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Exploring the Role of Cav1.2 VGCCs and PDGF-BB/PDGFRβ Signaling in Diabetes-Associated Wound Healing Impairment

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Abstract

Diabetic foot ulcers (DFUs) are a significant complication of diabetes with high recurrence and prolonged healing. To promote the healing of DFUs, relevant molecular signaling pathways must be modulated. Therefore, this study examines the role of Cav1.2 voltage-gated calcium channel (VGCC)-mediated platelet-derived growth factor (PDGF)-BB/platelet-derived growth factor receptor (PDGFR) β-extracellular signal-regulated kinase (ERK)1/2 signaling in impaired wound healing in diabetes. Immunohistochemistry was used to evaluate Cav1.2 VGCC, PDGFRβ, and collagen I; enzyme-linked immunosorbent assay (ELISA) was used to quantify PDGF-BB, ERK1/2, and α-smooth muscle actin (SMA); and hematoxylin and eosin staining was used to assess re-epithelialization. Twelve Wistar rats were allocated to normal and diabetic groups, with diabetes induced by streptozotocin (STZ) and nicotinamide (NA) administration. Four full-thickness skin wounds were generated on the dorsum of each rat using a punch biopsy. Wounds were treated every 2 days for a total of 6 days with standard treatments. Skin samples were collected 7 days after the initial injury. There was no correlation between Cav1.2 VGCCs and PDGFRβ ($r = –0.5885$, $p = 0.233$), as well as between PDGFRβ and ERK1/2 ($r = 0.3879$, $p = 0.447$). In contrast, a significant correlation was observed between PDGF-BB and α-SMA ($r = 0.8644$, $p = 0.026$). Furthermore, Cav1.2 VGCC expression, PDGF-BB levels, and ERK1/2 levels did not differ significantly ($p > 0.05$). However, PDGFRβ expression, level of α-SMA, collagen I expression, and re-epithelialization were significantly reduced in diabetic wound rats compared with those in normal rats ($p < 0.05$). Altogether, the findings support the involvement of PDGF-BB/PDGFRβ signaling in impaired diabetic wound healing. In contrast, no significant association was detected between Cav1.2 VGCCs and disrupted wound healing in diabetic rats. These findings underscore the need for further investigation to clarify the functions of these pathways and to identify potential therapeutic interventions.

Keywords: Collagen, Diabetic foot ulcer, ERK1/2, PDGFR, PDGF-BB, VGCCs, Wound healing

Introduction

Diabetes mellitus is a serious chronic disease that can cause multiple systemic complications and decrease quality of life; it is the seventh leading cause of death in the United States [1]. In 2017, 425 million people were living with diabetes worldwide, projected to increase to 629 million by 2045 [2]. Diabetic foot ulcers (DFUs) occur in 2% - 2.2% of patients annually [3], with a lifetime incidence of 19% - 34%. Further, the recurrence rate is high, with 40% of these ulcers recurring within 1 year, and 60% recurring after 3 years [4]. In patients with diabetes, wound healing is difficult, especially in cases of DFUs, and failure to heal leads to deterioration

of these ulcers into more severe forms, resulting in amputation [5]. Ulceration/destruction also leads to infectious reactions in deep tissues, along with neurological deviation into different types of peripheral arterial disease (PAD) affecting the lower extremities of patients with diabetes [6].

Wound healing is a complex process that involves interrelated, overlapping mechanisms of cell migration and proliferation, extracellular matrix synthesis, and orchestration of growth factors and cytokines. This complex process can be described in three phases: Inflammatory, proliferative, and remodeling phases [1]. Diabetic wounds take longer to heal than normal wounds [7], making them particularly difficult to treatmedically. These underlying conditions also affect cellular functions and cause inflammatory, immune [8-10], vascular [9-11], and neuropathic dysfunction [12], along with chronic hyperglycemia and oxidative stress [10,13] and growth factor dysregulation, which complicate the wound healing process in patients with diabetes [14,15].

Recent studies indicate the necessity of upregulating or downregulating DFU-associated molecular signaling pathways for their healing [16-19]. The coping and pathogenesis of DFUs involve a multifactorial process. As few treatment methods can efficiently promote the healing reaction, new ways that reduce expenditure and are effective at curing DFUs are urgently required. However, the molecular regulatory mechanisms specifically implicated in DFU healing remain poorly understood, and further investigation is needed to obtain a deeper insight into this pathology [19].

