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THE SEARCH FOR THE GENETIC BASIS OF AFRICAN KELOIDS

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SUMMARY

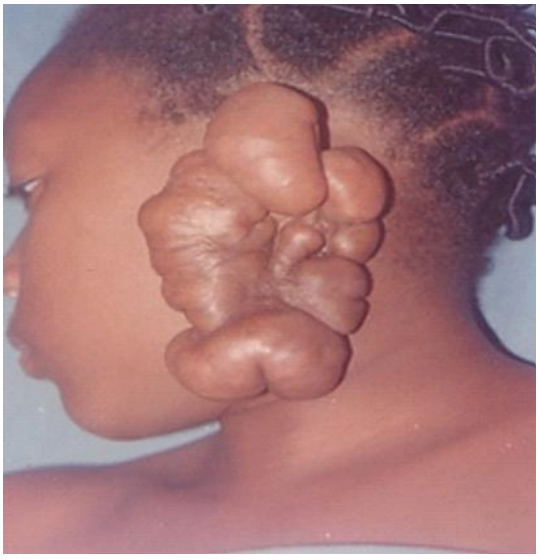
Keloids are benign hyperproliferative growths of dermal fibroblasts characterized by excessive, and often times extensive, deposition of extracellular matrix components especially collagen and fibronectin. First described in the Edward Smith papyrus in Egypt around 1700 BC, the aetiopathogenesis of the disease has become one of the greatest enigmas in modern medicine. Studies have shown that the condition is significantly more common in the coloured races, especially those of African origin. This brief exposition focuses on an exciting and potentially revolutionary study of this condition by the University College Hopital, Ibadan, team of plastic surgeons led by Professor Oluwatosin and collaborators from the University of Connecticut, USA. The team hopes to uncover the genetic basis of African keloids that may lead to the development of more effective diagnostic, therapeutic and prognostic interventions.

Perhaps the most fundamental process of primary interest to surgeons is wound healing. Wound healing involves a well-orchestrated sequence of events. The history of wound care is both ancient and modern. The treatment of acute and chronic wounds can be traced as far back as ancient Egypt and Greece. Galen of Pergamun, a Greek surgeon who served Roman gladiators circa 120–201 AD[1], made many contributions to the field of wound care. In more recent times (1860 onwards) notable names include Ignaz Phillipp Semmelweis, Joseph Lister, Paul Leopold Freidrich (who introduced wound excision), Theodor Billroth, Theodor Kocher and others. These heroes of surgery made major advances to wound care and wound healing.

With the advent of modern scientific techniques, the practice of surgery has become founded on well researched scientific principles. Advances in cell biology have showed that wound healing is a complex event involving cellular, host, psychological, and environmental factors. The process of wound healing can be divided into inflammatory, proliferative, and maturation phases[2]. These phases are associated with very complex cascades of signaling molecules and growth factors. Studies have continued to improve the outcomes of surgically inflicted wounds, however, in a small percentage of individuals the proliferative phase takes an abnormal course resulting in excessive formation of scar tissue. Such non-malignant, abnormal outcomes of cutaneous wound healing, are referred to as hypertrophic scars and keloids.

Keloids are defined as scars within the skin that grow beyond the confines of the original wound. This process may be delayed for months, rarely years after the initial injury before starting but once keloids are formed, they do not regress spontaneously. In contrast, hypertrophic scars are raised lesions that stay within the boundaries of the wound. They usually appear within weeks of the causative injury and tend to regress spontaneously over time[3]. The first description of abnormal scar formation in the form of keloids was recorded in the Smith papyrus regarding surgical techniques in Egypt around 1700 BC. The term keloids meaning 'crab claw' was coined by Jean Louis Albert in 1806 [3]. Since that time the condition has gained the reputation of being one of the greatest enigmas in modern medicine.

The specific aetiopathogenesis of keloids is unknown[4]. However, the process is known to be induced by skin trauma in predisposed individuals. In addition, the condition has been observed in only humans and they



Keloids

occur at any age. Studies have also shown that females may be more at risk of developing keloids, and interestingly, that the incidence of keloids in albinos is extremely low; they have been shown to be consistently more common in colored races especially Africans[5]. The reason for this racial difference is not known.

Rapid advances in molecular techniques have made it possible to identify molecular correlates of clinical characteristics of the disease. Findings indicate a varied inheritance pattern in keloids disease (predominantly autosomal dominant), linkage loci (chromosomes 2q23 and 7p11), several human leukocyte antigen (HLA) alleles (HLA-DRB1*15, HLA-DQA1*0104, DQ-B1*0501 and DQB1*0503), negative candidate gene case–control association studies and at least 25 deregulated genes reported in multiple microarray studies[6]. In summary, involvement of more than one gene is likely to be responsible for susceptibility to keloids disease. As keloid is a benign tumor, the possibility that the genetic basis of the disease is closely related to that of malignancies of similar tissues is of considerable significance.

