ORIGINAL ARTICLE

Relationship between maceration and wound healing on diabetic foot ulcers in Indonesia: a prospective study

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Abstract

The aim of this study was to clarify the relationship between maceration and wound healing. A prospective longitudinal design was used in this study. The wound condition determined the type of dressings used and the dressing change frequency. A total of 62 participants with diabetic foot ulcers (70 wounds) were divided into two groups: non-macerated ($n = 52$) and macerated wounds ($n = 18$). Each group was evaluated weekly using the Bates–Jensen Wound Assessment Tool, with follow-ups until week 4. The Mann–Whitney U test showed that the changes in the wound area in week 1 were faster in the non-macerated group than the macerated group ($P = 0.02$). The Pearson correlation analysis showed a moderate correlation between maceration and wound healing from enrolment until week 4 ($P = 0.002$). After week 4, the Kaplan–Meier analysis showed that the non-macerated wounds healed significantly faster than the macerated wounds (log-rank test = 19.378, $P = 0.000$). The Cox regression analysis confirmed that maceration was a significant and independent predictor of wound healing in this study (adjusted hazard ratio, 0.324; 95% CI, 0.131–0.799; $P = 0.014$). The results of this study demonstrated that there is a relationship between maceration and wound healing. Changes in the wound area can help predict the healing of wounds with maceration in clinical settings.

Introduction

The latest figures estimate that, in 2013, 415 million adults worldwide were living with diabetes, with an expected increase to 592 million people by 2035 (1). Based on the data of the International Diabetic Federation, 75% of people with diabetes live in developing countries (2). Indonesia is one such country. By 2000, 8·4 million Indonesian people were living with diabetes, and it is anticipated that this number will increase to 21·3 million people by 2030 (3).

The probability of people with diabetes developing diabetic foot ulcers (DFUs) is about 15–25% (4–6). DFUs are caused by poor circulation and are associated with peripheral neuropathy and peripheral vascular disease (7). At 54%, DFUs with neuropathy is the most common reason for admission to hospital in Indonesia (8), and an estimated 0·7% of people with DFUs will have a foot amputated (9).

Key Messages

- maceration, which is a periwound skin problem, is defined as the softening and breaking down of skin as a result of prolonged exposure to moisture. Maceration not only occurs in diabetic foot ulcers (DFUs) but also in other chronic wounds, such as leg ulcers, pressure ulcers, fungating wounds and burns
- maceration causes enhancement of the wound area and infection. The condition is caused by a breakdown in the skin resulting from an open wound, so the wound area is enhanced and contaminated by microorganisms. Consequently, wound healing is delayed, which negatively affects quality of life
- the aim of this study was to clarify the relationship between maceration and wound healing. A total of 62

participants (70 wounds) were divided into two groups: non-macerated (*n* = 52) and macerated wounds (*n* = 18). Each group was evaluated weekly, with follow-ups until week 4

- the Mann−Whitney *U* test showed that the changes in the wound area in week 1 were faster in the non-macerated group than the macerated group (*P* = 0·02). The Pearson correlation analysis showed a moderate correlation between maceration and wound healing from enrolment until week 4 (*P* = 0·002). After week 4, the Kaplan−Meier analysis showed that the non-macerated wounds healed significantly faster than the macerated wounds (log-rank test = 19·378, *P* = 0·000). The Cox regression analysis confirmed that maceration was a significant and independent predictor of wound healing in this study (adjusted hazard ratio, 0·324; 95% CI, 0·131−0·799; *P* = 0·014)
- the results of this study demonstrated that there is a relationship between maceration and wound healing. Changes in the wound area can help predict the healing of wounds with maceration in clinical settings

DFUs are chronic wounds. Unlike acute wounds, chronic wounds require long-term healing. The wound-healing process is influenced by many factors, both local and systemic. One of the local factors is excessive fluid (10). Excessive fluid is caused by exudate. In principle, exudate supports healing and creates a moist environment in the wound. Exudate contains water, electrolytes, nutrients, proteins, inflammatory mediators, matrix metalloproteinase (MMPs), growth factors (GH), neutrophils, macrophages and platelets (11). Nevertheless, increasing proteolytic activity, particularly MMPs in chronic wounds, has been implicated in damage to the wound bed, degradation of the extracellular matrix and the origination of periwound skin problems (12,13).

