

Research Article

Combining Negative Pressure Wound Therapy with Insulin Instillation Reduces Insulin Resistance and Accelerates Healing in Patients with Chronically Infected Wounds

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Abstract

Aim: This study aimed at evaluating the effects of negative pressure wound therapy (NPWT) combined with insulin instillation on wound healing and insulin resistance (IR) in patients with chronically infected wounds.

Methods: Sixty-three patients were recruited and randomly divided into three groups (21 cases each) according to treatments: NPWT only; NPWT+insulin; and controls (conventional dressings). Both NPWT treatments lasted for three weeks. Thereafter, wounds' healing conditions were assessed. At 1 day before and 7, 14, and 21 days posttreatment Interleukin-6 (IL-6), Interleukin-2 (IL-2), and Tumor Necrosis Factor- α (TNF- α) serum levels were assessed via specific double-antibody sandwich enzyme-linked immunosorbent assays; and plasma glucose and insulin were quantified via glucose-oxidase and radioimmunoassay, respectively. IR was appraised via homeostasis model assessment (HOMA-IR) and quantitative insulin sensitivity check index (QUICKI).

Results: At 7, 14, and 21 days after treatments onset the two NPWT groups had significantly ($P = 0.0001$) lower IL-6, IL-2, and TNF- α serum levels and HOMA-IR values than controls while wound

healing rates were higher ($P < 0.001$) than controls. Notably, the NPWT+insulin treatment results were better ($P < 0.01$) than those of NPWT alone.

Conclusion: NPWT+insulin instillation improved wound healing, mitigated inflammation, and reduced IR in patients with chronically infected wounds.

Keywords: Chronically infected wounds; Insulin resistance; Negative pressure wound therapy; Proinflammatory cytokines; Wound healing

Abbreviations

FBG: Fasting blood glucose

HOMA: Homeostasis Model Assessment

IL-6: Interleukin-6

IR: Insulin resistance

NPWT: Negative pressure wound therapy

QUICKI: Quantitative Insulin Sensitivity Check Index

TNF- α : Tumor Necrosis Factor- α

Introduction

Chronically infected wounds typically result from medical conditions, nutritional deficits, infections, and metabolic disorders and require intensive and time-consuming treatments. Although recent therapeutic advances have prolonged patients' life, the incidence of difficult-to-heal wounds (i.e. sores and diabetic feet ulcers) that occur with chronic diseases has been increasing in a way commensurate with the elderly population expansion. Chronic wounds are often infected by highly virulent bacterial organisms, namely methicillin-resistant *Staphylococcus aureus* (MRSA) and *Pseudomonas aeruginosa*, that colonize biofilms and make treatments more complicated [1,2]. Negative-pressure wound therapy (NPWT), which prevents the accumulation of fluids through continuous drainage applied at wound sites, makes daily dressing changes unnecessary, improves regional blood flow, and by hindering bacterial proliferation curbs the chances of infection. At the cellular level, NPWT promotes collagen synthesis, neoangiogenesis, and granulation tissue formation [3-5].

Recent modifications to traditional NPWT devices allow the concurrent application of a fluid instillation therapy. The latter is designed to reduce the bioburden within the wound, advance healing, and help control pain in select cases [6-8].

Currently, only normal saline is used for the instillation therapy coupled to NPWT. Solutions of insulin, phenytoin (Dilantin), sodium hypochlorite (Dakin's solution), and polyhexanide (Prontosan, Braun Medical) have also been proposed as therapeutically useful. Several studies have demonstrated that insulin promotes wound healing [9-13]. Notably, Lopez and Mena [14] used local insulin irrigation (30-60 IU isophane insulin daily) in two cases of diabetic infectious gangrene that were unaffected by all the other previous therapies. They found that the insulin accelerated wound healing with no systemic side effects.

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In the present study, we investigated the effects of NPWT combined with insulin instillation on insulin resistance (IR) and wound healing rates in patients suffering from chronically infected wounds.

Materials and Methods

Patients inclusion criteria

The following recruitment criteria were adopted: (i) patients with chronically infected wounds for over one month caused by all kinds of traumata or with continuously deteriorating wounds or with wounds having diameters larger than 5 cm; (ii) patients not previously treated with NPWT; (iii) patients showing no improvement after 7 days of standard drug therapy for a wound; and (iv) patients with infected wounds.