The global trend has shifted from clinical research to the identification of molecular basis of diseases in the search for effective cures. Keloids disease is being researched by many international groups. Here at the University College Hospital (UCH), the department of plastic surgery has been carrying out cutting edge research on keloids. This unique project started 5 yrs ago and involves UCH, Ladoke Akintola University of Technology (LAUTECH), and international collaborators from the University of Connecticut. This project, an individual collaborative effort, has received funding on a yearly basis that has led to high quality sample, data collection, and analyses.

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The team hopes to identify unique genetic associations in Africans with keloids disease. The research involves the collection of blood, saliva, and tissue samples from patients with keloids, regardless of other co-morbidities. Samples are ethically obtained from cases and controls (patients with normal scar tissue responses). These samples collected in Nigeria are processed and transported abroad where further work is carried out. Using cutting edge molecular techniques, specific DNA regions are amplified and sequenced. Gene associations studies are carried out to identify genetic polymorphisms linked with African keloids. Early results have identified molecular markers (SNPs) with significant linkages with clinical characteristics of keloids in the population studied. Some alleles that seem to increase the risk of keloids development in the mostly yoruba population have also been identified[7]. The research, however, is still ongoing and the results of the main objectives of the project are being determined.

The therapeutic implications of this keloids project are obvious. To date, the treatment of keloids remains a challenge. This is because the exact aetiopathogenesis of the disease has continued to elude researchers[4]. Molecular studies hold the potential of identifying exact biochemical pathways involved in disease and providing specific targets for effective therapies. Surgical excision followed by intra-lesional steroid injection seems to be the treatment option with the lowest recurrence rate, while radiotherapy is reserved for those who fail this treatment[8]. This is the current practice. However, using tissue culture techniques, the keloids group recently reported that oils rich in omega-3 fatty acids may be more effective and affordable than surgical excisions and intralesional steroids as a treatment option. The group was able to demonstrate rapid inhibition of actively proliferating keloids fibroblasts[9]. The role of vitamin D in the inhibition of keloid fibroblasts (KFs) [10] may not be unconnected to effects of omega-3 on KFs reported by the group. This early report is a pointer to the significance of this African study.

No endeavor is free of challenges. While the group has made progress within the set time frame, challenges have not been infrequent. Limited resources for molecular analysis led to heavy reliance on the international collaborators for the molecular aspects of the project. Frequent power outages resulted in the group's search for more robust storage facility and prompt shipping of samples. With a target of enrolling 20 patients/month, there were a few months where the expected number was difficult to attain. However, funding has been regular and the study has been a success, and continues to achieve set targets.

This is the first study to characterize the genetic basis of keloids in sub-saharan African patients. The keloids study group has shown that with good collaboration, focus, hard work, excellent leadership, and team work, cutting edge research is possible in our local setting. Perhaps there is no other region in the world where

Ibadan/University of Connecticut "Genetic Study of Keloid" Group
Photo (L-R): Mrs. Adenike Oyeniyi, Mrs. Elizabeth Josiah, Dr. Ersnt Reichenberger, Mrs. Victoria Odesina, Prof. O.M Oluwatosin, Dr. S.A. Ademola

disease occurs in its most natural form than Africa, this is the major advantage that the Ibadan-Connecticut keloids research group has over other keloids research groups. This advantage is also available for the study of other diseases prevalent in our sub-region. Great adventures in medical history are always similar to the humble efforts of the Ibadan-Connecticut keloid researchers.

BIBLIOGRAPHY

1. Wikipedia: *http://enwikipediaorg/wiki/Keloid.*
2. L.P N: The practice and science of wound healing: History and physiology of wound healing. *Professional nursing today* 2010, 14(3):17 - 21.
3. **Adeloye A,** Adekunle O, Awojobi OA: Davey's Companion to Surgery in Africa: Acecool Medical Publishers; 2009.
4. **Deodhar AK:** Aetiopathogenesis of keloids. *Indian J Med Sci* 1999, 53(12):525-528.
5. **Kelly AP:** Keloids. *Dermatol Clin* 1988, 6(3):413-424.
6. **Marneros AG,** Norris JE, Olsen BR, Reichenberger E: Clinical genetics of familial keloids. *Arch Dermatol* 2001, 137(11):1429-1434.
7. **Hooker S,** Olaitan P, Oluwatosin O, Fadiora S, Ademola S, Odesina V, Leal S, Reichenberger E: Keloid susceptibility loci 1q41, 3q22.3, and 15q21.3 replicated in a Nigerian population. *American Society of Human Genetics/CHG 2011 Meeting* 2011, Abstract/session poster number 737F.
8. **Alster TS,** Tanzi EL: Hypertrophic scars and keloids: etiology and management. *Am J Clin Dermatol* 2003, 4(4):235-243.
9. **Olaitan PB,** Chen P, Norris JE, Fein R, Oluwatosin OM, Reichenberger EJ: Inhibitory activities of Omega-3 fatty acids and traditional African remedies on keloid fibroblasts. *Wounds* 2011, 23(4):97 - 106.
10. **Zhang GY,** Cheng T, Luan Q, Liao T, Nie CL, Zheng X, Xie XG, Gao WY: Vitamin D: a novel therapeutic approach for keloid, an in vitro analysis. *Br J Dermatol* 2011, 164(4):729-737