Prevalence and Causes of Facial Hyperpigmentation in Egypt:
Dermoscopic and Histopathological Study.

Thesis

Submitted for Partial Fulfillment of Master Degree
in ***Dermatology, Andrology and Venereology***

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2019

بسم الله الرحمن الرحيم

يَسْتَبْشِرُونَ بِنِعْمَةٍ
مِّنَ اللَّهِ وَفَضْلٍ
وَأَنَّ اللَّهَ لَا يُضِيعُ
أَجْرَ الْمُؤْمِنِينَ

صدق الله العظيم

سورة آل عمران آية (١٧١)

Acknowledgments

First and foremost, I feel always indebted to ***Allah*** *the Most Beneficent and Merciful.*

I wish to express my deepest thanks, gratitude and appreciation to ***Prof. Marwa Abd-Elrahim Abdallah****, Professor of Dermatology, Andrology and Venereology, Faculty of Medicine, Ain Shams University, for her meticulous supervision, kind guidance, valuable instructions and generous help.*

Special thanks are due to ***Dr. Marwa Yassin Soltan****, Lecturer of Dermatology, Andrology and Venereology, Faculty of Medicine, Ain Shams University, for her sincere efforts, fruitful encouragement.*

I would like to express my hearty thanks to all my family for their support till this work was completed.

Aya Hassan Abd-Allah

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List of Abbreviations

Abb.	Full term
AN	*Acanthosis nigricans*
ANOM	*Acquired nevus of Ota-like macules*
DAG	*Diacylglycerol*
EDN3	*Endothelin 3*
EDP	*Erythema dyschromicum perstans*
EFFC	*Erythromelanosis follicularis faciei et colli*
EO	*Exogenous ochronosis*
EPM	*Erythrosis pigmentosa mediofacialis*
FGFR3	*Fibroblast Growth Factor Receptor 3*
FHP	*Facial hyperpigmentation*
HPV	*Human papilloma virus*
IGF	*Insulin-like growth factor*
IP3	*Inositol trisphosphate*
LPP	*Lichen planus pigmentosus*
LROs	*Lysosome-related organelles*
MD	*Maturational dyschromia*
Nonsig	*Non-significant*
OCP	*Oral contraceptive pills*
PAHs	*Polycyclic Aromatic Hydrocarbons*
PDLs	*Pigmentary demarcation lines*
PIH	*Post-inflammatory hyperpigmentation*
PKC-β	*Protein kinase C-beta*
POH	*Periorbital hyperpigmentation*
POMC	*Pro-opiomelanocortin*
PUVA	*Psoralens and ultraviolet-A light*
ROS	*Reactive oxygen species*
SCF	*Stem cell factor*
Sig	*Significant*
Sk	*Seborrheic keratosis*
TYRP1	*Tyrosinase-related protein 1*
Uv	*Ultra violet*
Uvr	*Ultra violet rays*

1. INTRODUCTION

One of the most common dermatological complaints from patients with skin of color is dyspigmentation, particularly hyperpigmentation. The challenge for clinicians is to establish correct diagnoses along with successful treatments to meet the needs of the increasingly diverse population ***(Vashi et al., 2017).***

Although hyperpigmentation is typically not harmful, it can cause deleterious emotional and psychological impact on the health-related quality of life of the affected individuals ***(Ikino et al., 2015).*** Darker skin phenotypes are characterized by the higher content of melanin, higher eumelanin to pheomelanin ratio, and more effective distribution of melanin for protection against ultraviolet (UV) radiation ***(Vashi et al., 2017).***

Hyperpigmentation is common in middle-aged women and is related to endogenous hormones and exogenous factors such as use of cosmetics, perfumes, and exposure to sun radiation ***(Perez-Bernal et al., 2000).***

Over the last decade, dermoscopy has been shown to be a useful supportive tool for the diagnosis of several inflammatory cutaneous diseases and other pigmentary and neoplastic disorders, and thus reducing the number of cases requiring biopsy ***(Errichetti et al., 2016).*** Depending on the skin

disorder, both dermoscopy and videodermoscopy may be useful for differential diagnosis, prognostic evaluation and monitoring response to treatment. It represents an important and relatively simple aid in the daily clinical practice ***(Micali et al., 2011).*** Dermoscopy might be a powerful tool to provide valuable information for the diagnosis of hyperpigmentations minimizing the need for skin biopsy. Thus, ***Garg and Kaur (2015)*** studied the dermoscopic findings and their correlation with histopathological findings in various lichenoid dermatoses that are usually associated with hyperpigmentation.