Patients exclusion criteria

The ensuing ruling out criteria were chosen: (i) patients with combined severe heart, brain, liver, kidney, or hematopoietic diseases; (ii) patients with malignant tumors originated in skin or soft tissues; (iii) patients with immunological diseases who had been exposed for extended periods of time to high doses of immunosuppressive agents, steroid hormones, or chemotherapy drugs; (iv) and patients with severe malnutrition or moderate to severe anemia.

Medical ethics

The Medical Ethics Committee of the Third People's Hospital of Hainan Province reviewed and approved the present study. Patients or their next-of-kin signed the informed consents.

Patients studied

In this study, a total of 33 males and 30 females with chronically infected wounds admitted to the Third People's Hospital of Hainan Province from January 2015 to December 2018 were enrolled. Their age ranged from 46 to 68 years, with a mean value of 57.5±9.4 years. Regarding wounds causes, 17 cases presented burn injuries; 9 cases had car accident injuries; 19 cases suffered from diabetic foot ulcers; and 18 cases had pressure ulcers. Concerning wounds locations, they were at the trunk (15 cases), the arms (9 cases), the legs (24 cases), and the hips (15 cases) (Table 1).

	Controls	NPWT alone	NPWT+insulin
Male/female	11/10	10/11	12/9
Age (years)	56.8±9.6	59.3±8.3	57.6±9.1
Wound causes			
Burn injury	6	5	6
Car accident	4	3	2
Diabetic foot	6	7	6
Pressure ulcers	5	6	7
Wound locations			
Trunk	5	4	6
Arms	3	3	3
Legs	8	9	7
Hips	5	5	5
Wound areas (cm ²)	48.6±9.3	50.1± 10.6	49.3±8.9

Table 1: General data of the enrolled patients.

Data are means ± SD. No statistically significant difference among the three groups. Each group's n = 21.

The 63 patients were randomly divided into three groups (21 patients/group) according to the treatment:

- control group (conventional dressings);
- NPWT only group; and
- NPWT+insulin instillation group.

Three groups underwent operative debridement under general anesthesia with intubation. Anesthesia was induced by infusing sevoflurane+TCI (target-controlled infusion), propofol (1 pg·mL⁻¹) and kept with sevoflurane+TCI propofol (1 pg·mL⁻¹). Next the patients were intubated for mechanical ventilation. After successfully inducing anesthesia, all wounds were rinsed thrice with benzalkonium bromide, povidone iodine, and 0.5% iodophor solution. This was followed by saline rinses to clean the wounds and surrounding areas and to remove the necrotic stratum corneum. The shapes and sizes of the wounds conditioned the specific application of the NPWT dressings (Shandong Chuangkang Biotechnology Co., Ltd.).

If the wound area was extended, the NPWT dressing was applied in an imbricate mode completely covering the wound and 2-3 cm of the contouring skin. If the wound was deep, the dressings filled the cavities to the bottom, leaving no dead spaces. A biologically permeable film applied above the dressing covered an area by 4-5 cm wider than the wound surface. After doubly checking the sealing tightness, the drainage tube was connected to a negative pressure drainage device (Shandong Weigao New Life Medical Devices Co., Ltd., Weihai, China). Next, a negative pressure of 80-125 mmHg was applied and maintained. Wounds dressings were replaced every 5 days. During the drainage period, the wounds of the two NPWT groups were rinsed daily with copious amounts of saline. In the NPWT+insulin treated group, the used NPWT devices allowed for insulin infusion according to the dosing defined by Wilson and associates [15]. NPWT was initiated soon after debridement on post-operation day and lasted for a period of three weeks. The intermittent streaming of insulin infusion through the NPWT device and the insulin infusion drip into the NPWT foam at 1000 ml/100 U/24 h continued for 3 weeks (Figures 1 and 2). Thereafter, the healing situation was assessed. The wounds were photographed and independently measured using ImageJ software to calculate their areas [16].

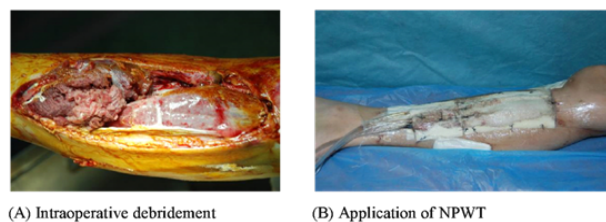


Figure 1: Infected wound at the right lower leg.

