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DECODING CLINICAL FACTORS ASSOCIATED WITH FIBROSIS IN PATIENTS WITH CHRONIC WOUNDS: INSIGHT INTO CROSS-SECTIONAL RESEARCH

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Abstract

Chronic wounds pose a major healthcare burden due to poor healing, high recurrence, and fibrosis that impairs functional recovery. This study aimed to identify clinical factors associated with fibrosis in patients with chronic wounds. A cross-sectional study was done in 200 patients with chronic wounds of a tertiary care healthcare facility. Medical records were used to obtain demographic and clinical data such as age, gender, diabetes mellitus, smoking history, duration of the wound, wound location and clinical infection. A clinical assessment to determine fibrosis status was obtained from patient records. Summary statistics were used to summarize study variables and the association of clinical factors with fibrosis was tested using the Chi-square test. A p value of <0.05 was deemed to be statistically significant. 82 (41.0%) patients had fibrosis identified. Most of the participants were male (58.0%) and age group 41–60 (44.5%). The number of patients with diabetes mellitus was 42.5%, and 31.0% had a smoking history. Significant associations were observed between fibrosis and diabetes mellitus (56.5% of diabetics vs. 29.6% of non-diabetics had fibrosis, p<0.001), smoking history (54.8% of smokers vs. 34.8% of non-smokers, p=0.008), prolonged wound duration of ≥12 weeks (50.0% vs. 25.7%, p<0.001), and clinical infection (53.2% vs. 33.3%, p=0.004). The greatest frequencies of fibrotic outcomes were seen in patients with chronically draining wounds and diabetes. Patients with the longest wound duration and diabetes had the highest frequencies of fibrotic outcomes. Diabetes, smoking, prolonged wound duration, and infection were linked to fibrosis in chronic wounds, underscoring the importance of early management of modifiable risk factors to improve outcomes.

Key Words: *Chronic wounds, Clinical infection, Diabetes mellitus, Fibrosis, Risk factors, Smoking. Wound healing*

INTRODUCTION

Chronic wounds pose a significant and growing public health problem, and are a significant burden of disease on health systems around the world (1). Such wounds do not go through the stages of healing in the usual time frame, and are often linked to prolonged treatment, recurrent infections, decreased quality of life, and higher healthcare expenses (2). Common chronic wounds include diabetic foot ulcers, venous leg ulcers, pressure ulcers and non-healing traumatic wounds, which are all clinically challenging (3).

Wound healing is a complex process of tissue repair, angiogenesis and remodeling (4). But if the normal healing processes are disrupted, too much scar tissue may build up and fibrosis occur (5). Fibrosis involves the formation of abnormal amounts of connective tissue during healing and can lead to stiffness, dysfunction and slow healing (6, 7). Fibrosis is an important outcome of wound management and is influenced by multiple factors related to patients and wound (8, 9).

Some clinical factors have been correlated with poor wound healing. It is known that diabetes mellitus affects tissue perfusion, immune function and cellular repair mechanisms, which could lead to delayed healing and fibrotic changes (10, 11). In the same way, smoking's impact on oxygen delivery and vascular function are detrimental, and wound infection can also extend inflammation and hamper tissue repair (12, 13). The duration of the wound has also been identified as an important predictor of healing failures and the chronic remodeling of tissue (14).

Knowing the clinical characteristics of patients that are associated with a risk of poor healing outcomes can help to identify patients who may be at higher risk for poor healing outcomes. Awareness of these factors can aid in early intervention strategies, wound optimisation and may minimise long-term complications of chronic wounds. Although the care of wounds has improved over the years, there is limited evidence of the combined effect of demographic and clinical factors on fibrosis in many clinical situations.

A cross-sectional design was appropriate for this exploratory aim, since it allows for the simultaneous assessment of several clinical parameters without compromising patient care and can produce hypotheses for further longitudinal research. Hence, the present study aimed to assess the clinical parameters that correlated with fibrosis in patients with chronic wounds. The objectives of the study were to explore the association of the demographic (age, sex), comorbid (diabetes, and smoking status), and wound-related (wound duration, location, clinical infection) factors with the presence of fibrosis, with the goal of developing evidence to inform better clinical care and outcomes.