A periwound skin problem, maceration is defined as the softening and breaking down of skin as a result of prolonged exposure to moisture (14). Maceration not only occurs in DFUs but also in other chronic wounds such as leg ulcers, pressure ulcers, fungating wounds and burns (15).

Maceration results in enhancement of the wound area and infection. This condition is caused by a breakdown of the skin resulting in an open wound so that the wound area is enhanced and contaminated by microorganisms. Consequently, wound healing is delayed, and quality of life is negatively affected.

The prevention of maceration is important, and exudate management offers a way to prevent maceration. Exudate management can reduce the healing time, exudate and frequency of dressing changes, and improve patient quality of life (16).

In the clinical setting, maceration is most likely to occur in chronic wounds. In general, maceration in DFUs is evident in thick, calloused skin (15). Chronic wounds commonly produce high exudate. The use of a selection of dressings and frequent dressing changes are usually required to prevent this (17); however, we continue to see chronic wounds with maceration in our clinical practice. To date, there is little evidence about the relationship between maceration and wound healing. The aim of this study was therefore to clarify the relationship between maceration and wound healing.

Methods

Research design

A cohort prospective longitudinal design was used in this study.

Setting and participants

This study was conducted at the Kitamura Wound Care Clinic in an urban area in Pontianak, West Kalimantan, Indonesia from March to October 2015. The subjects in the study were all patients who had attended the Kitamura Wound Care Clinic for type 2 DM treatment during the period of observation. We used a probability sampling technique for the sampling design as this allowed equal opportunities for all clinic attendees to be recruited for the study.

The study population comprised patients who attended the research setting during the period of observation and met our inclusion criteria. The inclusion criteria were patients who were ≥21 years of age and had received a diagnosis of type 2 DM according to the American Diabetes Association 2013 guidelines where glycated haemoglobin (HbA1c) ≥6·5%, fasting blood glucose (FPG) ≥126 mg/dl (7·0 mmol/l) or 2-hour plasma glucose ≥200 mg/dl (11·1 mmol/l) during an oral glucose tolerance test (OGTT) (18) or had classic hyperglycaemia symptoms and a random plasma glucose ≥200 mg/dl (11·1 mmol/l) (19). Patients not meeting these criteria were not permitted to participate in the study. Informed consent was obtained from the patients and their family members.

Validation of wound healing and maceration

Wound healing is defined as changes in the wound area. A photograph of each subject's wound was taken each week and used to measure the wound area with Image J software. Changes in the wound area were noted as the wound area in weeks b, c and d versus weeks a, b and c (a, wound area in week 1; b, wound area in week 2; c, wound area in week 3; d, wound area in week 4). A macerated area was defined as the wet and opaque or white skin of a periwound (15−17). The area of maceration was also assessed by measuring each photograph using Image J software.

Validation of wound area

The wound area was measured each week. The longest and largest wound area was determined by measuring with a ruler. The wound area was calculated by multiplying the length and width of the wound. In addition, a photograph was taken each week, and the wound area was measured using Image J software.

