Use of autologous whole blood clot for hard-to-heal diabetic foot ulcers: a case series

Objective: Diabetic foot ulcers (DFUs) are a severe complication of diabetes, contributing significantly to patient morbidity, healthcare costs and amputations. Current treatment approaches often fall short in addressing the challenges posed by hard-to-heal (chronic) wounds. This study evaluates the efficacy of autologous whole blood clot (AWBC) therapy in treating hard-to-heal DFUs.
Method: Patients with hard-to-heal DFUs who were unresponsive to previous treatments were included in this case series. Prior to AWBC application, the wounds underwent debridement and cleansing of the wound bed. For the treatment, 18ml of blood was drawn from the patients to create the clot placed on the wound. Patients were evaluated weekly for wound healing progress.
Results: AWBC treatment was initiated in 20 patients, resulting in an average wound size reduction of 59% ($p<0.001$). The mean number of applications per patient was 5.3±1.5. Adverse events included contact dermatitis in one patient and discontinuation by another due to slower-than-expected healing.
Conclusion: The results of this case series underscore AWBC's potential to restore the wound healing cascade by mimicking the extracellular matrix and promoting re-epithelialisation, angiogenesis and macrophage phenotype transition. AWBC represents a promising, cost-effective solution for DFU management, particularly in patients with complex comorbidities.
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autologous whole blood clot • case series • chronic wounds • diabetic foot ulcer • hard-to-heal • wound • wound care • wound dressing • wound healing

Diabetic foot ulcers (DFUs) represent a major health concern, particularly in Western countries, with significant implications for morbidity, mortality and healthcare costs.[1,2] These ulcers, which are a common complication among patients with diabetes, have a lifetime risk of occurrence estimated between 19–34%.[2] Furthermore, the recurrence rates of these ulcers are high, with 40% recurring within a year of healing and 65% within five years.[3] Complications, such as infection, ulceration and gangrene, are the leading reasons for hospitalisation among patients with diabetes.[1]

DFUs accounted for 3% of annual health expenditure in Turkey,[4] with approximately 400,000 DFU cases observed with a prevalence of 7700 amputations performed each year as a result.[5]

The pathophysiology behind DFUs is multifaceted. Neurological, vascular and biomechanical factors all play a role in ulceration. The normal wound healing cascade is a multifaceted process encompassing stages from haemostasis to remodelling.[5] The extracellular matrix (ECM) plays a pivotal role, offering structural support and modulating cellular activities.[6,7] A vital phase in wound healing involves scaffold formation, which is eventually replaced by a scar, facilitating subsequent steps including cell recruitment and angiogenesis.[8] However, this process can be altered in patients with diabetes, affected by the hyperglycaemic condition common in those patients, which disrupts this process by altering ECM elasticity, leading to compromised cell migration, proliferation and contraction, resulting in a prolonged inflammatory phase and delayed healing.[9,10] The outcome is often hard-to-heal (chronic) foot ulcers,[11] which, if not addressed promptly, can lead to amputation.

Although a range of treatments for DFUs have been developed, there is still a significant gap between the current and desired wound healing outcomes.[12] With the ongoing challenges in efficacy, side-effects and cost, there is a continued need for research and innovation in this field.

Autologous whole blood clot (AWBC) (RedDress Ltd., Israel) is an innovative solution that offers blood clot therapy. This bedside treatment, derived from the patient's peripheral blood, does not require specialised equipment or medical expertise. The patient's blood, activated with coagulation agents, is applied directly to the wound, forming a fibrin scaffold that fosters wound re-epithelialisation.[13] This groundbreaking technology has demonstrated its safety and efficacy in treating challenging cutaneous wounds.[14–19] The resultant blood clot, which is suggested to function as a substitute ECM, encompasses all essential factors for efficient wound repair, promoting reduced wound size and faster wound closure.[14–16] As the coagulation process unfolds, the clot adheres to the wound's exposed surface and contracts,

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drawing the surface closer together and forming a protective scab. The clot not only provides a physical infrastructure for cell growth but also is suggested to reduce bacterial bioburden, minimising the risk of wound infection.[19] The combined effects of the ECM, growth factors and chemokines foster granulation and angiogenesis, vital for tissue regeneration and wound closure.[20] In essence, AWBC initiates the wound healing cascade, restoring conditions that allow the wound to progress toward healing.

