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Determinants of Keloid recurrence: The Nairobi keloid recurrence scoring system; A cohort, prospective study

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ABSTRACT

Background: Keloid disease is a fibro-proliferative disorder characterized by excessive deposition of collagen. Keloids has shown high recurrence rate. We undertook this study to determine what factors influence recurrence of the disease with the aim of developing a keloid recurrence scoring system.

Methods: This was a cohort prospective longitudinal study of patients who presented with keloids, managed by surgical excision followed by post excision radiotherapy. Post-surgery patients were followed up for at least two years to determine recurrence. Variables analyzed included patients' history, clinical presentation and keloid histology. Data captured were analyzed using SPSS version 21. Student T-test and Chi-square test were used to compare means and frequencies respectively at 95% confidence level (*P*-Value <0.05). Multi regression analysis was done to determine the contributions of various variables to keloid recurrence.

Results: Ninety patients were followed up in the study for duration of two years. Overall keloid recurrence was 21% with male patients having a significantly higher recurrence rate of 31% compared to the female at 12%. The recurrence rates were also higher in familial keloids at 27.7% compared to sporadic keloids at 18.5%. Other factors that influenced recurrence included anatomical location, patient's blood group and histological composition of the keloid. Multiple regression analysis done demonstrated that gender and family history was the biggest contributor to keloid recurrence.

Conclusion: Keloid recurrence is influenced by many factors including family history, clinical presentation and keloid histology. A Keloid recurrence scoring system encompassing these factors could assist in the determination of post excision management as well as prediction of the likelihood of recurrence.

1. Introduction

Keloids are fibro-proliferative disorders of the skin resulting in excessive tissue overgrowth usually due to minor tissue injury (Fig. 1). Keloids are attributed to abnormal wound healing with an exaggerated inflammatory phase and a poorly controlled proliferative phase [1,2]. They have been shown to be heterogeneous in both clinical presentation and histological compositions suggesting that treatment modalities should be adopted to each [1–3]. They have also been shown to present as either familial or sporadic [4]. The recurrence rates are high with studies quoting between 10 and 70% [5].

Factors that influence keloid recurrence either locally or globally have not been well understood. Shin et al. demonstrated keloid recurrence to be more common in male patients than female patients [6]. Other studies by Park et al. and Sun et al. noted keloid recurrence to be more common in areas of high skin tension such as the chest implying that anatomical location of the keloids influences recurrence of the disease [7,8]. Whether clinical parameters such as keloid surface area, age of onset or even patient's blood group or histological composition of keloids influence recurrence is not known. Even further whether keloid recurrence is influenced by the etiological agent and whether familial or sporadic forms of keloids do influence recurrence is not documented to the best of our knowledge.

Understanding determinants of keloid recurrence is however critical

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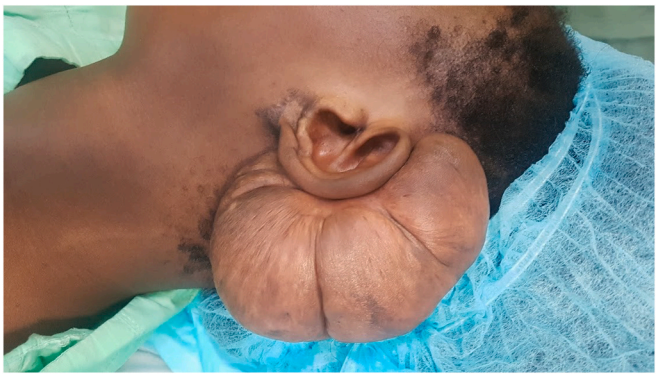

Fig. 1. A patient with a large auricular keloid.

in the management of the disease given its high tendency to recur and poor outcomes irrespective of the treatment options. Further post excision radiotherapy dosage is now recommended to be higher dosages in cases where recurrence is likely [9]. We undertook this study to determine factors that influence recurrence among patient cohorts with the aim of developing a keloid recurrence scoring system.

