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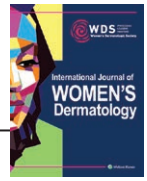

A retrospective study on the association of keloids with underlying health conditions in African-American Women

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ABSTRACT

Background: Keloids are disfiguring benign scars that develop due to an exaggerated response to cutaneous wound healing, growing beyond the boundaries of the cutaneous insult into normal, previously uninvolved skin. The association of keloids with other underlying health conditions has been postulated, but not well characterized.

Objective: This study aims to identify whether there is any association of keloids with underlying health conditions in African-American women.

Methods: This study was done via the use of the National Inpatient Sample, a subset of the Healthcare Cost and Utilization Project. African-American women with keloids who had undergone cesarean sections were compared with a control group of African-American women with no history of keloids who had undergone cesarean sections.

Results: A total of 301 African-American inpatient encounters with patients with keloids were compared with 37,144 encounters in the control group. The keloid patients had an increased association with peritoneal adhesions compared with the control group.

Limitations: results are limited to one race and restricted age range; also, unable to differentiate keloids from hypetrophic scarring with ICD-10 codes.

Conclusion: These findings suggest that keloids and peritoneal adhesions may have similar inflammatory processes.

Keywords: keloids, peritoneal adhesions, pregnancy, scars

Introduction

Keloids are exuberant proliferative scars that develop from wound healing after cutaneous insults. They most commonly present on the chest, upper back, shoulders, and ears, and frequently manifest on individuals with skin of color, including those of African, Asian, and Latinx descent. Although keloids are benign, they can negatively impact quality of life as they can be disfiguring, painful, and/or pruritic; in some cases, they can even limit joint mobility.[1] However, there is currently no gold standard of treatment for keloids. Keloids often recur even after surgical removal, with recurrence rates ranging from 45% to 100%.[2] The pathogenesis of keloids has long been poorly understood and is difficulty to study because keloids are a phenomenon that occurs only in humans.[1] Recent research suggests that keloid pathogenesis may be related to a variety of factors, including genetic, epigenetic, systemic, and local (such as mechanical tension).[3]

There have been some studies showing keloids are associated with osteoporosis,[4] leiomyomas,[5] as well as hypertension and obesity,[6–8] but the number of studies is limited. Furthermore, these studies typically have not controlled for a uniform insult to the skin, such as those who have undergone major surgical procedures. One such surgical procedure that has been associated with the development of keloids is the cesarean section (C-section). It inherently involves a large cutaneous insult that results in scar formation; the length and location of the incision tends to be fairly standard in nature. Moreover, pregnancy has been suggested as a risk factor for keloids.[9,10] For these reasons, this study aims to identify any possible associations between the formation of keloids and various underlying health conditions in women who have had C-sections.

What is known about this subject in regard to women and their families?

- Keloids predominantly affect people with skin of color and are thought to have genetic associations as they tend to run in families.
- Keloids commonly recur even after treatment, causing high burden of cost and decreased quality of life of those affected.
- There are limited studies on keloid associations with other underlying health conditions, especially in women.

What is new from this article as messages for women and their families?

- Predisposition to keloid formation in African-American women may be related to the development of peritoneal adhesions.
- Keloid formation is not associated with comorbidities such as gestational hypertension, gestational diabetes, or pre-existing type 2 diabetes mellitus.

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Supplementary data related to this article can be found at http://links.lww.com/IJWD/A17.

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Materials and methods

A retrospective chart review was performed using discharge data from the 2018 National Inpatient Sample (NIS), a subset of data from the Healthcare Cost and Utilization Project. Healthcare Cost and Utilization Project is a family of healthcare databases and related software tools and products developed through a Federal-State-Industry partnership and sponsored by the Agency for Healthcare Research and Quality. Of the 7,105,498 inpatient encounters included in the NIS Core database, 1,974 had keloids, identified using the International Classification of Diseases, Tenth Revision (ICD-10) diagnostic code for "keloid" or "hypertrophic scar," L910 (both diagnoses carry the same ICD-10 diagnostic code). In order to control for possible confounding variables such as race, encounters were filtered to include only African-American patients. Of the 1,974 inpatient stays with keloids, 692 of them were African American. Of those that did not have the diagnostic code for keloids, and were thus the normal control group, 1,040,963 were African American. In order to confirm that during an inpatient stay a patient had been subjected to an injury that could induce a keloid, we filtered for patients who had undergone a major surgical procedure. One such procedure is the C-section. The C-section, by its indication, also controls for both age and sex as only women of childbearing age undergo the procedure. Three ICD-10 procedure codes were matched against the 25 possible procedure codes for each patient entry in order to filter for C-sections: "10D00Z0" for extraction of products of conception (POC), high, open approach; "10D00Z1" for extraction of POC, low, open approach; and "10D00Z2" for extraction of POC, extra-peritoneal, open approach. Of the 692 inpatient stays with African-American keloid patients, 301 had C-sections included in their listed procedures. Of the 1,040,963 inpatient stays with African-American non-keloid control patients, 37,144 had C-sections included in their listed procedures. The age distribution of both the experimental group and control group is highlighted in Table 1.