Calcium channels, particularly L-type voltage-gated calcium channels (VGCCs), are involved in various cellular processes, including wound healing [19]. L-type VGCCs have the subunits Cav1.1, Cav1.2, Cav1.3, and Cav1.4 [20]. Cav1.2 is a subunit of L-type VGCCs and is expressed in the skin, especially in basal cells, fibroblasts, keratinocytes, and melanocytes [21]. In some experimental contexts calcium-channels blockade has been shown to promote wound healing [22]. Impaired calcium homeostasis in diabetic wounds hampers the cellular responses necessary for wound healing. This implies that the system is properly regulated by calcium channels, as their dysfunction can compromise effective wound healing. However, the cellular role of L-type VGCCs, including Cav1.2, in diabetic wound healing remains poorly understood [22].

The direct interaction between L-type VGCCs and PDGFRβ in the context of diabetic wound healing remains inadequately elucidated, and from our scoping review, no studies have examined the role of Cav1.2 VGCC in relation to the PDGF-BB/PDGFRβ signaling pathways. Furthermore, calcium signaling influences growth factor-activated pathways [23]. Upon PDGFR activation, the MAP kinase pathway, particularly ERK1/2, undergoes phosphorylation, thereby directly regulating gene expression at the DNA level. This modulation involves overexpression of transcription factors, including activator protein 1 (AP-1) and nuclear factor κB (NF-κB). The expression of these transcription factors subsequently regulates the activation of target genes implicated in collagen synthesis, including type 1 collagen, as well as matrix remodeling regulators such as tissue inhibitors of metalloproteinases (TIMPs) and matrix metalloproteinases (MMPs) [24].

Platelet-derived growth factor-BB (PDGF-BB), a ligand for PDGFRβ, is essential for wound healing [24]. PDGF-BB stimulates fibroblasts differentiation into myofibroblasts, which are defined by α-SMA expression. This process is important for wound retraction and extracellular matrix remodeling [25]. Hyperglycemia in diabetic conditions decreases PDGF-BB expression and inhibits wound healing [26] Lower PDGF-BB expression in diabetic wounds is associated with reduced α-SMA levels, which rescinds wound contraction and healing [5]. A previous study reported that α-SMA expression in diabetic rats was lower than that in normal rats [27].

In Indonesia, Metcovazin® Red cream is commonly used to treat diabetic wounds and contains hyaluronic acid, chitosan, and zinc oxide. Hyaluronic acid plays a critical role in diabetic wound healing by promoting angiogenesis [28], and modulating inflammation [29], and collagen remodeling [30]. Chitosan-based materials provide an effective solution for managing diabetic wounds by addressing key challenges such as infection, inflammation, and impaired tissue regeneration [31-33]. Zinc oxide nanoparticles (ZnO NPs) have garnered attention owing to their antimicrobial [34], anti-inflammatory [35], and tissue-regenerative properties, making them a promising approach for enhancing diabetic wound healing [34].

Skin impedance is a key measure for monitoring wound healing because changes in it reflect alterations in tissue hydration, inflammation, and cellular activity. These variations provide valuable insights into wound progression and health [36-38]. This study aimed to investigate the role of Cav1.2 VGCC-mediated PDGF-BB/PDGFRβ-ERK1/2 signaling in diabetes-related wound healing impairment under standard care, assessing healing using α-SMA, collagen I, re-epithelialization, and skin impedance as additional parameters.

Materials and methods

Animals

Wistar rats were randomly assigned to two groups (normal and diabetic; NG and DG), with 6 rats per group. The animals weighed between 210 and 240 g. All rats were bred and housed in a controlled environment (50% - 60% relative humidity, 18 - 35 °C), and acclimatized for 7 days prior to treatment. The study procedure was approved by the Medical and Health Research Ethics Committee (MHREC) of the Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada (Ref No. KE/FK/0854/EC/2024).

Establishment of the diabetic foot ulcer model and its treatment

Diabetes was induced in six rats by a single intraperitoneal injection of 110 mg/kg body weight nicotinamide (NA, Solarbio, catalog no N8070-25G) dissolved in normal saline and 45 mg/kg body weight streptozotocin (STZ, CAYMAN, catalog no 13104-1G) dissolved in citrate buffer solution (0.1 M, pH 4.5). Blood glucose was measured in tail vein blood at 7 days after injection using a glucometer (EasyTouch®GCU), and animals with fasting blood glucose > 150 mg/dL were defined as having diabetes [39]. The rats were injected with ketamine hydrochloride 25 mg/kg of body weight before the wounding procedure. A punch biopsy (RIBBEL India) was used to create four full-thickness skin wounds, each measuring 0.8 cm in diameter, on the dorsal surface of the rats. Every 2 days over a 6-day period, the wounds were treated with normal saline (NaCl 0.9%), the antiseptic Octedine®, and Metcovazin® Red cream containing hyaluronic acid, chitosan, and zinc oxide.