2. Patients and methods

This was a Prospective longitudinal observational study of patients who presented with keloids. Approval for the study was sought from the local ethics and review board. This study was registered in the research registry (registration number 8479). Consent for the study was attained from all patients. Included in the study were patients with keloids amenable for surgical excision followed by wound closure primarily. Exclusion from the study was patients with infected keloids, extensive keloids that could not be closed primarily and those who had surgery for the same keloid within one year. Dependent variables analyzed were keloids etiology, sex of the patients, family history of keloids, anatomical location of keloids, keloid size, pruritus score, pain score, patient's blood group and histological composition.

A detailed history was taken to determine the onset of keloids, causative agents and whether other members of the family had keloids. A thorough clinical examination was then done to determine the extent and anatomical location of keloids. The surface area of the keloids was measured using the grid iron technique. Pruritus and pain were assessed by the pruritus and pain visual analogue scales, respectively. Surgical excision of the keloids was done by the same plastic surgeon. Wounds were then closed in two layers with dermal stitch using vicryl 3/0 and transcutaneous stitch with nylon 3/0 interrupted sutures. The excised tissue was taken for histology and analyzed for lymphocytes, macrophages, mast cells and fibro-blasts (Figs. 2 and 3). Each patient's blood was taken to determine the blood group. Post-operative superficial radiotherapy was done with 12 Gy external beam radiotherapy within 24 h of surgery. X- Ray of 100 KV, 15 Milli Amperes, with filter of 0.2 mm copper at a distance of 30ssd (skin to source distance) were used.

Post-surgery patients were reviewed by the principal investigator at one week, one month, three months, six months, one year and at two years. At each review, the keloids were assessed to determine recurrence.

Recurrence was determined as either.

i. Any scar that healed beyond the margins of the initial scar at least at one year of follow up.
ii. Pruritus or pain scores that worsened in the course of follow up.
iii. Pruritus or pains scores that necessitated further medical interventions to control in the course of follow up.

Statistical analysis was done by STATA/SE statistics/data analysis

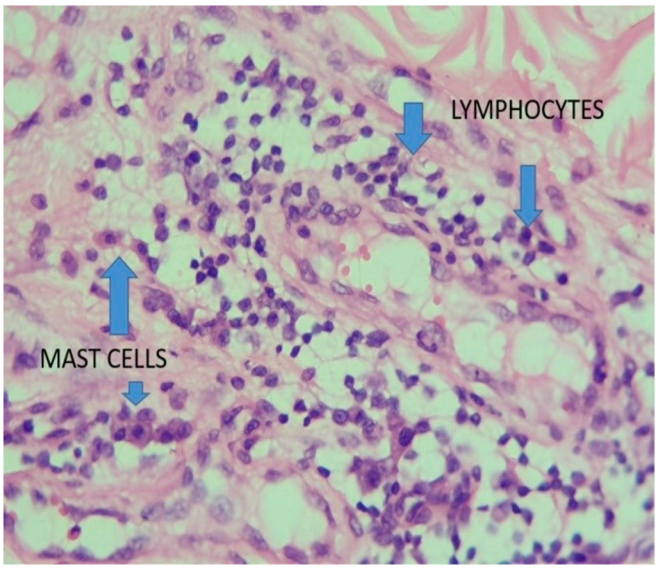

Fig. 2. Keloid histology with abundant mast cells and lymphocytes at high magnification.

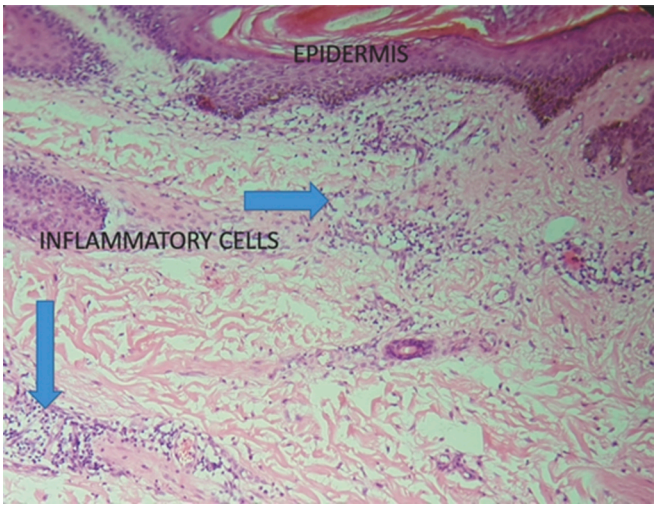

Fig. 3. Keloid histology with multiple inflammatory cells.

version 10 software.