Observational data

The observational data included demographic and clinical data. The demographic data were obtained using a developed
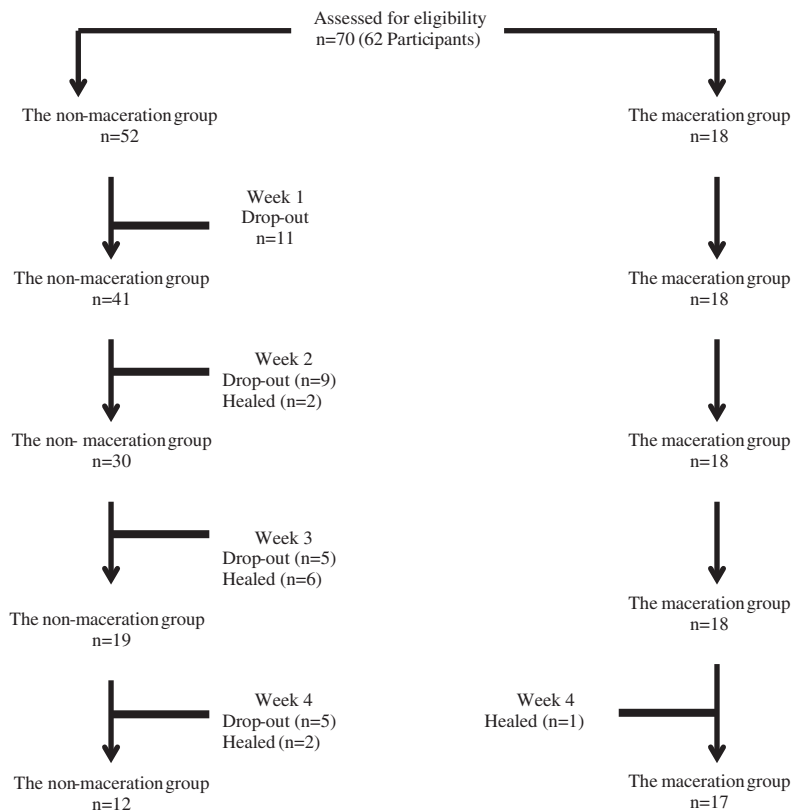
Figure 1 Wound flow diagram.

minimum data sheet. The questions related to age, gender, occupation, medical history, body mass index, glycaemic status, smoking status, type of diabetes mellitus (DM) therapy, year of onset of DM, treatment, the ankle-brachial index (ABI), wound status and the Wagner grading system. To validate the patients' DM status, we evaluated their glycaemic status, FPG or 2-hour post-prandial glucose (PPG) and glycated haemoglobin (HbA1c). The type of dressing and dressing change frequency were determined by the wound condition, which was assessed by the doctors and nurse wound specialists. The Bates–Jensen Wound Assessment Tool was used to evaluate wound development each week. Photographs were taken weekly until the end of the study period using a digital camera.

Ethical considerations

This study was approved by the ethics committee of the Department of Medical Sciences at Kanazawa University (ref. no. 549-3).

Data analysis

The Mann–Whitney U test or independent t-test and chi-squared or Fisher's exact tests were used to compare the patient characteristics. The wound characteristics (changes in the wound area) were analysed using the Mann–Whitney U test. The Pearson correlation analysis was used to analyse the relationship between maceration and changes in the wound area. The Kaplan–Meier curve and the log-rank test were used to compare the wounds with maceration and those with no maceration. Cox regression analysis was used to assess

whether maceration was a predictor of wound healing. IBM SPSS v. 22 was used for statistical analysis, and we established $P = 0.05$ as the level of significance.

Results

Characteristics of the participants

A total of 62 participants (70 wounds) were divided into two groups: non-maceration ($n = 52$) and maceration ($n = 18$). Each group was evaluated weekly, with follow-ups until week 4. In the non-maceration group, in week 1, 11 patients dropped out of the study. In week 2, nine patients dropped out, and two wounds healed. In week 3, five patients dropped out, and six wounds healed. In week 4, five patients dropped out, and two healed. In the maceration group, only one wound healed (Figure 1). Based on our clinical and laboratory data, there were no statistically significant differences between the non-macerated wounds and the macerated wounds (Table 1).