Immunohistochemistry

Immunohistochemical staining was performed to assess the production of various proteins, Cav1.2 VGCCs, PDGFRβ, and collagen I. For this purpose, paraffinized skin tissue sections were placed on glass slides and deparaffinized. The sections were then layered with one of the following primary antibodies: Anti-Cav1.2 VGCCs (Invitrogen, catalog no MA5-27717, dilution 1:200), anti-PDGFRβ (Abclonal, catalog no A2180, dilution 1:300), and anti-collagen I (Abclonal, catalog no A22090, dilution 1:400). All antibodies were diluted in 1x PBS pH 7.4. Tissues for staining Cav1.2 VGCCs were incubated overnight at 4 °C, tissues for staining PDGFRβ and collagen I were incubated 1 h at room temperature. The sections were washed with PBS and incubated with a biotin-conjugated secondary antibody (ABCAM, catalog no ab236466). Streptavidin-peroxidase was used to visualize the staining, and diaminobenzidine substrate (DAB, 1:50) was used as a chromogenic agent (ABCAM, catalog no ab236466). Lastly, hematoxylin was used as a counterstaining agent. After dehydration in gradient ethanol solutions and clearing with xylene, the protein expression of Cav1.2 VGCC, PDGFRβ, collagen I was observed under 400x magnification using a light microscope (Olympus, Tokyo, Japan) and images were captured randomly from 15 fields per sample. The acquired images were analyzed using ImageJ software in percentage expression [40].

Enzyme-linked immunosorbent assay (ELISA)

After homogenization and centrifugation, the supernatant of the skin ulcer tissue was collected and quantitatively assayed for PDGF-BB (ELISA Kit, FineTest, catalog no ER1242), ERK1/2 (ELISA Kit, FineTest, catalog no ER0927), and α-SMA (ELISA Kit, Reed Biotech Ltd., catalog no RE3336R) levels according to the manufacturer's instructions.

Histological examination

Histological analysis of wound tissues was performed as follows. After rats were euthanized, skin samples were harvested and fixed in 10% formalin. Each tissue underwent dehydration with a series of ethanol/xylene baths and was subsequently embedded in paraffin. Tissues were then embedded in paraffin, sectioned at 4 μm, and deparaffinized and rehydrated

with xylene and ethanol. Finally, sections were stained with hematoxylin and eosin (H&E) and observed under a light microscope. At 100x magnification, re-epithelialization was quantified, and images were randomly captured from 15 fields. Scoring system with scores ranging from 0 to 3 [41].

Skin impedance

The impedance of rat skin was measured using a GW Instek LCR8220 high-frequency LCR meter. The readings for impedance measurement were taken over the frequency range of 100 Hz to 10 MHz.

Statistical analysis

Statistical analysis was performed using GraphPad Prism software (version 10.6.1, USA). PDGFRβ expression and re-epithelialization data were analyzed using the Mann-Whitney U-test. Cav1.2 VGCCs, PDGF-BB, ERK1/2, α-SMA, and collagen I were analyzed using an independent t-test. Correlation analyses were performed using Spearman's rank and the Pearson product-moment correlation test. Statistical significance was set at $p < 0.05$. Data for Cav1.2 VGCCs, PDGFRβ, PDGF-BB, ERK1/2, α-SMA, and collagen I are presented as mean ± standard deviation (SD). Meanwhile, re-epithelialization data are presented as median with interquartile range.

Results and discussion

This study focusses on the role of Cav1.2 VGCC-mediated PDGF-BB/PDGFRβ-ERK1/2 signaling in diabetes-related wound healing impairment under standard care, assessing healing using α-SMA, collagen I, re-epithelialization, and skin impedance as additional parameters.

Expression of Cav1.2 VGCCs

This study observed a lower expression of Cav1.2 VGCCs in diabetic rat wounds (1.32 ± 0.36) compared with normal rat wounds (1.48 ± 1.08), although this difference was not statistically significant ($p > 0.05$; **Figure 1**). Cav1.2 is a subunit of L-type VGCCs expressed in skin cells, such as basal cells, fibroblasts, keratinocytes, and melanocytes [21]. VGCCs are fundamental regulators of intracellular calcium homeostasis. When electrical activity induces their activation, the calcium influx that they mediate or their interaction with intracellular players leads to changes in intracellular Ca^{2+} levels, which regulate many processes such as contraction, secretion, and gene expression, depending on the cell type [42]. Although limited data are available on the role of Cav1.2 in diabetic wound healing, other studies have demonstrated that dysregulation of calcium homeostasis can hinder these processes, as evidenced by calcium imbalance in diabetic wounds [43-45] VGCCs represent potential targets for modulating wound healing [19]. Furthermore, blocking these channels may affect healing outcomes; for instance, blockade of the L-type VGCCs is beneficial for wound healing [46].