A total of 49 comorbidities were selected for and tested using their respective ICD-10 diagnostic codes. These underlying health conditions included leiomyoma, dyslipidemia, anxiety, depression, atopic dermatitis, kidney disease, pre-eclampsia, hypertension, type 2 diabetes mellitus, liver disease, peritoneal adhesions, anemia, inflammatory disorders of the uterus, postpartum hemorrhage, respiratory diseases, and gastroesophageal reflux disease. The number of patients from each group who had each corresponding ICD-10 diagnostic code was calculated and recorded. For each ICD-10 diagnostic code, the proportions of each group (keloid and normal control) having the diagnostic code in their chart was compared using a 2-tailed z test with a p value of .05. To correct for multiple comparisons, an α value of 0.05 was divided by the number of analyses ($n = 50$) to give a Bonferroni corrected/adjusted p value of .001. Statistical calculations were performed using SPSS statistical analysis software (IBM; Armonk, NY).

Results

Table 2 highlights the diagnostic codes that showed significant differences between the experimental and control groups prior to the Bonferroni correction, while the Supplementary Table, http://links.lww.com/IJWD/A17, is a table detailing all of the diagnostic codes tested. Of the diagnostic codes tested, the ones with Bonferroni corrected significant differences between the keloid group and the normal group were peritoneal adhesions (K660 & N736), other specified noninflammatory disorders of uterus (N858), abnormality in fetal heart rate and rhythm complicated by labor and delivery (O76), diseases of the skin subcutaneously complicating childbirth (O9972), and other diseases and conditions complicating pregnancy/childbirth (O9989).

Some notable diagnoses that were not significantly different include full-term premature rupture of membrane with onset labor within 24 hours of rupture (O4202), unspecified leiomyoma of the uterus (D259), diseases of the digestive system complicating childbirth (O9962), gestational diabetes mellitus in childbirth (O24420), major depressive disorder (F329), generalized anxiety disorder (F411), atopic dermatitis (L209), and pre-existing hypertension (O113).

Table 1

The age distribution of African American (AA) women with keloids and AA control women who had undergone cesarean section (C-section)

	AA keloid patients with history of C-section	AA normal control patients with history of C-section
N	301	37144
Mean	30.16	29.02
Median	30	29
Standard deviation	6.12	6.08
Minimum	16	12
Maximum	50	55

Discussion

This study examined the associations between keloid development and the presence of various underlying health conditions in African-American women who underwent C-sections. Several conditions were found to be associated with the propensity to form keloids. African American females who develop keloids may be more likely to develop peritoneal adhesions (K660 & N736); this association has not been previously described in the literature. This suggests that keloids and peritoneal adhesions may have common underlying mechanisms that result in abnormal cutaneous and internal scarring, respectively. Other significant findings based on a standard p value and Bonferroni-corrected p value were expected, including the increased prevalence of diseases of the skin subcutaneously complicating childbirth (O9972) and other diseases and conditions complicating pregnancy/childbirth (O9989) in the keloid group, which suggest the usage of multiple codes to describe keloid development from surgical scarring. The abnormality in fetal heart rate and rhythm (O76) diagnostic code was the only significant finding where the normal patient group was more likely to have this risk than the keloid group. This may be due to the control group needing emergency C-sections at a higher rate than their African-American keloid counterparts. We do not know how many of the keloid group had keloidal scarring of a previous C-section scar, versus some other location.

