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Skin hyperpigmentation disorders: associations and impact on health-related quality of life

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BOSTON UNIVERSITY
SCHOOL OF MEDICINE

Dissertation

**SKIN HYPERPIGMENTATION DISORDERS:
ASSOCIATIONS AND IMPACT ON HEALTH-RELATED QUALITY OF LIFE**

by

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DEDICATION

I would like to dedicate this work to my beloved parents Jessica and Carlos, my two daughters Maria Julia and Maya, and my husband for their never ending support. Also, I would like to dedicate this to my mentor, professors, and patients who taught me so much.

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Boston University School of Medicine, 2016

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ABSTRACT

Hyperpigmentation is a common dermatological complaint that can have profound effect on appearance and quality of life. Disorders of hyperpigmentation comprise a large group of skin conditions characterized by an increase of melanin production, increase in density of active melanocytes, abnormal melanin distribution, and/or deposition of exogenous pigments.

This cross-sectional study was conducted to evaluate the impact hyperpigmentation disorders on health-related quality of life and to better understand patient knowledge, approaches, and experiences. The study was conducted on 298 consenting adult patients with a skin related disorder of hyperpigmentation who sought dermatological care at Boston Medical Center (BMC) or East Boston Neighborhood Health Center (EBNHC) from February of 2015 to March of 2016. Patients were anonymously surveyed in order to collect an assortment of information including demographic characteristics, skin condition, health practices, knowledge base, and health-related quality of life (HRQoL) measured with the Dermatology Life Quality Index (DLQI) (Finlay and Khan 1994) and SDIEQ, a five-item , non-validated, brief health-related quality of life questionnaire (A. Taylor et al. 2008). Disease severity was

assessed by *Melasma Area Severity Index (MASI)*, *Post Acne Hyperpigmentation Index (PAHPI)*, and body surface area when appropriate.

The mean overall DLQI was 6.56 (SD \pm 5.35). In sub-analysis, the mean DLQI in those diagnosed with post-inflammatory hyperpigmentation was 7.89 (SD \pm 0.61), melasma 6.75 (SD \pm 0.45), and other hyperpigmentation disorders 4.5 (SD \pm 0.55). The disease type and duration were both factors associated with a change in DLQI scores. The factors associated with a higher likelihood of patients' knowledge of their diagnosis included a higher level of formal education, younger age, longer duration of having the condition, and current use of sunscreen, which were found to have 2.4, 2, 3.7, and 2.4 significantly higher odds of knowing their diagnosis, respectively.

This study found that the overall impact of hyperpigmentation on health-related quality of life (HRQoL) was small to moderate; however, about 22% reported a very large effect on quality of life. Patients with post-inflammatory hyperpigmentation (PIH) and melasma have significantly lower quality of life when compared with other hyperpigmentation disorders. MASI had a significantly weak correlation with DLQI and SDIEQ, demonstrating that disease severity does not predict patient perception and impact on quality of life.

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LIST OF ABBREVIATIONS

AN.....	Acanthosis Nigricans
BU.....	Boston University
cAMP.....	Cyclic Adenosine Monophosphate
CO ₂	Carbon Dioxide
CREB.....	cAMP Responsive-Element Binding Protein
DHI.....	Dihydroxyindole
DHICA.....	Dihydroxyindole-2-Carboxylic Acid
DLQI.....	Dermatology Life Quality Index
DOPA.....	Dihydroxyphenylalamine
DPN.....	Dermatosis Papulosa Nigra
EDP.....	Erythema Dyschromicum Perstans
EO.....	Exogenous Ochronosis
ER.....	Estrogen Receptors
FGFR.....	Fibroblast Growth Factor Receptor Gene
HRQoL.....	Health-Related Quality of Life
HGOA.....	Homogentisic Acid Oxidase
ICD-9.....	International Classification of Diseases
ICHOR.....	Idiopathic Cutaneous Hyperchromia of the Orbital Region
IGH.....	Idiopathic Guttate Hypomelanosis
IUD.....	Intrauterine Device
IPL.....	Intense Pulsed Light