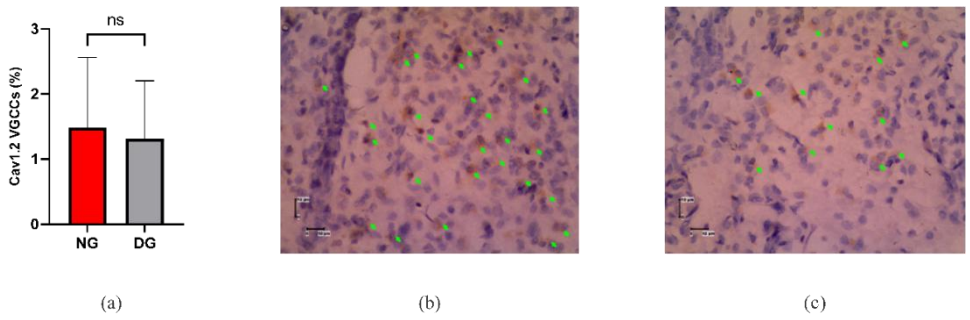


Figure 1 Expression of Cav1.2 VGCCs in normal (NG) and diabetic (DG) rats at day 7 post-wounding under standard care. (a) Quantitative expression scores; data are presented as mean ± SD (n = 6), and *p*-values were calculated using an independent t-test, $p < 0.05$ was considered significant. No statistically significant difference was observed between groups ($p > 0.05$; ns = not significant). (b, c) Representative images of Cav1.2 VGCC-positive cells in the dermis of normal (b) and diabetic (c) groups, detected using immunohistochemistry with DAB staining. Positive cells appear as brown-stained cells (green arrows). Magnification = 400x; scale bar = 10 μm.

Expression of PDGFRβ

This study showed a significantly lower PDGFRβ expression in diabetic rat wounds (3.46 ± 0.90) than in normal rat wounds (10.14 ± 2.93) ($p < 0.05$; **Figure 2**). This decrease occurs in multiple tissues, including the retina and kidneys, and is associated with the pathophysiology of diabetic complications [47-50]. Loss of PDGFRβ expression in diabetic conditions is likely due to hyperglycemia, which induces oxidative stress and inflammation, thereby adversely affecting PDGF-BB signaling and receptor expression [51,52]. PDGFR-β is essential for cell repair [24]. Loss of PDGFR impairs vital processes of wound healing, leading to delayed or insufficient healing [53].

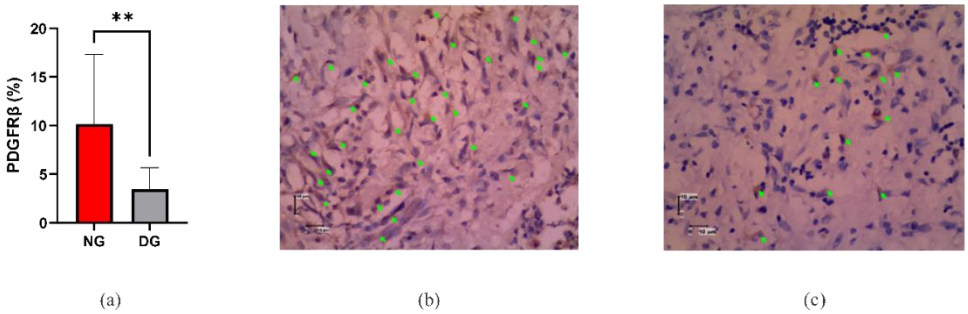


Figure 2 Expression of PDGFRβ in normal (NG) and diabetic (DG) rats at day 7 post-wounding under standard care. (a) Quantitative expression scores; data are presented as mean ± SD (n = 6). Statistical significance was assessed using an independent t-test; $p < 0.05$ was considered significant. Diabetic wounds showed significantly lower expression of PDGFRβ compared with normal wounds (**$p < 0.01$). (b, c) Representative images of PDGFRβ-positive cells in the dermis of normal (b) and diabetic (c) groups, detected using immunohistochemistry with DAB staining. Positive cells appear as brown-stained cells (green arrows). Magnification = 400x; scale bar = 10 μm.