Student T-test and Chi-square were used to compare means and frequencies at 95% confident levels (P-value <0.05). Multiple regression analysis was done to determine the correlation between dependent variables and recurrence.

3. Results

A total of 96 patients with 110 keloids were recruited in the study. Six patients did not complete the study leaving 90 patients with 104 keloids that were followed up to the completion of the study. The male to female ratio for the patients was 1:2. Nineteen patients with twenty keloids had keloid recurrence giving an overall patient recurrence rate of 21% and keloid recurrence rate of 19.2%. Out of the 104 keloids studied, 38 of them occurred in male patients with 66 in female patients. Male patients had a recurrence rate of 31% compared to female patients at 12% (P-value <0.05). Forty seven patients with 54 keloids had a positive family history of keloids and were classified as familial. The remaining 43 patients with 50 keloids operated on had no known family history and were thus classified as sporadic. The recurrence rate was

significantly higher in the familial group at 27.7% compared to 18.5% in the sporadic group ($P < 0.026$).

The etiological causes of keloids were as follows: spontaneous 16.6% (n = 17), infective 20% (n = 21) and post traumatic 63.4% (n = 66). A comparison between etiological causes and keloid recurrence demonstrated spontaneous keloids to have a higher recurrence rate at 29.2% compared to infective causes at 14% and post-traumatic causes at 18%. (*P*-value <0.05)(Table 1). The mean age of onset for the patients with no keloid recurrence (NKR) was 24.1 years with an age range of 17–65 years compared to the mean age of onset for the patients with keloid recurrence (KR) at 21.7 years with an age range of 15–63 years of age (*P*-value >0.05). The mean age of presentation for the KR was 28.5 years while the NKR was 29.8 years (*P*-value >0.05). The mean surface area of the keloids for the NKR was 9.4 cm^2 with a range from 2 cm [2] to 30 cm [2] while for the KR the mean surface area was 6.1 cm [2] with a range from 1 cm [2] to 36 cm [2] (*P* -value >0.05). Pain score for the patients with NKR ranged from 0 to 9 with a mean of 1.891 while those with KR the score ranged from 0 to 10 with a mean score of 2.22 (*P*-Value>0.05). For pruritus, the range for KR was from 0 to 10 with a mean pruritus score of 4.56 while for the NKR group the range was from 0 to 9 with a mean score of 3.04 (*P*-Value>0.05) (Table 2).

The most common anatomical location of the keloids were the ears accounting for 46% of the keloids with a recurrence rate of 17 0.5%, followed by the cheeks at 15% with a recurrence rate of 33%. Others were the chest, back and abdomen with a recurrence rate of 30, 23% and 10% respectively. There was a statistical significance difference between the ears and the cheek, the two most common anatomical locations (*P*-value <0.05). Comparison between blood groups in patients with KR and NKR patients demonstrated that keloid patients with blood group A were more prone to recurrence compared to the other blood groups (*P*-value <0.05), while patients with blood group B were least likely to have keloid recurrence (*P*-value <0.05) (Table 3).

Comparison of histological parameters assessment in patients who had keloid recurrence and those without recurrence revealed higher counts of lymphocytes, fibro-blasts and macrophages were associated with keloid recurrence. Absolute counts of mast cells were however not associated with keloid recurrence (Table 4). Multiple regression analysis demonstrated keloid etiology contributed to recurrence by a factor of 0.279, gender 0 0.431, family history 0.397, keloids histology 0.297 and blood group 0.354 (Table 5).