This manuscript presents a case series of patients with DFUs who had previously undergone other treatments for at least four weeks without improvement.

Methods

Patients

The adult patients enrolled had DFUs that had failed to achieve at least a 40% reduction in size after four weeks of standard of care (SoC). This included offloading, wound debridement, cleansing with antiseptic solution, and the use of antimicrobial and absorbent dressings tailored to the level of infection and drainage (e.g., alginate dressing, foams or negative pressure wound therapy (NPWT)). Additionally, zinc-based creams or absorbent dressings were used to control excessive moisture. Despite these interventions, the wounds had not shown the expected improvement.

Patient consent

All patients signed the informed consent agreeing to use of their medical history data, demographics and wound characteristics, including wound images.

Procedure

Before AWBC application, all wounds underwent standardised wound bed preparation, including debridement, infection assessment and moisture balance. For the AWBC blood clot formation, 18ml of venous blood was drawn from the patient into sterile acid citrate dextrose-A vacuum tubes and activated ex vivo using calcium gluconate and kaolin in a designated activation mould (RedDress, Ltd., Israel). The blood was gently mixed for 20 seconds and allowed to clot for 5–8 minutes. The clot formed was gently removed from the coagulation mould and attached to the wound bed using Steri-Strips. A non-adherent pad was placed over the clot and covered with a secondary dressing. A secondary dressing change was performed weekly or as clinically needed. Patients were discharged either upon wound closure or when transitioned back to a SoC treatment.

Results

A total of 20 patients, each with a DFU, comprising one female and 19 males, were part of this study. Mean age was 62.15±10.7 years (range: 47–88 years) with a mean haemoglobin A1c level of 8.3% (range: 5.3–10.6%). These patients had a mean wound duration of 16.4±16.5 weeks (range: 4–52 weeks) prior to treatment. The patients had several comorbidities, among them peripheral arterial disease (PAD) (70%), neuropathy (75%), pulmonary arterial hypertension (65%) and 15% undergoing dialysis (Table 1). All patients had failed prior treatments, including NPWT and advanced dressings.

Table 1. Patient demographics

Variable	Result
Age, years, mean±SD	63.25±10.73
Sex, n (%)	
Female	1 (5)
Male	19 (95)
Haemoglobin A1c, %, mean (range)	8.3 (5.3–10.6)
Wound duration, weeks, mean±SD (range)	16.4±16.5 (4–52)
Comorbidities, n (%)	
Dialysis	3 (15)
Peripheral arterial disease	14 (70)
Neuropathy	15 (75)
Pulmonary arterial hypertension	13 (65)

SD—standard deviation

AWBC treatment was initiated in all patients following debridement and cleansing of the wound. On average, patients received 5.3±1.5 AWBC treatments over a span of 5.6±1.7 weeks. Post-treatment, there was a significant reduction in the average wound size by 59±21% ($p<0.001$, paired t-test). A comprehensive summary of the findings is provided in Table 2.

Treatment was discontinued in one (5%) patient due to a slower healing response, with a 46% wound size reduction after eight treatments (from 1.30cm^2 to 0.6cm^2). Treatment was halted for another patient due to the onset of severe contact dermatitis. Additionally, one patient chose to forgo the final application.

To demonstrate the therapeutic effect of AWBC, two representative clinical cases are presented (Figs 1 and 2).

Discussion

The management of DFUs is a significant challenge in the medical community, especially given the multifaceted pathophysiology and the associated complications with such wounds.[21] The results of this case series indicated that AWBC was particularly effective in a patient population characterised by advanced age and a high number of comorbidities. Despite these challenges, AWBC succeeded where other treatments failed, moving the wounds in a timely manner towards healing. This is especially significant given the advanced age and comorbidities of most of the patients, factors that typically complicate and prolong the wound healing process. Comorbidities can delay wound healing by complicating and delaying diagnosis and negatively affecting the body's normal wound healing process.[22]