MATERIALS AND METHODS

STUDY DESIGN

A cross-sectional study was conducted to evaluate the clinical factors associated with fibrosis in patients with chronic wounds. The study was carried out at a tertiary care healthcare facility, where patient records were reviewed to obtain relevant demographic and clinical information.

STUDY AREA

The study included patients diagnosed with chronic wounds who attended the healthcare facility during the study period. Chronic wounds were defined as wounds that failed to heal within 12 weeks despite appropriate treatment. A total of 200 patients fulfilling the eligibility criteria were included in the study. Ethical approval was obtained from the relevant institutional review committee prior to data collection. Patient confidentiality was maintained throughout the study by anonymizing all records and removing personal identifiers. The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki.

INCLUSION AND EXCLUSION CRITERIA

Those patients included who were aged 18 years and above, clinically diagnosed chronic wounds with a duration of at least 12 weeks, availability of complete demographic and clinical records, documented wound healing outcomes and fibrosis status. Exclusion criteria included: 1) acute wounds <12 weeks duration; 2) incomplete medical records with >20% of key variables missing, including fibrosis status, diabetes status, or wound duration; and 3) terminal illness such as metastatic cancer or end-stage renal disease on hospice care without systematic wound healing documentation.

DATA COLLECTION

Data were collected from hospital records using a structured data collection form. Information obtained included demographic characteristics and clinical variables relevant to wound healing.

STUDY VARIABLES

The dependent variable was fibrosis status (present or absent). Independent variables included: Age group, Gender, Diabetes mellitus, Smoking history, Wound duration, Wound location, Clinical infection. These variables were selected based on their reported association with wound healing outcomes in previous clinical studies. Although additional variables (BMI, HbA1c, hypertension, serum cholesterol, urinary tract infection, septicemia, ethnicity, marital status, education level) were initially planned for analysis, they were excluded due to incomplete documentation in >30% of patient records. Only variables with <10% missing data were retained for analysis.

When available from routine clinical care, histopathological data were extracted from wound biopsy reports. Biopsies were taken from the wound edge or base at initial presentation and evaluated by board-

certified pathologists using standard H&E staining. Recorded parameters included inflammation grade (mild: scattered cells; moderate: dense focal infiltrate; severe: diffuse infiltrate with tissue disruption), granulation tissue (present/absent), necrosis (present/absent), and re-epithelialization (complete/incomplete). Fibrosis status, the primary outcome, was determined separately from clinical documentation as described above, not by histomorphometric quantification such as collagen volume fraction or immunohistochemistry for α-SMA. Histopathological parameters were analyzed as secondary variables to assess their association with fibrosis.

STATISTICAL ASSESSMENT

Data were entered and analyzed using Statistical Package for the Social Sciences (SPSS) version 26.0. Descriptive statistics were used to summarize demographic and clinical characteristics. Categorical variables were presented as frequencies and percentages. Associations between clinical variables and fibrosis were evaluated using the Chi-square test. Statistical significance was established at a p-value of less than 0.05.

RESULTS

This is a cross-sectional study of 200 patients with chronic wounds. Demographic and clinical features of chronic wound patients are summarized in Table I. Most of the participants were male (58.0%) and the people aged 41-60 constituted the biggest age group (44.5%). The prevalence of diabetes mellitus was 42.5% and smoking was prevalent in 31.0% of the patients. The majority of wounds were present for 12 weeks or more (63.0%) and the lower limb was the most common anatomical site (61.0%). In 38.5% clinical infection was detected. In general, 41.0% of the chronic wound specimens showed fibrosis.