The % wound healing rate was calculated according to the formula:

$$\% \text{ wound healing rate} = (\text{initial wound area} - \text{residual wound area}) / \text{initial wound area} \times 100.$$

Assay of proinflammatory factors

Upper limb venous blood (5 ml) was sampled in the morning after an overnight fast at 1 day before and 7, 14, and 21 days after treatments onset. The serum levels of Interleukin (IL)-6, IL-2, and Tumor Necrosis Factor (TNF)-α were measured using specific double-antibody sandwich enzyme-linked immunosorbent assays. The kits were from Shanghai Beyotime Biotechnology Inc. (Shanghai, China).



Figure 2: Infected wounds at the head and neck.

Measurement of biochemical parameters

While the hyper insulinemic euglycemic clamp technique is the gold standard for gauging insulin sensitivity, HOMA for IR (HOMA-IR) and QUICKI are widely used according to the method described by Matthews et al [17-20] as noninvasive surrogate markers of IR and insulin sensitivity, respectively.

At baseline, in the morning after an overnight fast, venous blood was sampled to quantify the plasma concentration of glucose via a glucose-oxidase method and serum insulin levels via radioimmunoassay. HOMA-IR values were calculated according to the formula:

$$\text{HOMA-IR} = (\text{Insulin} \times \text{FBG})/22.5.$$

FBG, fasting blood glucose. Low HOMA-IR values indicate a high insulin sensitivity, whereas high HOMA-IR values indicate a low insulin sensitivity. The QUICKI values were calculated according to the formula:

$$\text{QUICKI} = 1/[\log(\text{fasting insulin}) + \log(\text{fasting glucose})] [18].$$

Statistical analysis

Data were processed and analyzed using SPSS 20.0 statistical software (IBM SPSS, Armonk, NY, USA). Numerical data were expressed as mean values \pm SD. Before and after the treatments intergroup comparisons were carried out by *t*-test, whereas a paired *t*-test was used for intra-group comparisons.

Results

General data of patients

Age, sex ratios, and wound areas did not significantly ($p > 0.05$) differ among the three groups of patients (Table 1). There were statistically not significant ($P > 0.05$) differences of wound types or wound sites among the various groups.

Six, six, and seven cases out of 19 patients suffered from diabetic foot ulcers and were randomly entered in the: (i) control group (conventional dressings); (ii) NPWT only group; and (iii) NPWT+insulin instillation group. No patient withdrew from the study during the entire treatment duration.

Levels of proinflammatory factors

The pre-treatment differences in serum levels of three proinflammatory mediators, i.e. IL-6, IL-2, and TNF- α , were not

statistically significant ($P = 0.498, 0.799, \text{ and } 0.798$, respectively) in the three groups of patients. At 7, 14, and 21 days after treatments onset, the serum levels of the same proinflammatory mediators were significantly lower in the NPWT+insulin and NPWT alone groups ($P < 0.01, \text{ and } 0.001$, respectively) vs. the control group. At the same time-points, in the three groups of patients the levels of the three proinflammatory mediators were significantly lower ($P < 0.01, \text{ and } 0.001$, respectively) than 1 day before treatments start (Tables 2, 3, 4).

	Controls	NPWT alone	NPWT+insulin	p
1 day before treatment	35.5 \pm 2.5	36.6 \pm 3.0	36.2 \pm 4.2	0.498
7 day after treatment	26.8 \pm 1.5	14.8 \pm 2.6	14.1 \pm 2.6	0.0001
14 day after treatment	24.3 \pm 3.1	12.1 \pm 1.9	7.2 \pm 1.6	0.0001
21 day after treatment	20.2 \pm 2.9	8.6 \pm 1.1	5.3 \pm 2.1	0.0001

Data are means \pm SD. Each group's n = 21.

Table 2: Serum levels (ng/ml) of IL-6 before and after treatments.

	Controls	NPWT alone	NPWT+insulin	p
1 day before treatment	132.3 \pm 12.3	131.6 \pm 11.5	129.9 \pm 11.9	0.799
7 day after treatment	108.6 \pm 8.9	58.3 \pm 6.9	50.3 \pm 6.2	0.001
14 day after treatment	96.5 \pm 7.6	50.2 \pm 8.3	34.3 \pm 3.1	0.0001
21 day after treatment	88.6 \pm 6.8	41.6 \pm 7.2	20.6 \pm 4.1	0.0001

Data are means \pm SD. Each group's n = 21.

Table 3: Serum levels (ng/ml) of IL-2 before and after treatments.