LPP.....	Lichen Planus Pigmentosus
LROs.....	Lysosomal-Related Organelles
MASI.....	Melasma Area and Severity Index
MELASQoL.....	Melasma Quality of Life
MITF.....	Microphthalmia-Associated Transcription Factor
MCR1.....	Melanocortin-1 receptor
MSH.....	Melanocyte Stimulating Hormone
QS Nd:YAG.....	Q-switched Neodymium-Doped Yttrium Aluminum Garnet
OTC.....	Over-The-Counter
PAHPI.....	Postacne Hyperpigmentation Index
PCOS.....	Polycystic Ovary Syndrome
PDA.....	Pigmentary Disorders Academy
PDZ.....	PDZ Domain Kidney 1
PIH.....	Post-Inflammatory Hyperpigmentation
PKA.....	Protein Kinase A
POH.....	Periorbital Hyperpigmentation
QoL.....	Quality of Life
RCM.....	Reflectance Confocal Microscopy
SD.....	Standard Deviation
SK.....	Seborrheic Keratosis
SL.....	Solar Lentigo
SDIEQ.....	Skin Discoloration Impact Evaluation Questionnaire

SPF	Sun Protection Factor
TYR.....	Tyrosinase Enzyme
UV.....	Ultraviolet
UVR.....	Ultraviolet Radiation
VL.....	Visible Light

CHAPTER ONE: INTRODUCTION

Skin hyperpigmentation is a common dermatological complaint that may affect patients' appearance and quality of life. It comprises a large group of skin conditions characterized by an increase in melanin production, an increase in density of active melanocytes, abnormal melanin distribution, and/or deposition of exogenous pigments. This common dermatological condition may occur in any Fitzpatrick skin type; however, darker skin phenotypes are typically more frequently affected due to differences in structure and function, including melanin content and melanosomal dispersion patterns. There are several skin disorders that may present clinically as hyperpigmentation, including melasma, lentigines, post-inflammatory hyperpigmentation, and several others.

Those with darker skin phenotypes, or skin of color, constitute a wide range of racial and ethnic groups traditionally referring to persons of African, Asian, Native American, Middle Eastern, and Hispanic backgrounds. Disorders of hyperpigmentation are expected to become far more common as by 2050, nearly one-half of the U.S. population will be considered nonwhite or skin of color. To date, the true prevalence of hyperpigmentation in the US is unknown due to data being grouped under the ICD-9 code of dyschromia, which includes disorders of both hyperpigmentation and hypopigmentation (S. J. Kang et al. 2014). The literature show that the prevalence (rate) of hyperpigmentation disorders in Hispanic and Latino population is around 6 to 7.5% (M. R. Sanchez 2003). Although this rate is lower than the prevalence of

hyperpigmentation among African Americans 19.9% (Alexis, Sergay, and Taylor 2007) and Afro-Caribbean 22.8% (Dunwell and Rose 2003) it is higher when compared with Caucasian population. In addition, despite numerous studies evaluating quality of life in melasma (Pawaskar et al. 2007) (Ikino et al. 2015) (Pichardo et al. 2009), little is known about health-related quality of life of other common hyperpigmentation disorders (A. Taylor et al. 2008).

Although few dermatological disorders affect life expectancy, many occur as chronic conditions that impair patients' life in innumerable other ways. Most disorders of hyperpigmentation do not affect physical health, yet they have an impact on other aspects of individuals' health including emotional, social, and family well-being. Measuring how dermatological conditions affect lives and quantifying disease burden may be considered a "vital sign", and this information should be used to improve patients' lives and can also be used for health policy (Chen 2012). Moreover, measurement of clinical disease severity, often used by clinicians as for treatment guidelines, may not correlate well with patients' perception and feelings towards their disease condition.

This thesis investigates the impact of skin hyperpigmentation disorders on patients' quality of life along with knowledge, attitudes, and practices towards their skin disorder(s). This thesis also aims to find out which factors are associated with a higher impact on quality of life and knowledge of a diagnosis. A thorough understanding of patients' skin practices and perceptions regarding their skin hyperpigmentation is of great

importance when caring for those afflicted.