Table 2. Summary of results

Patient number	Age, years	Wound duration, weeks	Number of AWBC applications	Duration of treatment, weeks	Initial wound size, cm²	Final wound size, cm²	Percentage area reduction
1	70	4	7	7	3.6	1	72*
2	70	7	6	6	1.4	0.7	50
3	72	52	8	8	1.3	0.6	54†
4	67	24	10	10	28.1	17	40
5	60	4	4	4	10.9	6.4	41‡
6	65	52	4	4	5.7	3.1	46*
7	47	20	4	4	11.3	5.5	51
8	88	52	3	3	1.8	0.9	50*
9	49	8	5	5	9	2.5	72
10	59	24	5	5	0.9	0.8	11
11	49	4	5	5	1.8	0.4	78
12	56	12	5	5	34.8	7.3	79
13	56	7	5	5	12.1	4.2	65
14	52	9	5	5	27.1	11.7	57
15	54	8	5	5	5.2	0.3	94
16	66	10	5	5	9.1	3.6	60
17	64	6	5	5	16	11.2	30
18	69	8	5	8	15.3	6.9	55
19	74	4	5	5	21	5.6	73
20	78	12	5	8	17	1	94
Mean±SD	63.25±10.73	16.3±16.5	5.3±1.5	5.6±1.7	11.7±9.9	4.5±4.5	59.0±21.0

*Treatment was stopped because the wound became too small; †Treatment was stopped due to slow healing; ‡Patient developed dermatitis; AWBC—autologous whole blood clot; SD—standard deviation

AWBC, an innovative solution derived from the patient's own blood, offers a promising approach in this context. By forming a whole blood clot product, AWBC mimics the ECM which offers both a protective layer, suggested to reduce bacterial bioburden and lower infection risk,[23] while also fostering wound re-epithelialisation[15,16] by providing structural support and modulating cellular activities.[6,7]

Interestingly, the blood clot, by providing this scaffold, facilitates the transition of macrophages from the proinflammatory M1 phenotype to the anti-inflammatory M2 phenotype, promoting the proliferative phase of wound healing.[21,24,25] This is particularly crucial in hard-to-heal wounds, which often stall in the inflammatory phase due to macrophages remaining in their M1 phase.[26] By arresting this inflammatory stage, AWBC holds immense potential in treating these complex hard-to-heal wounds.

The efficacy of AWBC in treating DFUs was demonstrated in a randomised controlled trial involving 119 patients.[27] Participants were treated with either AWBC combined with SoC or SoC alone. The study included patients with hard-to-heal DFUs who had undergone 14 days of SoC treatment prior to enrolment. Wounds that reduced in size by >30% during this pre-enrolment period were excluded, ensuring the inclusion of only hard-to-heal wounds. Results showed that AWBC treatment was significantly more effective than SoC alone, achieving a 2.73-fold increase in wound healing within 12 weeks of active treatment.[27] These findings provide further evidence supporting the high efficacy of AWBC in managing DFUs. This comparison between AWBC and SoC highlights the superior efficacy of AWBC in treating DFUs, particularly in wounds that have failed to progress despite appropriate SoC.

Moreover, the cost-effectiveness of AWBC in treating DFUs is grounded in its ability to accelerate healing, reduce the need for costly advanced wound care products, and potentially decrease overall treatment expenses.[28] It is suggested that faster wound healing

may lead to fewer complications, such as infections or amputations, which are associated with considerable medical and economic burdens. Snyder et al.[28] highlight AWBC's role in improving patient outcomes while optimising healthcare resource utilisation, making it a valuable option for both patients and healthcare systems.[28] While most patients experienced significant wound size reduction, a few showed limited or delayed response. Potential factors contributing to poor healing outcomes may include persistent subclinical infection, inconsistent offloading, or systemic conditions, such as poor glycaemic control, which can have an effect on the healing process. These variables were not systematically stratified or analysed in this study, warranting further investigation.