PDGF-BB and ERK1/2 Levels

In contrast, PDGF-BB levels in the wound tissues in the diabetic group were lower (2,941 ± 664.1) than those in the normal group (2,941 ± 344.0), but the difference was not statistically significant ($p > 0.05$; **Figure 3(a)**). According to previous studies, chronic dermal ulcers exhibit lower PDGF levels than surgically created acute wounds. This finding supports the hypothesis that growth factor deficiency causes chronic wounds [50]. PDGF-BB is a powerful mitogen and chemoattractant for cells of mesenchymal origin, such as fibroblasts and smooth muscle cells, which are necessary for tissue healing and regeneration [5,53]. Low levels of PDGF-BB are associated with impaired angiogenesis, delayed re-epithelialization, and disordered collagen deposition, leading to prolonged wound healing [5,51]. PDGF-BB has a short half-life and is released in bursts, followed by a rapid decrease [52,54]. Very recently, the response of diabetic wounds to PDGF-BB was altered by high oxidative stress and chronic inflammation [55,56]; altered PDGFRβ expression in diabetic wounds coupled with prolonged inflammation catabolized the activity of PDGF-BB by affecting binding and signaling pathways, indicating functional redundancy between growth factors [57,58].

Furthermore, there were no study showing significant differences in ERK1/2 levels between the in diabetic (48.88 ± 3.59) and normal groups (48.91 ± 3.70) ($p > 0.05$; **Figure 3(b)**). Due to limited access, this study measured total ERK1/2 rather than phosphorylated ERK1/2 (p-ERK1/2). ERK1/2 exists in both activated and non-activated forms, with p-ERK1/2 representing the activated state, whereas the total ERK1/2 encompasses both phosphorylated and non-phosphorylated forms. Phosphorylated ERK1/2 is widely recognized as a marker of the ERK pathway activation under various cellular and pathological conditions [59]. Although total ERK1/2 expression generally remains stable, p-ERK1/2 levels may fluctuate in response to cellular stimuli or pathological alterations [60,61].

This study found no significant differences in PDGF-BB and ERK1/2 levels in wound tissues between normal and diabetic rat groups, likely because samples

were collected at a single time point—day seven post-injury. PDGF-BB is essential for wound healing because it promotes angiogenesis, cell migration, and collagen deposition. Its effects are mediated through pathways, such as PI3K/Akt and possibly ERK1/2, which are dynamic and time-sensitive [55,62]. ERK1/2 signaling typically fluctuates over time and may exhibit transient or oscillatory activation depending on the circumstances [63-65]. Therefore, the measurement of PDGF-BB and ERK1/2 levels at a single time point may not fully capture their roles in wound healing.

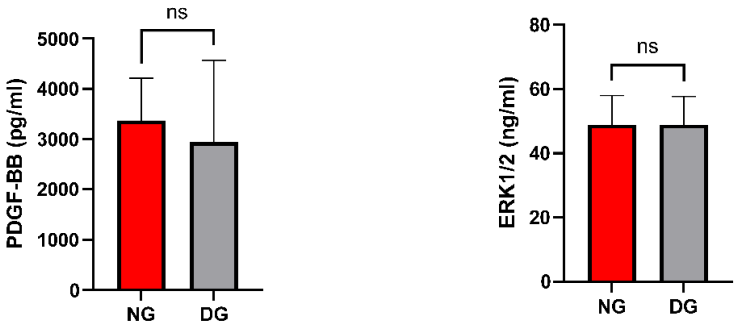


Figure 3 Levels of PDGF-BB (a) and ERK1/2 (b) in normal (NG) and diabetic (DG) rats at day 7 post-wounding under standard care. Quantitative analysis shows that PDGF-BB levels were lower in the diabetic group compared than the normal group, but the difference was not statistically significant ($p > 0.05$; ns = not significant). ERK1/2 levels also showed no statistically significant difference between groups ($p > 0.05$; ns = not significant). Data are presented as mean ± SD (n = 6), and *p*-values were calculated using an independent t-test, with $p < 0.05$ considered significant.

Myofibroblast activation, Collagen remodeling, and Re-epithelialization

Significant differences in wound healing were observed between the normal and diabetic rat groups. α-SMA was significantly lower in diabetic wounds than in normal wounds (mean ± SD: Normal = 44.39 ± 4.30, diabetic = 26.33 ± 5.79; **Figure 4**). Collagen I levels were also significantly reduced in diabetic wounds compared with normal wounds (mean ± SD: Normal = 41.06 ± 0.93, diabetic = 26.06 ± 5.43; **Figure 5**). Re-epithelialization was lower in diabetic wounds than in normal wounds (median [range]: diabetic = 0.5 (0 - 1), normal = 1.5 (1 - 2); **Figure 6**). All differences were statistically significant ($p < 0.05$). The expression of α-SMA and collagen I in diabetic wounds is significantly lower than those of normal wounds, as reported previously. This indicates decreased myofibroblast function and collagen deposition in the diabetic state [66]. Diabetic wounds exhibit reduced collagen deposition, which is important for wound strength and integrity. Altered collagen production is associated with dysfunctional behavior of fibroblasts and other extracellular matrix (ECM) components in a hyperglycemic environment [67,68]. Collagen provides a structural framework that supports keratinocyte migration and proliferation, facilitating reepithelialization and wound closure [69,70]. However, excessive matrix metalloproteinase (MMP) activity in diabetic wounds degrades the ECM, disrupting this scaffold and impairing reepithelialization [70-72].