Wounds characteristics

There was no statistically significant difference between the groups in terms of patient characteristics (Table 1). The baseline of the wound area was also not significantly different between the groups ($P = 0.26$). The Mann–Whitney U test showed that changes in the wound area in week 1 had occurred faster in the non-maceration group than the maceration group ($P = 0.02$). In week 2, there was also a marginally significant difference between the groups ($P = 0.05$) (Table 2).

Table 1 Demographics of the patients

	The non-maceration group (*n* = 44)	The maceration group (*n* = 18)	*P*-value†
Age (years)	53·16 ± 10·04	53·38 ± 10·73	0·30[a]
Gender, no. (%)			
Female	26 (59·1)	15 (83·3)	0·12[c]
BMI (Median kg/m^2)	22·03 ± 3·07	22·7 ± 4·83	0·65[a]
Occupation, no. (%)			0·47[c]
None	3 (6·8)	1 (5·5)	
Housewife	19 (43·2)	11 (61·1)	
Seller	4 (9·1)	2 (11·1)	
Civil servant	1 (2·3)	1 (5·5)	
Private worker	8 (18·2)	1 (5·5)	
Retire	3 (6·8)	2 (11·1)	
Farmer	4 (9·1)		
Teacher	2 (4·5)		
Duration of DM (years)	7·06 ± 7·65	5·61 ± 5·60	0·47[a]
Treatment of DM, no. (%)			0·96[c]
Oral	41 (93·2)	16 (88·9)	
Insulin	3 (6·8)	2 (11·1)	
Fasting Blood Sugar (mg/dl)	194·84 ± 69·43	186·27 ± 65·47	0·70[a]
HbA1c (%)	12·68 ± 2·29 (*n* = 6)	12·93 ± 1·51 (*n* = 3)	0·87[a]
Ankle-brachial index (median)	0·99 (0·82–1·21)	1·03 (0·76–1·27)	0·92[b]
Wound onset (days)	17·50 (1·00–600·00)	17·50 (4·00–60·00)	0·70[b]
Trigger, no. (%)			0·69[c]
Unknown	22 (50·0)	9 (50·0)	
Needle	6 (13·6)	2 (11·2)	
Trauma	11 (25·0)	6 (33·3)	
Footwear	5 (11·4)	1 (5·5)	
Wound status, no. (%)			0·60[c]
New	22 (50·0)	7 (38·9)	
Recurrent	22 (50·0)	11 (61·1)	
Wagner scale, no. (%)			0·40[c]
1	12 (27·3)	1 (5·5)	
2	17 (38·7)	7 (38·9)	
3	6 (13·6)	5 (27·8)	
4	7 (15·9)	4 (22·2)	
5	2 (4·5)	1 (5·5)	
Neuropathy, no. (%)	34 (77·2)	16 (88·9)	0·92[c]
Hypertension, no. (%)	19 (43·2)	11 (61·1)	1·00[c]

BMI, body mass index; DM, diabetes mellitus; n, participants.
†Data are presented as mean ± SD, median (min–max) and percentage. a. *t* independent test; b. Mann–Whitney, c. chi-square (*P < 0·05).

Outcome measures

The Pearson correlation analysis was performed to analyse the correlation between maceration and wound healing. There was a correlation between maceration and wound healing from enrolment until week 4 ($r = 0·40$, $P = 0·002$) (Figure 2). The Kaplan–Meier analysis was performed to compare the time to healing between the non-maceration and maceration groups until week 4. The Kaplan–Meier curve indicated that the non-macerated wounds healed significantly faster than the macerated wound (log-rank test = 19·378, $P = 0·000$) (Figure 3). The Cox regression analysis showed that maceration was a statistically significant and independent predictor of wound healing (adjusted hazard ratio, 0·324; 95% CI, 0·131–0·799; $P = 0·014$) regardless of the wound status (new ulcer and recurrence) and the Wagner scale (severity of the wound) (Table 3).