A keloid recurrence scoring system was calculated by getting the average keloid recurrence percentages of each variables and scored as follows; keloid recurrence percentages between 0 and 10% were given a score of 0.5, 10–20% score of 1, 20–30% a score of 2, greater than 30% a score of 3 (Table 6). Variables considered in the system were patient's sex, familial or sporadic keloids, anatomical location of keloids, blood groups and keloid histology. The highest score in the study of 16 corresponded to a recurrence rate of 32% and the lowest score of 6 corresponded to a recurrence rate of 11.2% (Table 6, Fig. 4).

Table 1
Etiological causes of keloids in KR and NKR.

Etiological cause	Total (N)	Recurrent (KR) (n) (%)	None recurrent (NKR) (n)(%)	P-Value (student T test)
Trauma	66	12 (18.2)	54 (81.8)	<0.001
Infective	21	3 (14.3)	18 (85.7)	<0.001
Spontaneous	17	5 (29.4)	12 (70.6)	0.05

Parameters	Sum of squares	Df	Mean squares	F	P-value
Between groups	732.05	1	732.05	3.178	0.036
Within groups	921.40	4	115.18		
Total	1653.45	5			

The Anova test for Variance demonstrated statistical significance between the various aetiological causes.

Table 2
Mean age of onset, Mean surface area of keloids, Pain score and Pruritus score in KR and NKR.

	KR	NKR	P-value (T Test)
Frequency	20	84	
Age of onset	21.70	24.12	0.494
Age of presentation	28.47	29.77	0.712
Surface area	6.1cm2	9.4cm2	0.354
Pain score	2.22	1.891	0.925
Pruritis	4.56	3.04	0.666

Table 3
Blood group types in KR and NKR.

Blood group	Total Count	(NKR) = 71 N (%)	(KR)N = 19 N (%)	P-Value (chi square Test)
O	45	35 (49..3)	10 (52.6)	0.124
A	28	19(26.8)	9 (47.4)	0.011
B	13	13(18. 3)	0	0.001
AB	4	4 (4.3)	0	0.516

Table 4
Fibroblasts and inflammatory cells counts KR and NKR.

Parameter Assessed	Count/ 100 HPF	No recurrence N = 84	Recurrence N = 20	P-value Chi square test
Lymphocytes				0. 00064
	<50	58	2	
	50–100	18	16	
	>100	8	2	
Macrophages				0.000066
	<50	64	1	
	50–100	16	15	
	>100	4	4	
Mast cells				0.128742
	<50	10	2	
	50–100	44	17	
	>100	30	1	
Fibro-blasts				0.007191
	<50	58	2	
	50–100	16	10	
	>100	10	8	

Anova test for Variance

Parameters	Sum of squares	Df	Mean squares	F	P-value
Between groups	1235.57	1	1235.57	9.537	0.005
Within groups	3368.29	26	129.55		
Total	4603.86	27			

Anova test for variance within the groups demonstrated a *P*-value of less than 0.005.

4. Discussion

Keloid characterized by high recurrence has no well-known pathogenesis. The disease seems to have a multi-factorial etiology with genetic, inflammatory and environmental factors playing a role [1,2]. Despite the fact that the disease has been studied extensively over many decades, the ability to determine or predict the outcome of keloid treatment has not been brought to the fore [5]. Due to its heterogeneous nature of presentation, a thorough history, clinical evaluation and histological examination may be crucial in determining the disease severity and thus the tendency for recurrence. In this study, we demonstrated that multiple factors influence the outcome of keloids and a combination of these factors could be used to determine the likelihood of recurrence. Factors that significantly influenced keloid recurrence in our study included; patients' gender, anatomical location, familial keloids, etiology, patients' blood group and keloid histology. On the other hand,

Table 5
Multiple regression analysis on variables of keloid recurrence.

