Assessment of the effect of vitiligo on choroidal thickness using spectral domain optical coherence tomography

Thesis

Submitted for Partial *Fulfillment of Master Degree in Ophthalmology*

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Cairo, Egypt

2019

Acknowledgment

*I would first and foremost like to thank to each and every **patient** who agreed to be part of this study and were not stigmatized by their illness; without them, I wouldn't be standing here.*

*I would then like to thank my dear **family and friends** who endured my meltdowns, were always there, and supported me to achieve this.*

*I also really appreciate the support of **Prof. Dr. Abd El Rahman Gaber**, whose support to the department's junior members is always tremendous, and whose facilitations made this work possible.*

*I would like to thank **Prof. Dr Thanaa Helmy**, whose guidance and kindness were always uplifting to my spirits.*

*My gratitude is also for **Dr Randa Hesham,** who was there every step of the way, and whose continuous revisions and encouragement pushed me step-by-step through this work.*

*Warm regards to **Dr Samah Ibrahim**, who honored us by collaborating on the project and brought a crucial angle to the study.*

*I would finally like to thank my **Derma resident friends** who were always helpful and collaborating, and my workmates in the **investigation unit** who took the time to capture needed imaging in the best way to serve my work.*

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List of Abbreviations

Abb.	Full term
AMD	*Age-related Macular Degeneration*
BUT	*Break Up Time*
CDVA	*Corrected Distance Visual Acuity*
D	*Diopter*
DAMPs	*Danger Associated Molecular Patterns*
HSPs	*Heat Shock Proteins*
IOP	*Intraocular Pressure*
NSV	*Non-Segmental Vitiligo*
OCT	*Optical Coherence Tomography*
ROS	*Reactive Oxygen Species*
RPE	*Retinal Pigment Epithelium*
SD-OCT	*Spectral Domain Optical Coherence Tomography*
SFCT	*Subfoveal Choroidal Thickness*
VASI	*Vitiligo Area Scoring Index*
VES	*Vitiligo Extent Score*
VETF	*Vitiligo European Task Force*
Σ	*Sigma*

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INTRODUCTION

Vitiligo is a common chronic depigmenting disorder affecting 0.5% of the general population **(Boniface et al., 2018)**. The exact pathogenesis that leads to selective loss of melanocytes remains to be understood but a combination of environmental and immune factors in a genetically predisposed individual is a probable explanation **(Picardo et al. 2015; Rodrigues et al., 2017)**.

In light of recent understanding of the condition, a realization that vitiligo is a systemic disease has been made **(Huggins et al., 2006; Lotti and D'Erme, 2014)**. Reports of melanocytes being affected in other parts of the body have been accumulating in the literature **(Lotti and D'Erme, 2014)**. The eye is rich in melanocytes, mainly in the uveal tissue and in the retinal pigment epithelium (RPE) **(Snell and Lemp, 2013)**, and thus has long been implicated as a target in the disease **(Wagoner et al., 1983)**.

Early reports could not utilize a modality except clinical examination; that included slit lamp biomicroscopy and fundoscopy to examine eyes of vitiligo patients. Even so, multiple pigmentary and non-pigmentary anomalies have been reported in such eyes, most prominently increased incidence of choroidal nevi, iris focal atrophy, hypopigmented spots in the fundus, and increased incidence of dry eye **(Albert et al. 1983; Albert et al., 1979; Wagoner et al., 1983)**.

With the recent advent of imaging and electrophysiological modalities, close dissection of eye anatomy and function in vitiligo patients has been made possible. Those included reports on RPE, retinal nerve fibers, choroid and electrophysiological function **(Fleissig et al., 2018; Ornek et al., 2013; Shoeibi et al., 2014)**.

New Optical Coherence Tomography (OCT) machines have allowed the measurement of choroidal thickness. The choroid is the most vascular part of the eye and gives direct nutrition to the retina, the light-perceiving layer **(Snell and Lemp, 2013)**. Recent reports have emerged linking choroidal thickness, especially the subfoveal choroidal thickness (SFCT), with various ocular **(Cheung et al. 2018; Mohamed et al., 2019)** and systemic **(Schuster et al. 2019; Sızmaz et al., 2013)** abnormalities.