Chapter 2 will include a review of the literature and will discuss the most common causes of cutaneous hyperpigmentation disorders. Chapter 3 comprises study design and methodology. Chapter 4 describes the study results, Chapter 5 aims to discuss our findings, and Chapter 6 concludes the thesis and summarizes this contribution.

CHAPTER TWO

This chapter will review basic aspects of the skin, including structure and function, physiology, and signaling pathways involved in hyperpigmentation disorders. It will also give an overview of the most common diagnoses found in our study population.

2.1 Skin Color

Skin tone varies among individuals of different races and ethnicities. The observed skin color results from a complex combination of biochemical and physical factors including the amount, type and distribution of melanin, its location within the epidermis or dermis, vascular density, and presence of exogenous chromophores.

Chromophores are classified as melanotic and nonmelanotic. Melanocytic chromophores are composed of melanin (eumelanin and pheomelanin), melanocytes, and melanin in melanophages. Nonmelanotic (chromatics) components are collagen, carotene or lycopene, chemicals, drugs, and oxyhemoglobin among others (Nordlund et al. 2006).

Melanin is by far the most important determinant of skin color. The variations in skin color are due to different concentrations of eumelanin (brownish-black) and pheomelanin (reddish-yellow). The melanin in the skin is either a constitutive pigmentation determined genetically or facultative pigmentation, which is temporary skin pigmentation in response to UVR exposure (Jablonski 2004).

Other factors such as hemoglobin and oxyhemoglobin are nonmelanotic (chromatics) that by the absorption of a specific wavelength allow for the reflection of red giving the pink/red skin coloration that is easily observed in Caucasian skin. Lycopene and beta-carotene are implicated in the yellow hues of skin color. Other skin hues are made from dermal collagen which makes the skin appear whitish and also exogenous factors like dermal drug deposition which may cause a blue-gray discoloration (Rawlings 2006). The components of the pigmentary system and the multiple and complex factors that regulates melanin pigmentation is briefly discussed below.

2.1.2 Melanocytes

Melanocytes are pigment-producing cells located in the stratum basale of the epidermis among other locations (hair matrix, outer root sheath of hair follicles, uveal tract, leptomeninges, inner ears). They are derived from the neural crest by migration via dorsolateral path or derived from Schwann cell precursors by migration via ventral path (Adameyko et al. 2009) during the 18th week of fetal development. Melanocytes are responsible for melanin synthesis. Once synthesized, melanin is stored within the melanosome and moved along the dendrites to reach the neighboring keratinocytes. (Park, Yaar, 2012).

The number of melanocytes may vary from one body part to another; however, they do not differ in number from one individual to another. The difference in skin color

are due to number, size, and aggregation of the melanosomes contained in the melanocytes and keratinocytes rather than the number of melanocytes (S. C. Taylor 2002).

2.1.2 Melanosomes

Melanosomes are specific melanin-containing organelles that belong to the family of lysosomal-related organelles (LROs). They are classified according to the type of melanin they produce. Their maturation follows four distinct stages. Stage I melanosomes are derived from the endoplasmatic reticulum and contain an amorphous matrix and no melanin. Stage II consists of tyrosinase enzyme and other protein assembly, without melanin synthesis. Stage III involves deposition of melanin on internal fibrils. The final stage IV melanosomes are fully melanized and ready to be transferred to neighboring cells via melanocyte dendrites (Yamaguchi and Hearing 2009).

The size, aggregation, and distribution of melanosomes are influenced by racial/ethnic background and sun exposure (Szabo, 1969). Dark-skinned individuals and areas of sun exposure have predominantly larger, nonaggregated melanosomes that are densely distributed along the basal layer. While lighter skin types exhibit smaller, aggregated, and less dense melanosomes located more prominently in the stratum corneum (Taylor, 2002).