Coefficients[a]							
Model		Unstandardized Coefficients		Standardized Coefficients	T	Odd Ratio	Sig.
		B	Std. Error	Beta			
1	(Constant)	2.335	0.466				
	Aetiology	0.279	0.085	0.698	3.2823	1.419	0.0115
	Gender	0.431	0.054	0.448	7.9814	0.651	0.005
	Family history	0.397	0.061	0.738	6.5081	0.576	0.0132
	Anatomic location	0.299	0.210	0.297	0.539	2.714	0.008
	Blood group	0.354	0.053	0.445	6.6792	0.793	0.016

[a] Dependent Variable: Keloids recurrence.

Table 5: Significance of the Coefficients of the Regression Model.

The regression equation used was.

$Y = \beta_0 + \beta_1X_1 + \beta_2X_2 + \beta_3X_3 + \beta_4X_4 + \beta_5X_5 + €€$

The established regression equation becomes.

$Y = 2.335 + 0.279X_1 + 0.431X_2 + 0.397X_3 + 0.299X_4 + 0.354X_5$.

Interpretation.

- Aetiology contributed to the recurrence of keloids ($\beta = 0.279$; $P = 0.0021$).
- Gender contributed to the recurrence of keloids ($\beta = 0.431$; $P = 0.005$).
- Family history contributed to recurrence of keloids ($\beta = 0.397$; $P = 0.0132$).
- Anatomic location contributed to recurrence of keloids ($\beta = 0.299$; $P = 0.008$).
- Blood group contributed to recurrence of keloids ($\beta = 0.354$; $P = 0.016$).

Table 6
Keloid recurrence scoring system
For summarizing factors that influenced keloid recurrence in the study, a keloid recurrence scoring system was developed as shown in the table below.

Factors for keloid recurrent	Percentage recurrence	Average Score
Aetiology		
Spontaneous	29	2
Infective	14	1
Traumatic	18	1
Gender		
Male	31	3
Female	10	1
Family history		
Familial	26.9.	2
Sporadic	18.5	1
Anatomic location		
Cheek	33	3
Chest	30	3
Others	10	1
Blood group		
A	32	3
Other groups	14	1
Histology (inflammatory cells)		
High	32	3
Moderate	20	2
Low	10	1

The highest score in the study 16 corresponded to a recurrence of 32 and the lowest score of 6 corresponded to a recurrence rate of 11.2%. The average keloid recurrence was 19.2%.

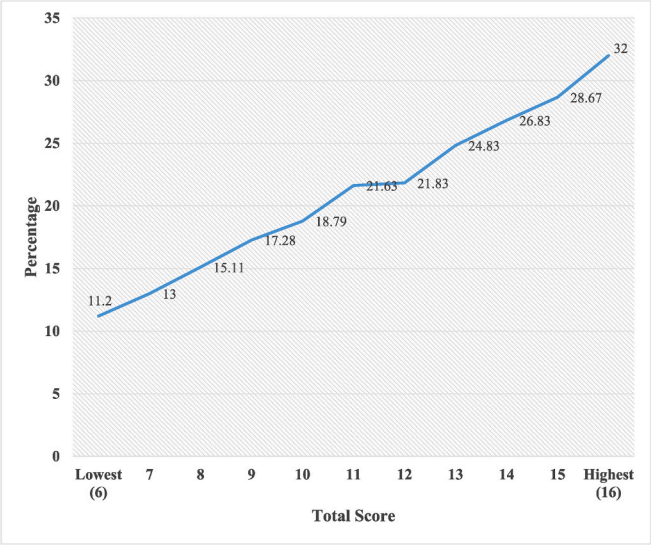

Fig. 4. X -Axis, Patient scores, Y-Axis percent Keloid recurrence.

clinical factors such as the keloid surface area, age of onset, pruritus score and pain score did not seem to influence recurrence.

Our study demonstrated that male patients were almost three times likely to have keloid recurrence compared to their female counterparts. The reason as to why male patients could have higher recurrence than female patients is not known. Whether this could be attributed to the differences in anatomical location or the influence of sex hormones on keloids is not known. Male as a factor in keloid recurrence was also reported by Shin et al. [6] Sun et al. in another study on determining the role of post-operative radiotherapy on the occurrence and recurrence of keloids had a recurrence rate of 50% in male patients (4 out of 8 Keloids) compared to 10% in female patients (3 out of 29) strongly implying that patients gender influences severity and recurrence [8].