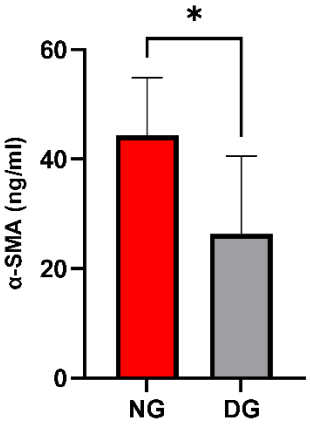


Figure 4 Levels of α-SMA in normal (NG) and diabetic (DG) rats at day 7 post-wounding under standard care. Quantitative analysis shows a significant decrease in α-SMA levels in the diabetic group compared with the normal group (*$p < 0.05$). Data are presented as mean ± SD (n = 6), and p values were calculated using an independent t-test, with $p < 0.05$ considered significant.

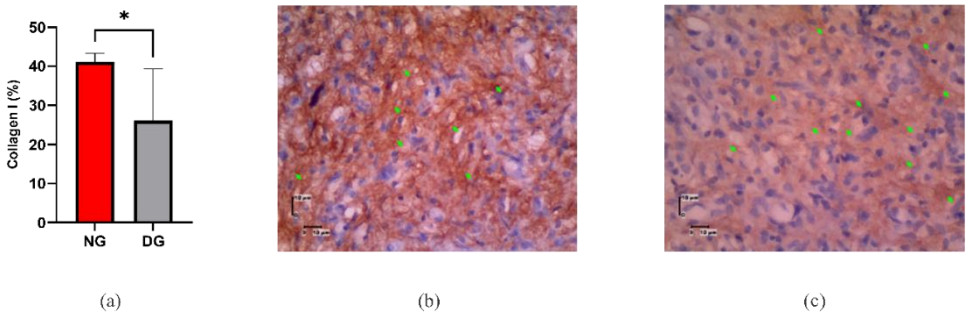


Figure 5 Expression of collagen I in normal (NG) and diabetic (DG) rats at day 7 post-wounding under standard care. (a) Quantitative expression scores; data are presented as mean ± SD (n = 6). Statistical significance was assessed using an independent t-test; $p < 0.05$ was considered significant. Diabetic wounds showed significantly lower expression collagen I compared with normal wounds (*$p < 0.05$). (b, c) Representative images of collagen I-positive areas in the dermis of diabetic (b) and normal (c) groups, detected using immunohistochemistry with DAB staining. Positive areas appear as brown-stained regions (green arrows). Magnification = 400x; scale bar = 10 µm.

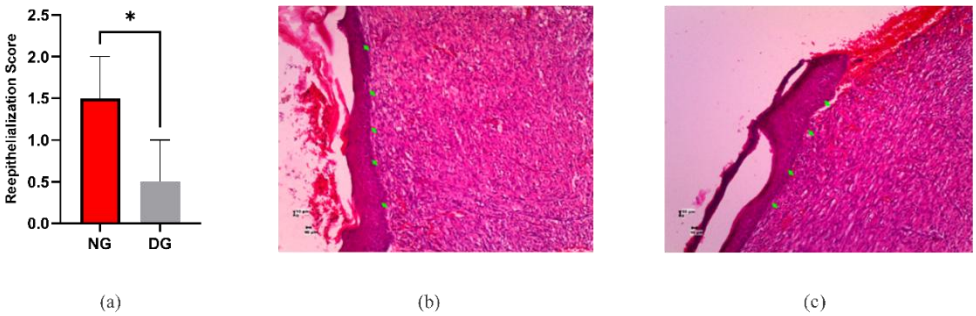


Figure 6 Re-epithelialization in normal (NG) and diabetic (DG) rats at day 7 post-wounding under standard care. (a) Quantitative re-epithelialization scores were significantly higher in the normal group than in the diabetic group (*$p < 0.05$). Data are presented as mean ± SD (n = 6), and p-values were calculated using the Mann-Whitney U test, with $p <$

0.05 considered significant. (b, c) Representative images of re-epithelialization in the wound of normal (b) and diabetic (c) groups, with green arrows indicating the re-epithelialized areas. Magnification = 100x; scale bar = 10 μm.