Conclusion

In conclusion, AWBC emerges as an effective treatment for DFUs. Its simplicity, reported cost-effectiveness, and non-surgical nature make it a primary treatment option for challenging wounds. The findings from this case series further validate the efficacy of AWBC in promoting significant wound closure, emphasising its potential in wound care. Future studies should focus on a larger patient cohort to further validate these findings, and explore the long-term benefits and potential challenges of AWBC treatment. Studies should also explore patient selection criteria and real-world cost–benefit analyses to optimise clinical use. JWC

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Fig 1. A 56-year-old male patient presented with a three-month-old diabetic foot ulcer on the left foot. Prior treatments included larvae therapy, negative pressure wound therapy and silver dressings. At baseline (day 0) the wound measured 38.40cm^2. Autologous whole blood clot was applied weekly for five consecutive weeks. After the first two applications, the wound was covered with granulation tissue and showed a slight reduction in size (week 3). Continued progress was observed with the additional three applications reaching a 79% area reduction (week 7). Subsequently, standard of care treatment was implemented thereafter, until complete wound closure (week 36)

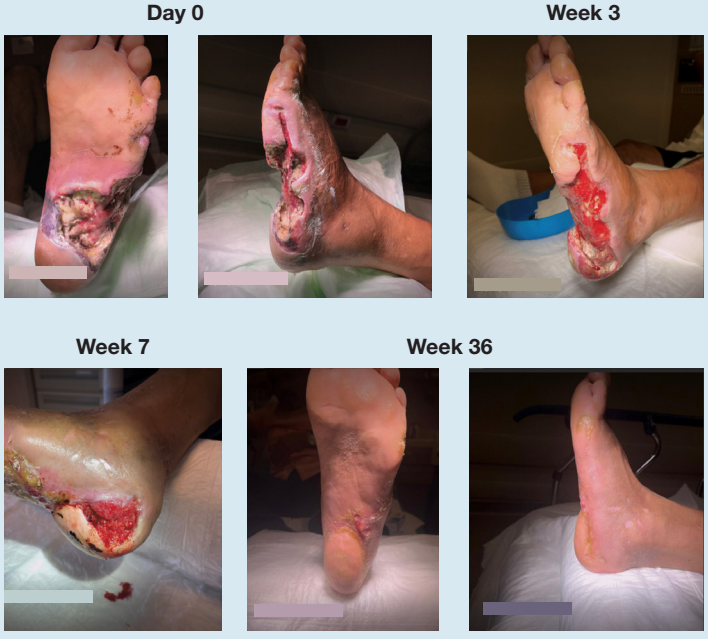
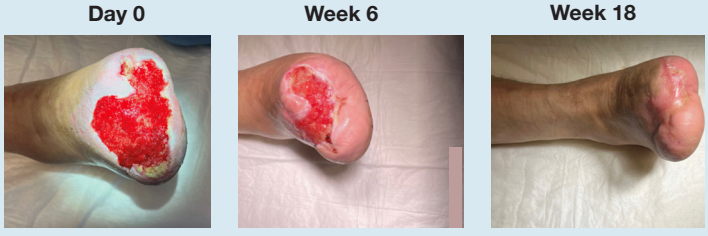


Fig 2. A 52-year-old male patient presented with a nine-week-old diabetic foot ulcer on the right forefoot amputation stump. The patient also had peripheral arterial hypertension and neuropathy. Prior treatments included boric acid and negative pressure wound therapy with no improvement. The wound failed to reduce in size, albeit conventional treatment and autologous whole blood clot (AWBC) treatment was introduced to the wound. At baseline (day 0), the wound measured 27.11cm^2 (post debridement). AWBC was applied weekly for five consecutive weeks, resulting in a wound reduction of 57% in wound size (week 6). Treatment continued with a standard of care until complete wound closure (week 18)



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Reflective questions

- How does the unique mechanism of autologous whole blood clot (AWBC) therapy compare to traditional diabetic foot ulcer (DFU) treatments in addressing the challenges of hard-to-heal wound healing?
- What role do factors such as patient comorbidities and the prolonged inflammatory phase in DFUs play in determining the effectiveness of AWBC treatment?
- What are the broader healthcare implications of adopting AWBC therapy, particularly regarding cost-effectiveness, accessibility and patient outcomes?
- Based on the findings, what further research would be necessary to validate AWBC as a standard treatment for DFUs across diverse patient populations?

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