A number of studies have shown keloids to either occur sporadically or in families with an autosomal dominant inheritance pattern [4,9–11]. The clinical presentation of these two modalities of disease have however been shown to be different with familial keloids being more common in keloid endemic communities such as in African [4,5]. Familial keloids have also been shown to be a more severe disease with a higher occurrence of multiple keloids, severe pruritus and pain [4,5]. Familial keloids in this study demonstrated a recurrence rate that was 1.5 times more than sporadic keloids confirming the fact that they are a more severe disease than sporadic keloids. Bayat et al. also found out those keloids that were severe in presentations was familial in nature [12]. Sun et al. in another study demonstrated a positive maternal family history to be more associated with keloid recurrence [8]. The role of anatomy in keloid formation has been demonstrated by a number of studies to be predominantly located in the chest, head and neck regions of the body [1,5,13,14]. However only a few studies have demonstrated a correlation between these anatomical locations and keloid recurrence [7,8]. Park et al. noted in pediatric patients that chest keloids were more prone to recurrence compared to other sites [7]. Ogawa et al. found keloid recurrence to be more on the chest and helical rim compared to

other anatomical sites [9]. He advocated for a higher dose of radiotherapy in such locations so as to reduce on the recurrence rates. In our study, we noted higher recurrence rates on the cheek and anterior chest wall compared to other anatomical regions such as the ears and the abdomen. Keloids in these anatomical areas may therefore need close monitoring and probably a higher dose of superficial radiotherapy as suggested by Ogawa et al.

Other factors that seemed to influence recurrence included keloid histology and patients' blood group, with blood group-A patients being almost twice as likely to have recurrence compared to the other blood groups. Previous studies by Sheen et al. and Ramakrishna had demonstrated patients with blood group-A to be more prone to keloid formation compared to the other groups [13,14]. However, no correlation had been done between this blood group and keloid recurrence. On the other hand, the role of keloid histology on recurrence has mainly focused on whether the excision margins were involved or not, with studies suggesting that clear margins were associated with low recurrence rates [15,16]. This study however demonstrated that keloids with either increased lymphocytes, macrophages and or fibro-blasts were more prone to recurrence suggesting that inflammation seems to play a critical role in keloid formation and severity.

5. Conclusion

Based on our study we proposed keloid recurrence scoring system that encompasses factors that influence recurrence. This included the patient's sex, family history of keloids, and anatomical location of keloids, keloids etiology, blood group and keloid histology. The weighting of each factor was based on the relative contribution to keloid recurrence and the odds ratio. With these factors, a total score of 16 correlated to keloid recurrence of 30%. This scoring system enables the clinician to understand which keloids are likely to recur and thus improve on the patient's surveillance or start on the second line medication early. Further, patients with high likelihood of recurrence using this scoring system should be given a higher dose of post - excision superficial radiotherapy so as to mitigate this from happening. Ogawa et al. were able to reduce keloid recurrence rate to less than ten percent by giving higher doses of superficial radiotherapy to areas that were more prone to recurrence.

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Ethical approval

Ethical approval was given By KNH/UON ethics and research committee Ref NO. P291/041/2018.

Consent

All patients who participated in the study consented/assented to do so. as described in the manuscript.

Author contribution

Below is the contribution for the authors.

Nangole FW; Study concept/design, data collection, data analysis or interpretation, writing the paper.

Agak G; Study concept/design, data collection, data analysis or interpretation, writing the paper.

Anzala Omu; Study concept/design, data collection, data analysis or interpretation, writing the paper.

Ogeng'o J; Study concept/design, data collection, data analysis or interpretation, writing the paper.

Registration of research studies

The study was registered in the •https://www.researchregistry.com/Ref No, 8479.

Guarantor

The Guarantor is DR Ferdinand W Nangole Email address, nangole2212@gmail.com.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijso.2023.100596.

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