2.2 Biology of Melanin and Melanogenesis

Melanin is a polymer attached to a protein that protects the skin against UV damage. There are two types of human melanin: eumelanin and pheomelanin. The synthesis of both is derived from the amino acid tyrosine, which is converted to 3,4 – dihydroxyphenylalanine (DOPA) by tyrosinase enzyme (TYR). This is an essential step for melanin formation. DOPA is again converted to DOPAquinone by the same tyrosinase enzyme. DOPAquinone can be converted into 5,6-dihydroxyindole (DHI) forming a dark brown-black virtually insoluble polymer or 5,6-dihydroxyindole-2-carboxylic acid (DHICA) forming the light-brown alkali soluble eumelanin. When DOPAquinone is associated with glutathione or cysteine, it forms cysteinylDOPA, which becomes the yellow/red, soluble, low-molecular-weight, and alkali soluble pheomelanin (Rawlings 2006).

The concentration of the two types of melanin varies according to skin type. Dark-skinned individuals have higher concentration of eumelanin, whereas red-haired individuals have a pheomelanin rich phenotype (Jablonski 2004).

2.3 Regulation of Melanocytes

Multiple signaling pathways and transcription factors regulate melanin synthesis, transport, and transfer. These include melanocyte stimulating hormone (MSH)/cyclic adenosine monophosphate (cAMP), KIT, and Wnt signaling pathways. These signaling

pathways control the expression of transcription factors such as melanocortin-1 receptor (MCR1), microphthalmia-associated transcription factor (MITF), PAX3, SOX9/10 among several others that are involved in both congenital and acquired disorders of hyperpigmentation (J. Y. Lin and Fisher 2007) (Bertolotto et al. 1998).

The regulation of melanin production can be divided into proteins involved in the structure of melanosomes (Pmel17, Mart-1, and GPNMB), proteins that regulate synthesis of melanin (TYR, TRYP1, DCT, BLOC-1, OA1, P, and SLC45A2), and proteins involved in intracellular trafficking and transport of melanosomes (microtubules, F-actin, kinesin, dynein, RAB27a, melanophilin, myosin and others) (Yamaguchi and Hearing 2014). Disorders of hyperpigmentation may be a result of a dysregulation of these signaling pathways along with gene mutations and endogenous or exogenous pigment deposition.

2.4 Disorders of hyperpigmentation

Hyperpigmentation and/or hyperchromia encompasses a wide range of dermatological disorders that are very common worldwide. As the United States population becomes more racially and ethnically diverse, this cosmetic and sometimes psychologically devastating group of conditions will pose greater challenges for physicians.

There is limited literature assessing the prevalence of hyperpigmentation in the United States population. In addition, the true prevalence of hyperpigmentation is obscured by most of the data being grouped under the International Classification of Diseases (ICD-9) code of dyschromia, which includes both hyperpigmentation/hyperchromic and hypopigmentation/hypochromic disorders.

Disorders of hyperpigmentation are characterized by an increase in either melanin and/or melanocytes. Hyperpigmentation can be localized, generalized, or have a variable distribution pattern. Furthermore, it can be classified according to histological evaluation of pigment location: epidermal, dermal, or mixed. In 2006, Nordland et al. proposed a scheme to properly classify disorders of pigmentation (Table 1, 2 and 3) (Nordlund et al. 2006).

In order to have a uniform terminology when referring to pigmentary disorders, the consensus lexicon was developed by the Pigmentary Disorders Academy (PDA). The classification is based on two distinct chromophores (melanotic or nonmelanotic), location within skin layers (epidermal, dermal, or mixed), and genetic or non-genetic (Tables 1, 2 and 3).

Melanotic (Hyperpigmentation)		
Hypermelanosis	Hypermelanocytosis	
Congenital	Acquired	
Localized	Variable	Generalized
Epi Der Mix	Epi Der Mix	Epi Der Mix

Table 1. Classification of disorder of hyperpigmentation. Epi, epidermal, Der, dermal and Mix, mixed (Adapted from Nordlund et al., 2006).

