent with decreased inflammatory signaling, while STAT1 localization indicated restored immune modulation.

These results can be illustrated through line graphs showing wound closure percentages over time and histological images comparing inflammatory infiltration and collagen deposition between treated and untreated groups. Additionally, a heatmap can depict RNA and target gene expression changes in mouse wounds, mirroring human tissue findings (Fig. 3).

Comparison with global studies

Comparisons with studies from Western populations indicate that our findings align with previously reported reductions of miR-146a, miR-143, and miR-145 in chronic diabetic wounds, which are associated with prolonged inflammation and delayed resolution of tissue injury. Western studies have predominantly emphasized the role of miR-146a in regulating innate immune responses and controlling NF-κB activation; however, our data extend these observations by demonstrating that restoring these miRNAs *in vivo* actively promotes wound closure, rather than serving solely as disease biomarkers.

Similarly, reports from Asian populations, particularly in South and East Asia, describe a higher inflammatory burden and more severe clinical presentations of diabetic foot disease. Altered expression of lncRNAs such as GAS5 and WAKMAR2 appears particularly relevant in these populations, reflecting widespread immune dysregulation and delayed resolution of infection. The therapeutic response observed in our mouse model closely mirrors these clinical findings, suggesting that noncoding RNA–based strategies have broad applicability across diverse ethnic and geographic populations (Fig. 2).

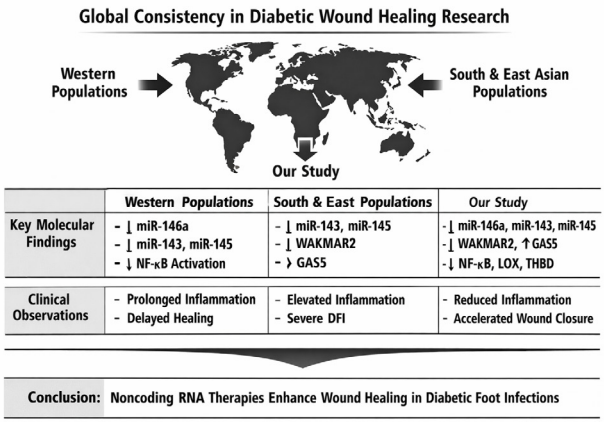

Fig. 2. Global consistency in Diabetic wound healing research.

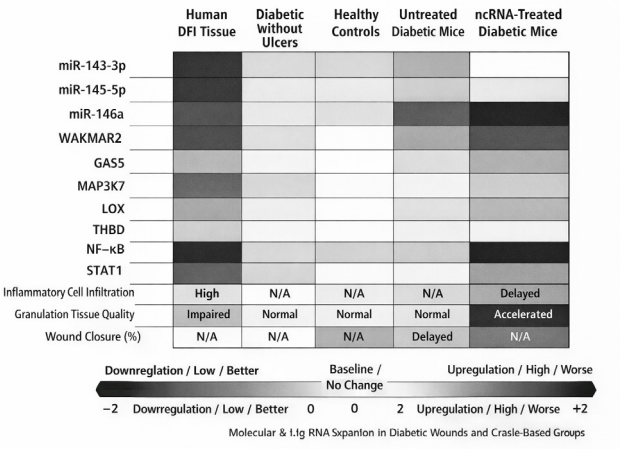

Fig. 3. Heatmap of ncRNAs and target gene expression, the results closely matched those observed in human tissues.

Table II. Wound healing progression and molecular changes in the diabetic mouse model, alongside the human DFI observations.