Correlation analysis between Cav1.2 VGCCs, PDGFRβ, PDGF-BB, ERK1/2, and wound healing markers in diabetic groups

Table 1 presents the correlation results between various molecular markers involved in diabetic wound healing. Significant positive correlations were observed between PDGF-BB and α-SMA (r = 0.8644, $p = 0.026$). No significant correlations were found between Cav1.2 VGCCs and PDGFRβ (r = −0.5885, $p = 0.233$), PDGFRβ and PDGF-BB (r = −0.2997, $p = 0.564$), PDGFRβ and ERK1/2 (r = 0.3879, $p = 0.447$), highlighting the complexity of diabetic wound healing.

Table 1 Correlation analysis between Cav1.2 VGCCs, PDGFRβ, PDGF-BB, ERK1/2, and α-SMA in diabetic rats at day 7 post-wounding under standard care (n = 6).

Variable	r	*p*
Cav1.2 VGCCs vs. PDGFRβ	–0.5885	0.233*
PDGFRβ vs. PDGF-BB	–0.2997	0.564**
PDGFRβ vs. ERK1/2	0.3879	0.447**
PDGF-BB vs. α-SMA	0.8644	**0.026****

Data were analyzed using the Pearson product-moment (**) and Spearman's rank correlation tests (*), with significance set at $p < 0.05$.

In the diabetic group, no significant correlations were found between Cav1.2 VGCCs and PDGFRβ, PDGFRβ and PDGF-BB expression, or ERK1/2 levels ($p > 0.05$; **Table 1**). Calcium influx through the VGCCs regulates cell migration and proliferation. However, our results suggest that calcium signaling via Cav1.2 VGCCs may not significantly activate PDGFRβ-dependent pathways involved in diabetic wound healing. This differs from previous research, which showed that calcium channels influence fibroblast activation and matrix production during healing [44,73]. Other studies indicate that RTKs can modulate calcium channels; for instance, IGF-1/RTK signaling increases Cav1.3 channel activity through calcium/calmodulin kinase II [74]. Strong correlations were observed between PDGF-BB levels and α-SMA expression ($p < 0.05$; **Table 1**), demonstrating their important roles in the diabetic wound healing process. PDGF-BB stimulates α-SMA, a marker of myofibroblast differentiation that is necessary for wound contraction and closure [66]. These results suggest a multi-factorial mechanism of diabetic wound healing, in which multiple pathways and factors interact. PDGF-BB is an important regulator of fibroblast migration and proliferation, and is necessary for normal wound healing [26,72]. It acts on various receptors and activates several signaling pathways that do not always correlate in a simple manner. PDGF-BB promotes cellular migration and proliferation during wound healing. However, its signaling interaction is altered in hyperglycemic and oxidative stress environments, thereby reducing its efficacy in damaged diabetic cells [26,49,75]. Further, PI3K/AKT, HIF-1, TGF-β, and MAPK/ERK pathways, which regulate critical stages of wound healing including inflammation, proliferation, and remodeling, are frequently dysregulated in diabetic wounds. These pathways are crucial for the inflammatory, proliferative, and remodeling phases of wound healing. These results indicate that other factors may compensate for or impede the anticipated local effects of PDGF signaling during diabetic wound healing [76,77].

Skin Impedance

Skin impedance was measured in normal and diabetic rats over a frequency range from 100 Hz to 10 MHz. Normal rats exhibited impedance values ranging from 0.31 to 93.40 kΩ, decreasing with increasing frequency. Diabetic rats showed markedly higher impedance, ranging from 0.91 to 1686.76 kΩ, with the greatest differences observed at lower frequencies (**Figure 7**), suggesting changes in the electrical properties of the diabetic skin. The results of this study

differ from those of previous studies that found that higher blood glucose levels were associated with lower bioimpedance [78,79]. However, other studies found that blood glucose levels are not related to bioimpedance [80]. By shifting the focus to skin impedance, wound healing can be effectively monitored by detecting changes in the electrical properties resulting from tissue damage and repair. A breach in the skin significantly alters its impedance, which can be used to track the healing progress [37]. Impedance changes correlate with cellular behaviors, such as migration and proliferation, during wound healing. For example, nanogroove electrodes have been shown to accelerate cell migration while slowing proliferation, thereby providing insights into tissue recovery dynamics [81]. Immediately after wounding, skin impedance drops significantly compared to that of healthy skin. This is attributed to disruption of the skin barrier and increased extracellular fluid accumulation due to inflammation and tissue damage. As re-epithelialization progresses and the skin barrier begins to recover, the impedance gradually increases. This reflects the restoration of tissue integrity and a reduction in inflammation [37,82,83].