	Controls	NPWT alone	NPWT+insulin	P
1 day before treatment	109.4 \pm 10.5	115.5 \pm 12.3	113.6 \pm 11.6	0.798
7 day after treatment	87.3 \pm 12.8	64.6 \pm 10.3	58.3 \pm 9.1	0.001
14 day after treatment	65.3 \pm 11.8	35.2 \pm 6.8	20.3 \pm 3.2	0.0001
21 day after treatment	59.9 \pm 6.4	29.6 \pm 4.2	15.5 \pm 3.6	0.0001

Data are means \pm SD. Each group's n = 21.

Table 4: Serum levels (ng/ml) of TNF- α before and after treatments.

Residual wound areas and wound healing rates

The residual wound areas and wound healing rates were compared among the three groups patients at 7, 14, and 21 days after treatments onset. The mean residual wound area was smallest, and the healing rates were highest in the NPWT+insulin group ($P < 0.01$ vs. controls in both instances).

The NPWT alone group also had better results ($P < 0.01$) than the controls (Tables 5, 6, 7).

	Controls	NPWT alone	NPWT+insulin	P
Residual wound area (cm ²)	35.3 \pm 5.4	28.6 \pm 2.9	25.6 \pm 2.1	0.01
Wound healing rate (%)	27.4 \pm 4.7	42.9 \pm 3.4	48.1 \pm 2.6	0.01

Data are means \pm SD. Each group's n = 21.

Table 5: Wound healing in the three groups at 7 days of treatment.

	Controls	NPWT alone	NPWT+insulin	P
Residual wound area (cm ²)	30.3±4.6	18.9±2.6	13.3±1.9	0.001
Wound healing rate (%)	37.0±4.7	62.2±3.6	73.0±3.9	0.001

Data are means ± SD. Each group's n = 21.

Table 6: Wound healing in the three groups at 14 days of treatment.

	Controls	NPWT alone	NPWT+insulin	P
Residual wound area (cm ²)	28.1 ± 2.9	15.6±1.9	8.9±1.3	0.01
Wound healing rate (%)	42.2±3.9	68.9±3.4	81.9±3.1	0.01

Data are means ± SD. Each group's n = 21.

Table 7: Wound healing in the three groups at 21 days of treatment.

Fasting blood glucose, insulin, HOMA-IR, and QUICKI

The values of fasting plasma glucose, insulin levels, HOMA-IR, and QUICKI did not significantly differ ($P = 0.58, 0.38, 0.42,$ and $0.52,$ respectively) among the three groups at 1 day before the treatments start. At 7, 14, and 21 days after treatments onset, both the NPWT alone and NPWT+insulin groups had significantly lower ($P < 0.01, 0.001,$ and $0.001,$ respectively) fasting serum insulin levels than the control group (Tables 8, 9, 10, 11).

	Controls	NPWT alone	NPWT+insulin	p
FBG (mmol/l)	10.7 ± 0.6	11.3 ± 0.8	11.1 ± 0.9	0.58
Insulin (pmol/l)	123.6 ± 13.6	128.9 ± 12.6	121.7 ± 13.4	0.38
HOMA-IR	58.8 ± 6.7	64.7 ± 5.6	60.1 ± 6.2	0.42
QUICKI	0.32(0.25,0.41)	0.32(0.23, 0.45)	0.32(0.28, 0.39)	0.52

Except where otherwise indicated, values are means (95% confidence interval) ± SD. FBG, fasting blood glucose. QUICKI, Quantitative Insulin Sensitivity Check Index = $1 / [\log (\text{Insulin}) + \log (\text{FBG})]$.

HOMA for insulin resistance (HOMA-IR) = $(\text{Insulin} \times \text{FBG}) / 22.5$. Each group's n = 21.

Table 8: Fasting blood glucose, insulin, HOMA-IR, and QUICKI at 1 day before treatment.

	Controls	NPWT alone	NPWT+insulin	p
FBG (mmol/l)	9.9 ± 0.7	10.1 ± 0.6	9.8 ± 0.8	0.37
Insulin (pmol/l)	118.6 ± 4.5	61.7 ± 2.9	59.6 ± 2.4	0.01
HOMA-IR	52.2 ± 4.5	27.7 ± 3.1	25.9 ± 3.8	0.001
QUICKI	0.33 (0.29, 0.36)	0.36 (0.31, 0.53)	0.36 (0.28, 0.45)	0.001

Except where otherwise indicated, values are means (95% confidence interval) ± SD. FBG, fasting blood glucose. QUICKI, Quantitative Insulin Sensitivity Check Index = $1 / [\log (\text{Insulin}) + \log (\text{FBG})]$.