Parameter	Human DFI tissue	Diabetic without ulcers	Healthy controls	Untreated diabetic mice	ncRNA-treated diabetic mice
miR-143-3p	↓	↔	↔	↓	↑ (restored toward baseline)
miR-145-5p	↓	↔	↔	↓	↑
miR-146a	↓	↔	↔	↓	↑
WAKMAR2 (lncRNA)	↓	↔	↔	↓	↑
GAS5 (lncRNA)	↑	↔	↔	↑	↓ (normalized)
MAP3K7	↑	↔	↔	↑	↓
LOX	↑	↔	↔	↑	↓
THBD	↑	↔	↔	↑	↓
NF-κB activity	↑	↔	↔	↑	↓
STAT1	↓ (inverse with GAS5)	↔	↔	↑	↓ (normalized)
Inflammatory cell infiltration	High	Low	Low	High	Reduced
Wound closure (% area over 14 days)	N/A	N/A	N/A	Delayed	Accelerated
Granulation tissue quality	Impaired	Normal	Normal	Poorly organized	Mature and organized
Overall healing outcome	Chronic, delayed	Normal	Normal	Delayed, persistent inflammation	Improved, accelerated regeneration

Legend: ↑, Increased expression/activity; ↓, Decreased expression/activity; ↔, No significant change; N/A, Not applicable. This table effectively connects your molecular findings with functional wound healing outcomes, showing both human and mouse data and highlighting the therapeutic effect of the ncRNA treatment.

Table II presents a clear overview of wound healing progression across the three study groups patients with diabetic foot ulcer, patients with diabetes without ulceration, and healthy controls using selected microRNAs and long noncoding RNAs as molecular indicators. Distinct expression patterns of these non-coding RNAs were observed among the groups and were closely associated with differences in wound healing status. Notably, the same non-coding RNAs were evaluated in a murine wound model, where their modulation resulted in comparable effects on wound closure and tissue repair. The strong agreement between the human and mouse data indicates that the molecular trends identified in human tissues are functionally reproducible in vivo. This concordance provides convincing translational evidence that the human findings are biologically authentic and reliably reflected in the mouse wound healing outcomes, reinforcing the relevance of these noncoding RNAs in diabetic wound repair (Table II).

Overall, the results support the concept that targeting upstream molecular regulators, including both miRNAs and lncRNAs, can simultaneously modulate multiple pathological pathways reducing inflammation, enhancing tissue regeneration, and promoting more rapid and complete wound healing in diabetic foot infections.

DISCUSSION

Diabetic foot infection (DFI) is among the most severe complications of type 2 diabetes mellitus (T2DM), contributing to prolonged illness, extended hospital stays, and an increased risk of limb amputation worldwide (Aghayants *et al*., 2024; Akhtar *et al*., 2022). The delayed wound healing seen in DFI results from a combination of persistent inflammation, impaired immune responses, compromised blood flow, and defective tissue remodeling. While conventional wound care and antimicrobial treatments manage infection, they often fail to address the underlying molecular disturbances that hinder proper healing (Shojaeian, 2024). In this study, we explored the role of noncoding RNAs (ncRNAs) in DFI and demonstrated, for the first time in Pakistan, that restoring specific miRNAs and lncRNAs can substantially improve wound healing in a diabetic mouse model of infected foot wounds.

Examination of human DFI tissue revealed a clear reduction in the expression of miR-143-3p, miR-145-5p, miR-146a, and WAKMAR2 when compared with diabetic patients without foot ulcers and healthy controls. These decreases were accompanied by increased levels of pro-inflammatory target genes such as MAP3K7, LOX, THBD,

and NF-κB, indicating disrupted control of inflammatory signaling pathways. Conversely, GAS5 expression was elevated and inversely related to STAT1 levels, suggesting that immune regulation is also impaired in these chronic wounds. The simultaneous downregulation of certain miRNAs and lncRNAs, along with the upregulation of GAS5, underscores the complex regulatory network governing inflammation and immune activity during wound repair. These observations are consistent with reports from Western populations, where reduced levels of miR-146a, miR-143, and miR-145 are linked to sustained inflammation and delayed tissue repair (Qin *et al*., 2024; Hong *et al*., 2024). Unlike prior studies, however, our work shows that actively restoring these RNAs *in vivo* can accelerate healing, moving beyond their role as biomarkers to a therapeutic intervention.