In our study, the risk of developing leiomyomas (D252 and D259) trended toward but was not statistically significant after the Bonferroni correction. A similar study done on the relationship between keloids and the development of leiomyomas in Chinese women in Taiwan reported an increased prevalence of leiomyomas.[5] One possibility for this discrepancy is that there may be differences in the association between keloids and uterine fibroids based on genetic ancestry. The vast majority of diagnostic codes tested resulting in no significant difference further strengthens the findings of diagnostic significance between the African-American female keloid patients and their normal counterparts. One such example is there being no significant difference in the full-term premature rupture of membrane with onset labor within 24 hours of rupture (O4202). Moreover, the lack of an increased prevalence of gestational hypertension, gestational diabetes, and pre-existing type 2 diabetes mellitus suggests that keloid pathogenesis is dissimilar to that of the aforementioned processes. Our lack of significance with hypertension differs from multiple published studies.[6–8] It is possible that pregnancy obfuscates the difference in rates of hypertension between those that keloid and those that do not.

It may be possible that peritoneal adhesions are more prevalent in African American keloid patients because a common pathogenesis between keloids and peritoneal adhesion formation. Peritoneal adhesions and keloids are purely benign fibrotic

Table 2

The various diagnostic codes tested between African American (AA) women with keloids and AA control women who had undergone cesarean section (C-section) are listed in the first column, with their descriptions in the second column

ICD-10 diagnostic code	ICD-10 diagnostic code description	Proportion of AA keloid C-section patients with diagnosis	Proportion of AA normal C-section patients with diagnosis	Significant difference with *p* value of .05	Significant difference with Bonferroni correction (*p* value of .001)
D252	Subserosal leiomyoma of uterus	3.32%	1.42%	Yes, .0056	No, .0056
D259	Leiomyoma of uterus, unspecified	6.98%	4.21%	Yes, .018	No, .018
K660	Peritoneal adhesions (postprocedural) (postinfection)	5.32%	1.67%	Yes, <.0001	Yes, <.0001
N736	Female pelvic peritoneal adhesions (postinfective)	9.63%	3.38%	Yes, <.0001	Yes, <.0001
N858	Other specified noninflammatory disorders of uterus	14.62%	7.06%	Yes, <.0001	Yes, <.0001
O34211	Maternal care for low transverse scar from previous cesarean delivery	78.07%	42.41%	Yes, <.0001	Yes, <.0001
O76	Abnormality in fetal heart rate and rhythm complicating labor and delivery	11.30%	30.30%	Yes, <.0001	Yes, <.0001
O9962	Diseases of the digestive system complicating childbirth	8.97%	5.25%	Yes, .0040	No, .0040
O9972	Diseases of the skin and subcutaneous tissue complicating childbirth	63.12%	0.64%	Yes, <.0001	Yes, <.0001
O9989	Other diseases and conditions complicating pregnancy, childbirth, and the puerperium	14.62%	6.88%	Yes, <.0001	Yes, <.0001

ICD-10, International Classification of Diseases, Tenth Revision.

processes. Furthermore, transforming growth factor-beta 1 and 3 (TGF-β1 and TGF-β3) have been suggested to play a key role in the fibrosis that occurs in peritoneal adhesions.[11] Similarly, the TGF-β pathway plays a significant role in the development of keloids.[12] It is possible that the same inflammatory process causing the development of peritoneal adhesions could be causing keloids.