Discussion

Our results confirmed that there is a relationship between maceration and wound area as the non-macerated wounds in our study healed faster than the wounds with maceration.

To the best of our knowledge, this is the first study that aimed to clarify the relationship between maceration and wound healing in DFUs. DFUs are chronic wounds for which healing is required over the long term. One of the factors that may influence wound healing is maceration.

Maceration can delay healing and cause the enlargement of a wound (15). Moreover, wounds with maceration are weaker than non-macerated wounds, and they can become damaged by physical trauma and eroded by proteolytic enzymes (20). Other studies of pressure ulcers have suggested that there is a strong relationship between excessive skin moisture and the development of pressure ulcers (21,22).

Besides exudate, maceration may also be caused by urinary incontinence (23). In normal healthy healing, MMPs are regulated by the tissue inhibitors of metalloproteinases (TIMPs) (24) so that MMPs are produced equally; however, the production of MMPs in chronic and acute wounds is different: wound fluids in chronic wounds contain high concentrations of

Table 2 Wounds characteristics

Variables	The non-maceration group	The maceration group	P-value†
Baseline wound area (cm^2)	1·35(0·20–30·90), (n = 52)	4·75(0·50–28·80), (n = 18)	0·26
Changes in the wound area (median, cm^2)			
Week 1	−0·25(−4·50–0·30), n = 41	0·95(−6·50–18.80), n = 18	0·02*
Week 2	−0·20(−6·80–1.40), n = 30	0·05(−5·20–16·80), n = 18	0·05
Week 3	0·00(−2·30–4.50), n = 19	−0·20(−4·00–15·30), n = 18	0·37
Week 4	−0·45(−1·70–6·30), n = 12	−0·90(−15·00–21·00), n = 17	0·28

†Data are presented as Median (min−max). Mann−Whitney test (*$P < 0.05$).

Relationship between maceration area and changes in the wound area (n=71)
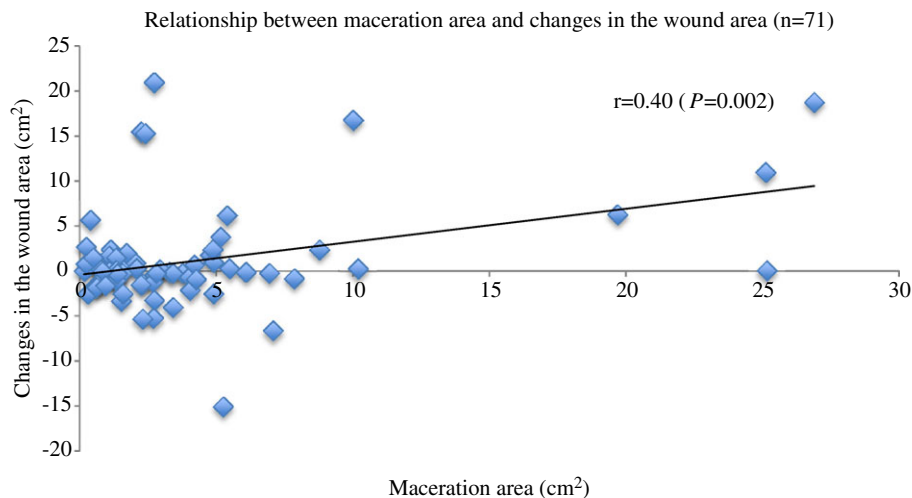
r=0.40 (P=0.002)

Figure 2 Relationship between maceration area and changes in the wound area. There was a moderate relationship between maceration area and changes in the wound area with Pearson coefficient correlation (r) = 0·40 (P = 0·002).