A single recent report has examined choroidal thickness in vitiligo patients and the results demonstrated a significant reduction in thickness in such patients with no relation to disease duration or severity **(Demirkan et al., 2018)**.

Aim of the Work

The objective of this study was to investigate the subfoveal choroidal thickness in vitiligo patients as compared to a control group, and its correlation to disease severity, duration, and/or periorbital skin involvement.

Chapter 1

VITILIGO

The definition of vitiligo

Vitiligo is a prevalent skin-depigmenting disorder with a stigmatizing impact on the patient's life **(Picardo et al., 2015)**. The exact dysregulation underlying the condition and its comorbidities, together with how our arsenal of management options combat the disease are both poorly understood **(Bishnoi and Parsad, 2018)**.

For these reasons, the Vitiligo European Task Force (VETF) was founded in 2003, and it proposed a definition for the disease for clinical research purposes that came as follows: "an acquired chronic pigmentation disorder characterized by white patches, often symmetrical, which usually increase in size with time, corresponding to a substantial loss of functioning epidermal and sometimes hair follicle melanocytes" **(Taïeb and Picardo, 2007)**.

It is to be noted that this definition refers to the most common form of vitiligo, the non-segmental type (non-segmental vitiligo NSV, also known as vitiligo vulgaris). This excludes other skin depigmenting disorders as post-inflammatory, post-traumatic, and post-infectious hypopigmentation, drug-induced depigmentation, tumor-associated leukoderma, and other

monogenic hypomelanoses as tuberous sclerosis **(Taïeb and Picardo, 2007)**.

The prevalence of vitiligo

The prevalence of vitiligo varies by region, with an average rate of 0.5% worldwide **(Boniface et al., 2018)**. Kruger and Schallreuter have done a huge effort reviewing the distribution of the disease in different countries **(Kruger and Schallreuter, 2012)**. The overall prevalence ranged between 0.06% to 2.28% in adults, and 0 to 2.16% in children and adolescents. Figure 1 depicts a world map with reported prevalence rates in different regions.

The aforementioned review remains the largest to date on vitiligo prevalence and is thus the source of the common 0.5-2% range reported in most of the recent studies. However, it is to be taken into consideration that the review was not systematic and did not consider the study design of the selected studies, including sampling techniques, representativeness of the general population, and sources of bias. More rigorous studies are needed to estimate the exact prevalence of the disease.

In Egypt, two reports exist to date in the literature that mention prevalence rates of vitiligo in samples of the Egyptian population **(Abdel-Hafez et al., 2003; Fathy et al., 2004)**. One of them examined skin disorders in a house-to-house manner in

a rural setting in Upper Egypt and found the prevalence of vitiligo to be 1.22% **(Abdel-Hafez et al., 2003)**. The other study examined the prevalence of skin disorders in handicapped children and found vitiligo to be present in 0.4% of deaf-mute children and in 0.9% of mentally-challenged ones **(Fathy et al., 2004)**. Neither study adopted a proper cluster sampling method, and neither could be regarded as representative of the Egyptian population, rather a very rough estimate of comparable prevalence rates in Egypt to those across the rest of the globe.