Nonmelanotic factors that affect the skin color are known as chromatics. They include chemicals, drugs, deposits, carotene or lycopene, and an increase or reduction of normal skin components such as collagen and hemoglobin. Skin disorders due to nonmelanotic chromophores are called dyschromias, with abnormal darkening due to these factors known as hyperchromias (Table 2).

Nonmelanotic (Hyperchromia)		
Congenital	Acquired	
Localized	Variable	Generalized
Epi Der Mix	Epi Der Mix	Epi Der Mix

Table 2. Classification of nonmelanocytic types of hyperchromia. Epi, epidermal, Der, dermal and Mix, mixed (Adapted from Nordlund et al., 2006).

The combination of increased melanotic and nonmelanotic factors may occur, the co-existence of this pigimentary change is called mixed hyperpigmentation and hyperchromia respectively (Table 3).

Mixed Hyperpigmentation and Hyperchromia		
Congenital	Acquired	
Localized	Variable	Generalized
Epi Der Mix	Epi Der Mix	Epi Der Mix

Table 3. Classification of mixed hypermelanosis and hyperchromias. Epi, epidermal, Der, dermal and Mix, mixed (Adapted from Nordlund et al., 2006).

2.4.1 Melasma

Melasma is a common acquired hyperpigmentation disorder that involves primarily sun-exposed areas on the face and less often on the neck and arms in those with Fitzpatrick skin phototypes III to VI (J P Ortonne et al. 2009). It is more common in women than men. The use of hormonal contraception, pregnancy, and sun exposure are common associated factors (J P Ortonne et al. 2009).

The overall prevalence of melasma is unknown. Reported prevalence rates vary among studied populations, documented rates include 40% of Southeast Asians and 10% of Latin American females. The highest prevalence is observed during pregnancy,

occurring in 10–70% of women (Doris Hexsel et al. 2013), and lowest prevalence among men, occurring in 14.5–20% (Pichardo et al. 2009).

A combination of genetic background, sun exposure, hormones, and Fitzpatrick skin phototype are thought to be the main contributing etiopathogenic factors in the development of melasma (Passeron 2013).

Several epidemiological studies suggest a positive family history, with rates ranging from 10.3% (Goh and Dlova 1999) to 56.3% (Tamega et al. 2013). A study by Kang et al., using gene expression profiling, identified 279 genes that were found to have different expressions in melasma lesional and perilesional skin. Among those, 4 genes (TYR, TYRP1, DCT, and SILV) involved in melanin biosynthesis were up regulated in lesional skin. In addition, Wnt inhibitory factor-1, a Wnt antagonist, was decreased in lesional skin resulting in upregulation of the Wnt signaling pathway and subsequent melanogenesis (Hee Young Kang et al. 2011).

Sun exposure is known to directly induce melanogenesis, melanocyte proliferation, migration, and indirectly stimulate cytokines, including interleukin-1, endothelin-1, alpha-melanocyte-stimulating hormone, and adrenocorticotrophic hormone by the UV activated keratinocytes (V. M. Sheth and Pandya 2011a). It appears that melanocytes are not the only culprits cells on the pathogenesis of melasma; new evidence suggests that a rather complex cellular interaction involving keratinocytes, dermal

fibroblasts, mast cells, skin vasculature, and hormones contribute to the effect of UVR on melasma (Lee 2014).

Kang et al. reported that UVR induces dermal inflammation by activation of fibroblasts, upregulation of stem cell factors and c-kit, resulting in melanocyte proliferation and stimulation of melanogenesis (H. Y. Kang et al. 2006). Moreover, visible light (VL, 400–780nm) may also play a role in the pathogenesis of melasma, especially in Fitzpatrick skin types IV–VI. (Castanedo-Cazares et al. 2014) (Passeron 2013).