HOMA for insulin resistance (HOMA-IR) = $(\text{Insulin} \times \text{FBG}) / 22.5$. Each group's n = 21.

Table 9: Fasting blood glucose, insulin, HOMA-IR, and QUICKI at 7 days of treatment.

In the two NPWT groups, significant ($P < 0.001, 0.001,$ and $0.001,$ respectively) decreases in HOMA-IR values, and as well significant ($P < 0.001, 0.001,$ and $0.001,$ respectively) increases in QUICKI values occurred at 7, 14, and 21 days of treatment.

	Controls	NPWT alone	NPWT+insulin	p
FBG (mmol/l)	9.8 ± 0.5	9.6 ± 0.6	9.4 ± 0.7	0.374
Insulin (pmol/l)	111.8 ± 2.6	38.6 ± 2.9	22.2 ± 3.1	0.001
HOMA-IR	48.7 ± 5.2	16.5 ± 2.3	9.3 ± 1.8	0.001
QUICKI	0.33 (0.27, 0.45)	0.39 (0.36, 0.53)	0.43 (0.38, 0.60)	0.001

Except where otherwise indicated, values are means (95% confidence interval) ± SD. FBG, fasting blood glucose. QUICKI, Quantitative Insulin Sensitivity Check Index = $1 / [\log (\text{Insulin}) + \log (\text{FBG})]$. HOMA for insulin resistance (HOMA-IR) = $(\text{Insulin} \times \text{FBG}) / 22.5$. Each group's n = 21.

Table 10: Fasting blood glucose, insulin, HOMA-IR, and QUICKI at 14 days of treatment.

	Controls	NPWT alone	NPWT+insulin	p
FBG (mmol/l)	9.5 ± 1.4	9.2 ± 0.9	9.3 ± 0.6	0.588
Insulin (pmol/l)	108.3 ± 9.4	26.6 ± 2.8	8.4 ± 2.1	0.001
HOMA-IR	45.7 ± 5.2	10.9 ± 2.3	3.5 ± 0.6	0.001
QUICKI	0.33 (0.27, 0.45)	0.42(0.36, 0.54)	0.53 (0.40, 0.69)	0.001

Except where otherwise indicated, values are means (95% confidence interval) ± SD. FBG, fasting blood glucose. QUICKI, Quantitative Insulin Sensitivity Check Index = $1 / [\log (\text{Insulin}) + \log (\text{FBG})]$. HOMA for insulin resistance (HOMA-IR) = $(\text{Insulin} \times \text{FBG}) / 22.5$. Each group's n = 21.

Table 11: Fasting blood glucose, insulin, HOMA-IR, and QUICKI at 21-day of treatment.

Notably, already after one week the NPWT brought about significant ($P < 0.001,$ and $0.001,$ respectively) improvements in insulin sensitivity vs. controls as shown by the reductions in HOMA-IR and increases in QUICKI values (Table 9).

Therefore, our findings show that NPWT improves insulin sensitivity in patients with chronically infected wounds. They also suggest that the metabolic effects of the NPWT may be more pronounced in such patients.

Discussion

Chronically infected wounds are quite commonly encountered in clinical settings. These wounds do not heal for extended periods, and their conventional treatment consists mainly in dressing changes. Chronic wound healing takes a long time, and if the wound does not heal at all, eventually a repairing skin graft must be surgically applied. Chronic ulcer wounds often associate with chronic infections that resist to multiple antibiotics, thus resulting in shortened survival rates of the repairing skin grafts and posing serious challenges to clinical treatment [21, 22].

Several studies [23-26] have shown that NPWT can effectively shorten wound healing times, lessen the pain associated with dressing changes, and effectively prevent cross-infections. NPWT is performed in a closed system, and the negative pressure drainage promptly removes any local exudate and necrotic tissue thus achieving zero necrotic tissue accumulation. In addition, NPWT protects the wound from contaminations, stimulates a fast and healthy growth of the granulation tissue, promotes healing, curbs antibiotics use, and increases blood flow close to the wound surface. The continuous negative pressure can be adjusted to match physiological conditions so that it does not adversely affect blood circulation. Moreover, it

can effectively prevent the formation of residual abscesses and of dead spaces [27]. More importantly, the negative pressure promotes a continuous flow of body fluids from the wound surface to the drainage tube, which provides an effective and sustained auxiliary push to blood circulation [26].