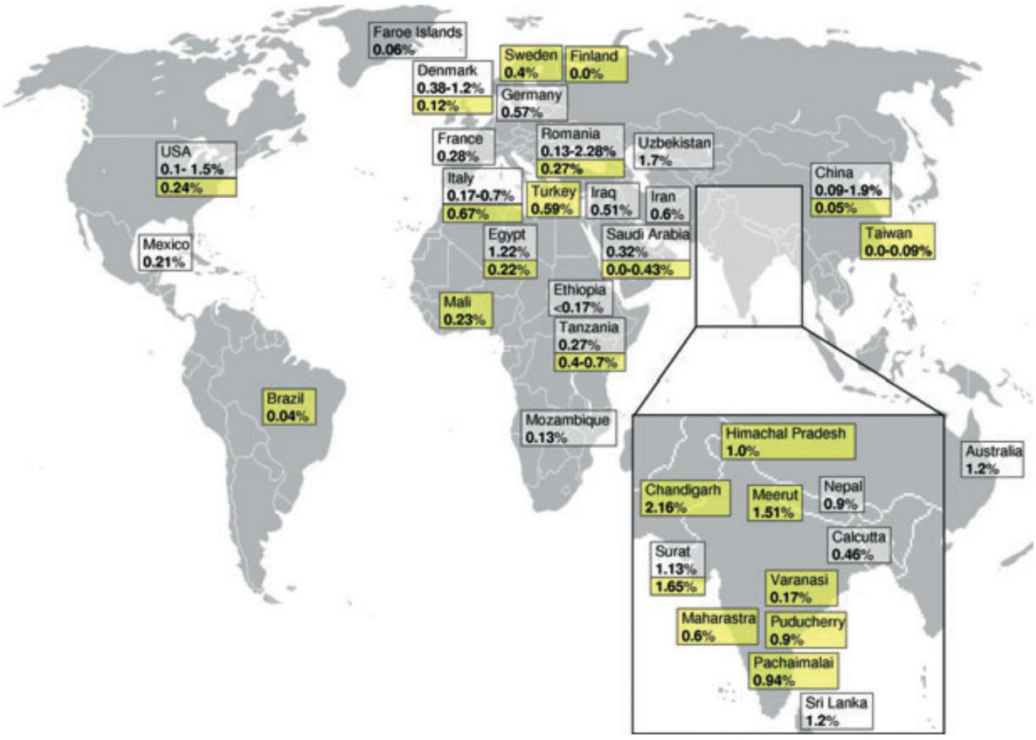

Fig. (1): Worldwide prevalence of vitiligo. Non-colored boxes are for adult rates and yellow boxes are for pediatric/adolescent rates **(Kruger and Schallreuter, 2012)**.

The pathophysiology of Vitiligo

Many theories have long been proposed to explain the pathogenesis of vitiligo. The disease has proven, however, to be multifactorial (or polygenic) with contributions of genetic, inflammatory, and immunomodulatory factors **(Speeckaert and van Geel, 2017)**. The exact strength of contribution of each factor remains to be elucidated **(Picardo et al., 2015)**.

The higher rates of occurrence of vitiligo in relatives have raised suspicion early on towards the genetic component of the disease. Concordance in monozygotic twins was reported to be as high as 23% **(Wang et al., 2019)**. No single responsible gene has been identified, and up till now approximately 50 different loci have been linked to an increased risk of vitiligo, all of which are related to immune regulation, cell function, and apoptosis **(Spritz and Andersen, 2017)**.

High levels of oxidative stress have been observed in the environment of melanocytes in vitiligo animal models. This has implicated reactive oxygen species (ROS) as the initiating offender in vitiligo pathogenesis **(Wang et al., 2019)**. The source of such ROS could be exogenous, for example ultraviolet radiation or chemical exposure, or endogenous, related to mitochondrial defects **(Speeckaert and van Geel, 2017)**. In both events, ROS exhaust the coping mechanisms of melanocytes (that could already be genetically susceptible) and lead to eventual melanocyte loss **(Wang et al., 2019)**.

Dysregulation of immune response patterns has emerged as a key component and linking hub in vitiligo pathogenesis. Aspects of both innate and adaptive immunity have been implicated in the disease. Koebner phenomenon, which describes the higher incidence of vitiligo at friction sites, could be explained by the release of Danger Associated Molecular Patterns (DAMPs) and Heath Shock Proteins (HSPs) together with a myriad of inflammasomes and cytokines **(Boniface et al. 2018; Speeckaert and van Geel, 2017)**. The adaptive immune response probably follows this ensuing inflammation, with the

dendritic cells playing key role in melanocyte-specific antigen presentation to lymphocytes. This leads to the production of both antibodies and cytotoxic T-cells that eventually lead to selective melanocyte loss **(Picardo et al. 2015; Speeckaert and van Geel, 2017)**. Figure 2 shows a detailed schematic representation of immune dysregulation in vitiligo.