Additional studies are required to elucidate the molecular pathways mediating the correlation between Cav1. 2 VGCCs activity with PDGF-BB/PDGFRB-ERK1/2 in diabetic wound healing. *In vivo* longitudinal studies integrating bioimpedance profiling with molecular analyses may allow the validation of impedance parameters as non-invasive biomarkers [84] of calcium channel activity and growth factor signaling. Further, the potential role of Cav1.2 VGCC and PDGFRβ function might provide new therapeutic directions to improve wound healing and reduce slow-healing-associated complications in patients with diabetes.

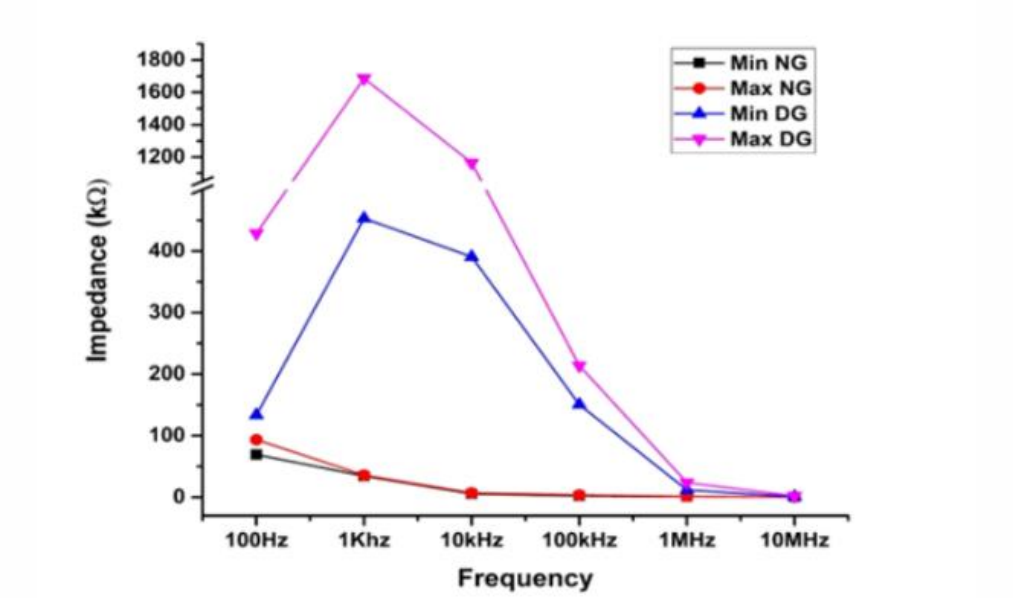


Figure 7 Skin impedance as a function of frequency from 100 Hz to 10 MHz in normal (NG, n = 6) and diabetic (DG, n = 6) rats.

Conclusions

In this study, significant reductions in PDGFRβ expression, α-SMA levels, collagen I expression, and re-epithelialization were observed in diabetic rats compared with normal controls receiving standard care. However, no significant differences were observed in Cav1.2 VGCC expression, PDGF-BB levels, or ERK1/2. Additionally, no significant correlation was found between Cav1.2 VGCCs and PDGFRβ, nor between PDGFRβ and ERK1/2. In contrast, a significant positive correlation was observed between PDGF-BB and α-SMA. These findings support the involvement of PDGF-BB/PDGFRβ signaling in impaired diabetic wound healing. However, the findings regarding Cav1.2 VGCCs require further investigation to better understand their potential role in wound healing. It is important to note that this study was conducted at a single time point (day 7 post-wounding), which may not

fully capture the dynamic changes in these biological parameters during wound healing. Although total ERK1/2 levels were analyzed, the absence of p-ERK1/2 measurements may have hindered a precise depiction of signaling pathway activation. In addition to these molecular observations, skin impedance measurements from 100 Hz to 10 MHz showed higher impedance in the diabetic group than in the normal group. Future research could include assessing p-ERK1/2, longitudinal sampling throughout the wound-healing process, and pathway-specific interventions, such as blocking or knockout approaches, to clarify molecular mechanisms. Additionally, the potential of skin impedance measurements as a non-invasive tool for evaluating diabetic wound healing could be further explored.

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Declaration of Generative AI in Scientific Writing

During the preparation of this manuscript, the authors used tools (e.g., Scopus AI, QuillBot, Grammarly) primarily for language editing and grammar correction. The article was then proofread by Editage™ professionals. Following the application of this tool/service, the authors thoroughly reviewed and edited the content as necessary and take full responsibility for the final published version.

CRediT Author Statement

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