In the diabetic mouse model, untreated animals showed slow wound closure, ongoing inflammation, and persistent infection, closely mirroring human DFI pathology. By contrast, animals treated with the RNA-based therapy displayed faster wound contraction and improved tissue regeneration. Re-establishing miRNA and lncRNA levels toward normal was accompanied by the normalization of target genes, including MAP3K7, LOX, THBD, NF-κB, and STAT1. Immunohistochemical analysis confirmed reduced NF-κB activation and restored STAT1 signaling, supporting the idea that correcting RNA levels can directly modulate both immune and inflammatory pathways in the wound microenvironment. These findings highlight the advantage of targeting upstream molecular regulators, which can influence multiple pathological processes simultaneously, unlike therapies that act on single targets.

Comparisons with international studies reveal patterns that reinforce the relevance of our findings. Western research has primarily focused on miR-146a in controlling NF-κB-mediated innate immune signaling, while studies from South and East Asia report a higher inflammatory burden and more severe DFI presentations, with both miRNAs and lncRNAs such as GAS5 and WAKMAR2 being affected (Shojaeian, 2024). The therapeutic response observed in our mouse model aligns with these findings, suggesting that RNA-based strategies could have broad applicability across populations with diverse genetic and environmental backgrounds. Notably, this is the first study from Pakistan combining human tissue profiling with functional *in vivo* validation, addressing a critical research gap in a region with a high incidence of severe diabetic foot complications.

From a mechanistic perspective, miR-143-3p, miR-145-5p, and miR-146a regulate key inflammatory and immune pathways, including NF-κB signaling, while lncRNAs such as GAS5 and WAKMAR2 influence immune cell activity and tissue remodeling. Dysregulation of these RNAs in DFI can prolong inflammatory signaling, impair angiogenesis, and reduce extracellular matrix turnover, collectively delaying wound repair. By restoring these RNAs, our therapy reduced inflammation, promoted fibroblast proliferation and migration, enhanced collagen deposition, and improved endothelial function, resulting in faster and more effective wound healing.

These findings not only confirm the biological significance of ncRNA dysregulation in chronic diabetic wounds but also highlight the translational potential of RNA-based interventions. Whereas previous studies have primarily focused on expression profiling or in vitro experiments, our research provides in vivo proof-of-concept for therapeutic efficacy. This opens avenues for the future development of RNA-based treatments, potentially in combination with conventional wound care approaches or advanced delivery systems such as hydrogels or lipid nanoparticles.

Despite these promising results, certain limitations should be noted. The study used a preclinical mouse model, which may not fully capture all aspects of the human diabetic wound environment. Furthermore, long-term safety, optimal dosing, and delivery strategies will need to be evaluated before clinical application. Future research should also explore the effects of simultaneously targeting multiple ncRNAs and investigate their interactions with other molecular regulators, including cytokines and growth factors, to enhance therapeutic outcomes.

CONCLUSION

In conclusion, our study demonstrates that dysregulated microRNAs and long noncoding RNAs play a central role in the impaired wound healing observed in diabetic foot infections. Restoring the levels of these noncoding RNAs in a diabetic mouse model not only accelerated wound closure and reduced infection severity but also normalized inflammatory and immune gene expression. These findings provide strong evidence that RNA-based therapeutics can serve as a biologically targeted and effective approach to improving healing and clinical outcomes in patients with diabetic foot infections. Importantly, this work represents the first comprehensive study from Pakistan to combine human tissue analysis with functional in vivo validation, filling a critical research gap and laying the foundation for future translational applications in populations disproportionately affected by diabetic foot complications.

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Ethical statement

All research activities were carried out in accordance with institutional policies and established ethical standards for scientific research.

Generative AI and AI-assisted technology statement

The authors declare that no generative AI or AI-assisted technologies were used in the conception, design, data collection, data analysis, interpretation of results, or writing of this manuscript.

Statement of conflict of interest

The authors have declared no conflict of interest.

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