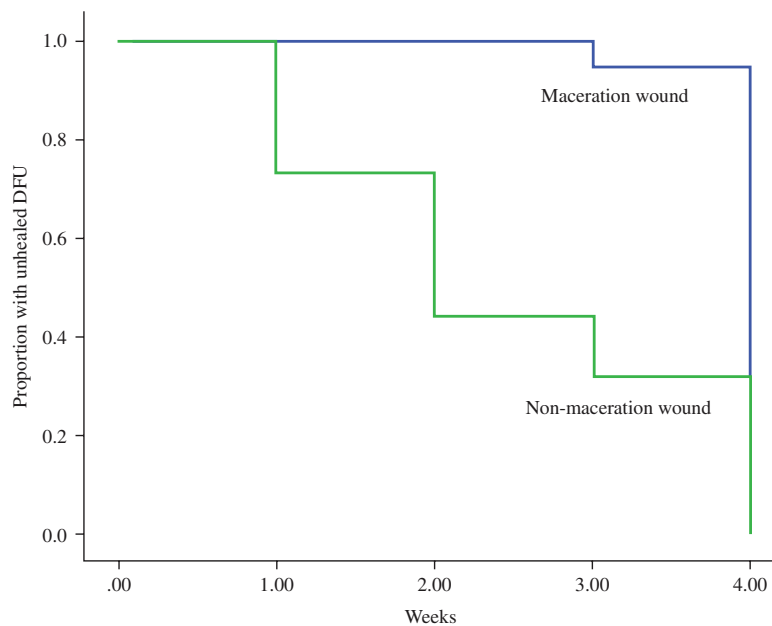| Wounds characteristics (n)				
Maceration	118	18	18	18	17
Non-maceration	52	41	30	19	12

Figure 3 Kaplan−Meier analysis of the time to healing. The non-maceration group healed significantly faster than the maceration group as indicated by Kaplan−Meier curve (log-rank test = 19·378, P = 0·000).

Table 3 Cox regression analysis: predictor of changes in the wound area†

Variables	Adjusted hazard ratio	95% CI	P-value
Maceration	0·324	0·131−0·799	0·014*
Age	0·990	0·959−1·022	0·540
Wound onset	0·999	0·996−1·002	0·527
BMI	0·959	0·866−1·062	0·420
FBS	0·994	0·998−1·001	0·075
ABI	1·098	0·095−12·665	0·940
Wound status	1·323	0·585−2·994	0·501
Wagner	0·769	0·547−1·082	0·132

ABI, ankle-brachial index; BMI, body mass index, FBS, fasting blood sugar.

†Cox regression analysis demonstrated that maceration status was a significantly independent predictor of changes in the wound area (Adjusted hazard ratio (HR), 0·324; 95%CI, 0·131−0·799; $P = 0.014$) *$P < 0.05$ regardless of wound status (new ulcer and recurrence) and Wagner (severity of wound).

enzymes, or MMPs levels are increased, and TIMP levels are decreased (25,26). The variety of highly concentrated enzymes in exudate in chronic wounds (27) may actively damage healthy tissues (28).

We previously reported that non-macerated wounds heal faster than wounds with maceration. When macerated tissue is present, it can become infected by organisms that prefer an environment with high water activity (29). The most common organism in non-healing wounds, including DFUs, to cause infection is *Staphylococcus aureus* (30). Infection is one of the most frequent complications of non-healing wounds and can result in major amputations or life-threatening conditions (31).

One of the most important aspects of wound management is how to predict wound healing. In general, maceration will negatively affect the wound area and consequently delay the healing time. Maceration is not only caused by exudate but also by the use of inadequate dressing (32). Clinicians should therefore pay attention to the appropriate selection of dressings and frequency of dressing changes.

Limitations

This study had some limitations. During the study, the kinds of dressings used could not be documented; however, wound care was based on accepted standards. The fact that this study was not a randomised controlled trial presents another limitation.

Conclusion

The present study investigated the relationship between maceration and wound healing in DFUs in a prospective longitudinal cohort study. A relationship between maceration and wound area was established. Our results suggest that changes in the wound area could help predict the healing of wounds with maceration in clinical settings.

Acknowledgements

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