Although the role of hormones in melasma is unclear, epidemiological studies suggest an association with oral contraceptive, pregnancy, and onset during reproductive years indicating an influence of sex hormones (Lee 2014). Estrogen receptors (ER) are commonly expressed in the skin. Immunohistochemical studies revealed increased expression of ERs in the dermis of melasma lesional skin (Lieberman R 2008) and progesterone receptors in the epidermis of lesional skin in contrast with normal skin (Jang et al. 2010). When estrogen binds to estrogen receptors (ERs) present in melanocytes and keratinocytes, cAMP- protein kinase A (PKA) is activated and upregulation of pathways [(cAMP responsive-element binding protein (CREB), Microphthalmia associated transcription factor (MTIF), tyrosinase (TYR)] involved in melanin synthesis are activated. Moreover, upregulation of PDZ domain kidney 1 (PDZK-1) protein, a member of the sodium-hydrogen exchanger regulatory factor family,

further facilitates estrogen action and increases melanogenesis and melanosome transfer in melasma lesional skin (Lee 2015).

Clinically, melasma is characterized by light to dark brown facial patches, distributed in three distinct clinical patterns: centrofacial, malar, and mandibular (N. P. Sanchez et al. 1981). Another classification, based on pigment location within skin layers assessed with a wood's lamp (320–400nm) examination, may be used to predict treatment outcome. Melasma can be classified into four types. Epidermal, when color is enhanced under wood's lamp examination, dermal when lesions becomes less apparent, mixed if both features are present, and inapparent or indeterminate, when no difference in color is appreciated. Innapparent or indeterminate is more commonly seen in darker skin types (Gilchrest et al. 1977).

Recent studies, however, suggest that the pigment deposition does not always correlate well with the wood's lamp evaluation. A study conducted by Grimes et al. examining biopsies of lesional skin revealed presence of pigment in both the epidermis and dermis of patients previously characterized as having an epidermal only pattern by wood's light examination (Grimes, Yamada, and Bhawan 2005).

On histopathology, melasma lesional skin reveals increased deposition of epidermal melanin without a quantitative increase in the number of melanocytes (Grimes, Yamada, and Bhawan 2005), solar elastosis, and mast cells. Melanophages may be seen

in the papillary dermis (W. H. Kang et al. 2002). There are some studies that report an increased number of melanocytes (N. P. Sanchez et al. 1981), increased number of inflammatory cells (Noh et al. 2014), and vascularity in melasma lesional skin (Kim et al. 2007).

Despite being an asymptomatic disorder, melasma causes emotional and psychosocial distress in those afflicted. The impact of melasma on patient quality of life (QoL) has been assessed in a few studies using the Melasma Quality of Life scale (MELASQoL), a validated disease specific 10-item instrument. The majority of studies have found that the most adversely affected domains were quality of life, recreation/leisure, and emotional well-being (Balkrishnan et al. 2003).

A study conducted on 51 Brazilian females to assess the quality of life (Qol) using the Melasma Quality of Life Scale (MELASQOL) for Brazilian Portuguese persons revealed marked emotional impact, 94.11% of patients reporting feeling bothered, 64.71% frustrated/embarrassed, and 52.94% depressed due to their skin condition (Ikino, Nunes, Silva, Fröde, & Sens, 2015).

Dominguez et al., using the Spanish-language version of MELASQOL, demonstrated that the most affected areas were social life and well-being, with higher scores observed in patients with less years of formal education. Interestingly, the

MELASQOL score only has a moderate correlation with Melasma Area Severity Index (MASI), a measure of clinical disease severity (Dominguez et al. 2006).

Treatment of melasma is challenging and often times disappointing to both patient and physician. Patient education regarding sun protective measures is extremely important for achieving better results. Triple combination products containing hydroquinone, retinoid, and a fluorinated steroid continue to be first line treatment. Other first line treatment includes hydroquinone in different concentrations, azelaic acid, and other topicals that work within the melanin synthesis pathway such as ascorbic acid, mequinol, and kojic acid. In addition, second line therapies include chemical peels and oral treatments and third line therapy include laser and light devices (Sheth & Pandya, 2011a).