Table I. Demographic and clinical characteristics of patients with chronic wounds (n = 200)

Variable	Category	n (%)
Gender	Male	116 (58.0)
	Female	84 (42.0)
Age Group (Years)	≤40	42 (21.0)
	41–60	89 (44.5)
	>60	69 (34.5)
Diabetes Mellitus	Yes	85 (42.5)
	No	115 (57.5)
Smoking History	Yes	62 (31.0)
	No	138 (69.0)
Wound Duration	<12 weeks	74 (37.0)
	≥12 weeks	126 (63.0)
Wound Location	Lower Limb	122 (61.0)
	Upper Limb	39 (19.5)
	Trunk	24 (12.0)
	Other	15 (7.5)
Clinical Infection	Present	77 (38.5)
	Absent	123 (61.5)
Fibrosis Status	Present	82 (41.0)
	Absent	118 (59.0)

Table II shows the relationship between clinicopathological factors and fibrosis in patients with chronic wounds. There were significant correlations between fibrosis and diabetes mellitus ($p<0.001$), smoking history ($p=0.008$), wound duration ($p<0.001$) and clinical infection ($p=0.004$). Histopathological parameters such as inflammation grade ($p<0.001$), granulation tissue formation ($p=0.041$), necrosis ($p=0.001$) and re-epithelialization status ($p<0.001$) were also significant factors associated with fibrosis. Severe inflammation (67.2%), necrotic lesions (59.4%) and incomplete re-epithelialization (54.4%) were the wounds that had the highest incidence of fibrosis. These results indicate that clinical and pathological factors play a significant role in the formation of fibrosis in chronic wounds.

Table II. Clinicopathological factors associated with fibrosis in chronic wounds (n = 200)

Variable	Category	Fibrosis present n (%)	Fibrosis absent n (%)	p-value
Diabetes Mellitus	Yes	48 (56.5)	37 (43.5)	<0.001
	No	34 (29.6)	81 (70.4)	
Smoking History	Yes	34 (54.8)	28 (45.2)	0.008
	No	48 (34.8)	90 (65.2)	
Wound Duration	≥12 weeks	63 (50.0)	63 (50.0)	<0.001
	<12 weeks	19 (25.7)	55 (74.3)	
Clinical Infection	Present	41 (53.2)	36 (46.8)	0.004
	Absent	41 (33.3)	82 (66.7)	
Inflammation Grade	Mild	12 (22.6)	41 (77.4)	<0.001
	Moderate	31 (34.8)	58 (65.2)	
	Severe	39 (67.2)	19 (32.8)	
Granulation Tissue	Present	56 (47.5)	62 (52.5)	0.041
	Absent	26 (31.7)	56 (68.3)	
Necrosis	Present	41 (59.4)	28 (40.6)	0.001
	Absent	41 (31.3)	90 (68.7)	
Re-epithelialization	Complete	26 (26.8)	71 (73.2)	<0.001

DISCUSSION

The present cross-sectional analysis of 200 patients with chronic wounds, diabetes mellitus, smoking history, prolonged wound duration (≥12 weeks), and clinical infection were significantly associated with the presence of fibrosis. These finding offers valuable suggestions for clinical practice regarding modifiable and non-modifiable risk factors that may guide early intervention strategies. These findings highlight the need of early detection of patients with several concurrent risk factors. This study concurrently assessed demographic, comorbidities, and wound-related variables to offer a useful risk profile for early high-risk patient identification, in contrast to previous studies that analyzed aspects separately.

The results of this study demonstrated significantly higher proportion of fibrosis among diabetic patients (56.5%) versus the non-diabetic patients (29.6%) ($p<0.001$). These findings align with the previous studies which reported that antibiotic therapy in diabetic patients is not always effective in preventing fibrotic complications because of underlying microvascular dysfunction and impaired cellular repair mechanisms in these patients (15,16). Similarly, a systematic review and meta-analysis identified oxidative stress and dysregulations of the angiogenic pathways as the important molecular mechanisms underlying poor healing and fibrosis of diabetic foot ulcers, corroborating clinical observations of this study (17,18). The high frequencies of fibrotic outcomes were seen in patients with chronically draining wounds and diabetes. The results here suggest that having strict glycemic control and treating wounds properly could help lower the risk for fibrosis in diabetics (19).