We noticed during our clinical practice that there is a high prevalence of hyperpigmentation disorders that affect the face. Owing to the limited studies in the literature about dermoscopy of hyperpigmentation disorders affecting the face, we were interested to study the dermoscopic patterns in different disorders incriminated in facial hyperpigmentations among Egyptians, especially in the view of rarity of the studies investigating causes of facial hyperpigmentation in Egypt and the possible correlation between histopathology and dermoscopic finding in the hyperpigmentary disorders other than nevi and lentigines.

2. Aim of the Work

Our study aims to identify the causes of facial hyperpigmented lesions in patients attending at Ain Shams Hospital Outpatient Clinic by using dermoscope and histopathological examination of query cases.

Chapter 1

PHYSIOLOGY AND REGULATION OF SKIN PIGMENTATION

3.1. Physiology of Skin Pigmentation

In order to understand the underlying pathophysiology of cutaneous disorders of hypopigmentation and hyperpigmentation, as well as the process of normal physiologic pigment production, an appreciation of the structure and function of the melanocyte is required.

3.1.1. Origin and function of the melanocyte

The melanocyte is a neural crest-derived cell. During embryogenesis, precursor cells (melanoblasts) migrate along a dorsolateral pathway via the mesenchyme to reach the epidermis and hair follicles. Additional sites of melanocyte migration include the uveal tract of the eye (choroid, ciliary body and iris), the leptomeninges, and the inner ear (cochlea). It was shown that cutaneous melanocytes can also arise from neural crest-derived Schwann cell precursors that are found along nerves within the skin, having migrated there by a ventral pathway ***(Tsatmali et al., 2002; Schiaffino et al., 2004).***

3.1.2. Process of Melanogenesis

The skin has epidermal units that are responsible for melanin production and distribution in a process called melanogenesis. These units are composed of a melanocyte surrounded by keratinocytes and regulated by a closed paracrine system ***(Schiaffino et al., 2004).*** The "starting material" for the production of melanin, both the brown–black eumelanin and the yellow–red pheomelanin, is the amino acid tyrosine ***(Tsatmali et al., 2002; Schiaffino et al., 2004).***

Melanin is the primary determinant of skin, hair, and eye color. Besides defining an important human phenotypic trait, it has a critical role in photoprotection due to its ability to absorb ultraviolet radiation (UVR)**.** The key regulatory enzyme in the pathway is tyrosinase, which controls the initial biochemical reaction in this pathway, tyrosine hydroxylation. Tyrosinase also catalyzes additional steps in the biosynthesis of melanin as the oxidation of dihydroxyindole. The activity of tyrosinase is enhanced by DOPA and is stabilized by tyrosinase-related protein 1 (TYRP1) ***(Schiaffino et al., 2004; Park et al., 2009).***

Differentiation of melanoblasts into melanin-producing cells depends on mediators produced by cells of the dorsal neural tube, ectoderm and keratinocytes like the family of WNT glycoproteins, endothelin 3 (EDN3) and stem cell factor (SCF). These mediators bind the c-Kit receptor tyrosine kinase in melanocytes and melanoblasts ***(Costin et al., 2007)***. Bone

morphogenic proteins antagonize these events, and their expression is reduced in melanocyte migration ***(Costin et al., 2007)***.

Melanin synthesis occurs in melanosomes and lysosome-related organelles (LROs). The key proteins involved in skin pigmentation, such as the components of the fibrillar matrix that binds to melanin (glycoprotein Pmel17) and melanogenic enzymes are located in melanosomes. In which, the structural matrix is arranged, the tyrosinase enzyme is acquired, and melanin is synthesized along four maturation stages ***(Tsatmali et al., 2002).***

The epidermis melanin unit consists of a melanocyte that interacts through dendrites with 30 to 40 keratinocytes, allowing the transfer of mature melanosomes to the cytoplasm of keratinocytes positioned strategically over nuclei ***(Tsatmali et al., 2002; Lin et al., 2007)***. This transfer is not fully understood and different mechanisms such as exocytosis, fusion of plasma membranes and transfer by membrane vesicles are described ***(Lin et al., 2007).***

There are two types of melanin; eumelanin brown-black or dark insoluble polymer and pheomelanin which is the red-yellow soluble polymer formed by the conjugation of cysteine or glutathione ***(Schiaffino et al., 2010).*** Eumelanin is the major type in individuals with dark skin and hair and is more efficient in photoprotection; however, pheomelanin is predominantly found