There are several limitations to the study. There is some ambiguity of the ICD-10 diagnostic codes as well as the patient data present within the NIS. The NIS documents inpatient stays, not individual patients. Keloids currently do not have their own ICD-10 diagnostic code. The diagnostic code of keloids, L910, is named as "hypertrophic scar," so there may be patients sampled within the study who were not predisposed to developing keloids, but rather had a hypertrophic scar. Moreover, similar diagnostic codes exist for the same condition, such as L905, which is indicated for scar conditions and fibrosis of the skin but is sometimes used to classify hypertrophic scars when billing as well. Such labels for the ICD-10 codes suggest possible miscoding for certain diagnoses, because many of the diagnostic codes have verbiage that can be considered non-specific (eg, N858 for "other specified noninflammatory disorders of the uterus"). There may be a bias in the patient discharge data included within the NIS. Because keloids are not a life-threatening condition, patients predisposed to developing keloids and presenting for a different medical condition may not be having their keloid diagnosis documented within their chart. The NIS data being restricted to inpatient stays, only provides a snapshot of the individual's health during the stay—making it difficult to examine temporal associations. It is unclear whether keloids were already present prior to C-section or if they developed after C-section. Another limitation is that, given that the NIS data only provides a snapshot of an individual's health, it is not possible to capture diagnoses either for keloids or for underlying health conditions outside of each stay, which can potentially bias the study estimates. Keloids most commonly present on the chest, upper back, shoulders, and earlobes, rather than the abdominal area where C-sections are normally performed. The location of the keloids in those patients in the keloid group is unknown. The time of keloid formation and the area in which it developed can be confounding variables in the determination of whether the diagnostic code refers to a keloid or hypertrophic scar. Our study was also limited to one race, one sex, and a restricted age range (childbearing years). A robust database containing keloid patients, a specific ICD-10 diagnostic code for keloids, and future research can help in the endeavor to better identify health conditions associated with keloids. From a clinical standpoint, further studies can also be done on whether there is a significant difference between certain surgical procedures and the likelihood of developing a keloid scar. From a basic science standpoint, further studies can determine whether the fibrotic signaling pathways associated with keloids mimic those associated with peritoneal adhesion formation.

Conclusions

Keloid patients have an increased association with peritoneal adhesions and other uterine non-inflammation conditions than non-keloid patients. The aforementioned findings suggest that keloids and peritoneal adhesions may have a similar inflammatory pathogenesis. Further research is needed to understand these relationships within the keloid patient.

Conflicts of interest

None.

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Study approval

N/A.

Author contributions

PM participated in research design, performance of the research, data analysis, and writing of the manuscript. DAG participated in research design and writing of the manuscript.

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References

1. Glass DA II. Current understanding of the genetic causes of keloid formation. J Investig Dermatol Symp Proc 2017;18:S50–3. doi:10.1016/j.jisp.2016.10.024.
2. Berman B, Maderal A, Raphael B, et al. Keloids and hypertrophic scars: pathophysiology, classification, and treatment. Dermatol Surg 2017;43(Suppl. 1):S3–18. doi:10.1097/DSS.0000000000000819.
3. Tsai CH, Ogawa R. Keloid research: current status and future directions. Scars Burn Heal 2019;5:2059513119868659. doi:10.1177/2059513119868659.
4. Lu CC, Qin H, Zhang ZH, Zhang CL, Lu YY, Wu CH. The association between keloid and osteoporosis: real-world evidence. BMC Musculoskelet Disord 2021;22:39. doi:10.1186/s12891-020-03898-8.
5. Sun LM, Wang KH, Lee YC. Keloid incidence in Asian people and its comorbidity with other fibrosis-related diseases: a nationwide population-based study. Arch Dermatol Res 2014;306:803–8. doi:10.1007/s00403-014-1491-5.
6. Rutherford A, Glass DA II. A case-control study analyzing the association of keloids with hypertension and obesity. Int J Dermatol 2017;56:e187–9. doi:10.1111/ijd.13618.
7. Snyder AL, Zmuda JM, Thompson PD. Keloid associated with hypertension. Lancet 1996;347:465–6. doi:10.1016/s0140-6736(96)90042-2.
8. Woolery-Lloyd H, Berman B. A controlled cohort study examining the onset of hypertension in black patients with keloids. Eur J Dermatol 2002;12:581–2.
9. Ibrahim NE, Shaharan S, Dheansa B. Adverse effects of pregnancy on keloids and hypertrophic scars. Cureus. 2020;12:e12154. doi:10.7759/cureus.12154.
10. Park TH, Chang CH. Keloid recurrence in pregnancy. Aesthetic Plast Surg 2012;36:1271–2. doi:10.1007/s00266-012-9947-5.
11. Chegini N, Kotseos K, Zhao Y, et al. Differential expression of TGF-beta1 and TGF-beta3 in serosal tissues of human intraperitoneal organs and peritoneal adhesions. Hum Reprod 2001;16:1291–300. doi:10.1093/humrep/16.6.1291.
12. Lei R, Li J, Liu F, et al. HIF-1alpha promotes the keloid development through the activation of TGF-beta/Smad and TLR4/MyD88/NF-kappaB pathways. Cell Cycle 2019;18:3239–50. doi:10.1080/15384101.2019.1670508.