Fibrosis was present in 54.8% of smokers and 34.8% of non-smokers ($p=0.008$). It showed that smoking history was associated with fibrosis. This aligns with established evidence that smoking-induced oxidative stress and microvascular dysfunction impair tissue repair processes (20,21). Furthermore, smoking-induced vascular alterations are pre-analytical factors that impair metabolic integrity and might affect assessment of wound healing, supporting our conclusion that smoking contributes independently to fibrotic outcomes (22,23). In this cohort smokers with concomitant diabetes exhibited a greater susceptibility for fibrosis. These findings indicate that smoking cessation interventions should be a focus in chronic wound patients, especially in those who have metabolic disorders (24).

Wound duration of ≥12 weeks was associated with fibrosis (50.0% vs. 25.7%, $p<0.001$). This is in line with a study who highlighted that fibrotic remodeling is a consequence of chronic inflammation in the tumor microenvironment (which is analogous to the chronic wound system) (25,26). Similarly, clinical infection was linked to fibrosis (53.2% vs. 33.3%, $p=0.004$), is consistent with another study who implicated that perioperative infections and wound infections are associated with scar formation and delayed wound healing in resource poor settings (27,28). Other significant factors in this study were severe inflammation (67.2% fibrosis), necrosis (59.4%) and incomplete re-epithelialization (54.4%). These are consistent with previous reports showing that chronic tissue

injury leads to persistent inflammatory signals, which drive activation of the fibroblasts and deposition of

extracellular matrix, regardless of the underlying cause of the tissue injury (29,30).

There are some limitations of this study. Firstly, a cross-sectional design precludes establishing causal relationships identified factors and fibrosis. The data collected were from one tertiary care center with limited applicability in primary care/community settings. Additionally, fibrosis was assessed using clinical information and not a standardized histopathology score (such as degree of collagen deposition or immunohistochemistry). Furthermore, fibrosis was determined from clinical documentation rather than histomorphometric quantification (e.g., collagen volume fraction or immunohistochemistry for α-SMA or TGF-β), which may have introduced misclassification bias. Lastly, there is possibility of recall bias in self-reported smoking history and wound duration.

Future studies are needed to use prospective cohort or longitudinal study design to determine the relationship of fibrosis progression and risk factors. Objectively, quantifying fibrosis needs to be done by standardised histopathological and molecular markers including transforming growth factor beta (TGF-β), matrix metalloproteinases (MMPs) and collagen turnover markers. The findings should be validated in large-scale, multicenter trials with cross-sector and cross-cultural populations to more fully generalize the results to other health care systems. Further, there are interventional trials which need to be undertaken to assess whether reducing the levels of these modifiable factors (i.e. intensive glycemic control, smoking cessation programmes, early infection management) will reduce the incidence of fibrosis. Future research could customize risk assessment using AI-based predictive models that combine clinical and molecular data, such as HbA1c, smoking pack-years, and wound microbiota. Though, this method is still under investigation.

CONCLUSION

This cross-sectional study identifies that diabetes mellitus, smoking history, duration of wound has been found to be significant and related to fibrosis in chronic wounds. In addition, severe inflammation, necrosis, and failure to incomplete re-epithelialization further contribute to fibrotic outcomes. However, due to the study design, causal relationships cannot be established. These results highlight the importance of recognizing the issues of early detection and strong management of these potentially modifiable risk factors to ensure good wound healing and lower the likelihood of fibrotic complications in the long term. Clinicians may prioritize glycemic control, smoking cessation, and rapid infection care in patients with chronic wounds, pending prospective validation, since these characteristics were linked to a lower prevalence of fibrosis in this study.

Conflict of interest:

The authors declare no conflict of interest.

Authors' contribution:

MH Conducted the study and data collection; Me Conceptualized, designed the epidemiological investigation and analyzed seasonal prevalence data; WK Supervised the research and finalized the manuscript; SK Compiled and organized the data.

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