Insulin can be applied topically with minimal systemic side effects while successfully decreasing the time required for wound healing. In experimental diabetic wound models, insulin significantly increased the healing rate by mitigating the inflammatory response and rescuing cell functions [12]. Topical insulin applications after injuries rapidly upregulate insulin signaling-related proteins in the wounded areas [13]. Lines of evidence also show that systemic insulin administration to diabetic mice leads to an increased prevalence of biofilms in the wound areas [28]. Topical application of insulin may be a promising therapeutic approach because it activates insulin signaling and accelerates wound healing without any of the noxious effects that sometimes associate with its systemic administration. Scimeca et al. [29] reported the use of insulin as a chemotherapeutic agent in continuous-instillation NPWT. In fact, NPWT coupled with a continuous streaming of insulin may provide a promising approach to promote a healthy wound environment. Preliminary reports seem to suggest that topically applied insulin evokes minimal systemic side effects while successfully decreasing the wound healing time. In our study, we found that the continuous streaming of insulin infusion through the NPWT device improved wound healing, mitigated inflammation, and reduced IR in patients with chronically infected wounds. To our knowledge, this is the first report in the Literature that local insulin infusion reduces IR in patients with chronically infected wounds.

In this study, we found that combined NPWT+insulin instillation was beneficial already after the first week of treatment, and quickly reduced the wound-related symptoms. In addition, NPWT+insulin increased the wound-healing rate. These findings show that the growth-promoting effects of insulin on the epidermal cells is enhanced under the NPWT's continuous negative pressure because of the blood circulation boost and the inflammatory response mitigation.

Patients with chronically infected refractory wounds experience strong local inflammatory responses as proved by the elevated circulating levels of proinflammatory mediators such as IL-6, IL-2, and TNF- α [30]. Nasole et al. [30] reported that IL-6 and TNF- α are general inflammation crucial pivots, which both directly and indirectly induce the production of other cytokines and growth factors affecting the functions of the endothelial cells and fibroblasts. The proinflammatory cytokine TNF- α is a central regulator of IR [31]. Proinflammatory IL-6, a biomarker of obesity and type 2 diabetes mellitus (T2DM) [32], is also a critical contributor to IR [33, 34].

With the healing of wounds, local inflammation rapidly vanes, and the levels of inflammatory factors go back to normal, resulting in a decreased decay of wound tissue proteins and in the promotion of wound healing. In this study, the NPWT+insulin treatment proved to be more effective than standard dressings in lowering the levels of proinflammatory factors.

IR is the lost ability of metabolic tissues like liver, skeletal muscle, skin, and adipose tissue to respond to insulin [35]. IR has long been considered as a major hallmark of the etiology and pathogenesis T2DM. IR development is mainly associated with low-grade tissue-

specific inflammatory responses induced by various proinflammatory and/or oxidative stress mediators, particularly cytokines such as IL-1 β , IL-6, and TNF- α , numerous chemokines, and adipokines [36-38]. Chronic exposure to proinflammatory mediators stimulates the activation of cytokine signaling-related proteins, which ultimately block the activation of insulin receptors' signaling in the β -cells of pancreatic islets [36].

In the clinical settings, IR results from a combination of factors such as an altered function of insulin-targeted cells, the noxious effects of circulating insulin antagonists, and the local accumulation of macrophages that secrete proinflammatory mediators [39]. At the molecular level, the pathological progression of IR is crucially favored by a reduced expression of insulin receptors on the part of the target cells along with an impaired insulin dependent PI3K activation and downstream signaling [40]. Over one hundred known pathologic factors contribute to deficits in wound healing [41]. A relevant one of these factors might be the disruption of insulin's signaling pathways, which is the most distinctive pathological change in T2DM [42]. In addition to the effect on glucose disposal, insulin stimulates DNA synthesis and cell proliferation. Insulin's dysfunction often associates with proliferative abnormalities at the skin (e.g. acanthosis nigricans), ovary, and heart level [43].

In this study of patients with chronically infected wounds, a significant ($p < 0.05$) fall in serum insulin levels occurred already after one week of NPWT treatment, as manifested by the significant improvements in both HOMA-IR and QUICKI values when compared with control ones. These changes for the better persisted at 14 and 21 days of treatment. Notably, under these respects NPWT+insulin was more beneficial than NPWT used alone.

In conclusion, the combined NPWT+insulin treatment mitigates the inflammatory response, lessens IR, and improves wound healing in patients with chronically infected wounds.

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