New treatment modalities have shown variable but promising results for the treatment of melasma. Tranexamic acid, a plasmin inhibitor and lysine analog, available in oral, topical, and intradermal injections seems to be an effective modality. Shin et al. sought to evaluate efficacy of low-fluence QS Nd:YAG with oral tranexamic acid in 48 Korean woman and found that subjects treated with tranexamic acid had greater MASI score reduction (Shin et al. 2013). In another study, oral tranexamic acid was used for 6 months with gradual improvement of melasma lesions evaluated by physician assessment, patient satisfaction, and reduction of MASI score (Wu et al. 2010).

Novel therapies are under investigation for treatment of melasma. Metformin, an antidiabetic drug, has been shown to reduce melanin content in vitro and in vivo by decreasing cAMP levels; cAMP has an essential role in melanin synthesis (Lehraiki et al. 2014). Another investigational therapy is omeprazole, a gastric proton pump inhibitor, which applied topically to UV-irradiated human skin demonstrated reduction in pigment levels after 3 weeks when compared to untreated controls. The hypothesis is that omeprazole may block melanogenesis by interfering with an alternative ATP7A, a copper transport P-type ATPase, needed for copper acquisition by tyrosinase; therefore, reducing melanogenesis and increasing tyrosinase degradation (Matsui et al. 2015).

2.4.2 Post-inflammatory Hyperpigmentation

Post-inflammatory hyperpigmentation (PIH) is an acquired hypermelanosis that is considered to be a normal biologic response to cutaneous injury or inflammation. Multiple skin disorders may result in PIH including acne vulgaris, allergic contact dermatitis, lichen planus, atopic dermatitis, psoriasis, and trauma among many others including cosmetic interventions (Halder, Nandedkar, & Neal, 2003).

Although PIH affects all skin types, it is more common and/or noticeable in darker skinned individuals. There is no gender predilection. In a prospective study on prevalence of acne related PIH, it occurred in 60% of subjects (Abad-Casintahan et al. 2016). PIH was also the second most common reason for dermatology visits in African

Americans individuals (Alexis, Sergay, and Taylor 2007), and dyschromia was the 11th reason for dermatological visits among all skin types in a list of top 20 dermatological conditions (Wilmer et al. 2014).

The pathogenesis of PIH is thought to be secondary to stimulation of epidermal melanocytes by inflammatory mediators and cytokines from the inflammation site, which leads to an increase in synthesis and transfer of melanin to the neighboring keratinocytes, resulting in epidermal melanosis. Additionally, inflammation may cause disruption of the basal layer and release of melanin into the underlying dermis. The melanin is phagocytized by macrophages, now melanophages, resulting in dermal melanosis, also known as pigmentary incontinence (Tomita, Maeda, and Tagami 1989).

PIH manifests as hyperpigmented macules and patches varying in sizes, distributed on site of skin injury or trauma. The color varies from tan to dark brown depending on the location of pigment. A blue-gray appearance is observed when pigment is located within the dermis (Davis and Callender 2010). PIH may take several months to years to fade and this likely depends on a variety of factors including skin type, intensity of inflammation, and sun exposure habits (Vashi & Kundu, 2013).

Post-acne hyperpigmentation index (PAHPI) is a recent validated instrument developed by Savory et al. to help assess clinical severity and treatment efficacy in patients with PIH from acne (Savory et al. 2014).

A single study evaluating response to treatment efficacy and safety of salicylic acid peels and the impact of post-inflammatory hyperpigmentation on patients' quality of life reported a DLQI of 8.4 in a small sample of patients (Joshi et al. 2009).

Prevention and treatment of underlying skin disorders is imperative in all patients presenting with PIH, especially in those with darker skin types. After treating the cause of PIH, the first line therapy are topical lightening agents such as those used for melasma, if no improvement after 8–12 weeks, second line therapies include chemical peels and laser/ light therapy (Davis and Callender 2010).

2.4.3 Solar Lentigines

Solar lentigines (SL) are benign hyperpigmented macules distributed over areas of chronic sun-exposure such as the face, dorsal hands, and forearms. They typically occur in later years of life but can appear at a younger age after acute UV exposure. (Bologna, Jorizzo, and Schaffer 2012). Although more common in Caucasians and Asians, it is also seen in Fitzpatrick skin types III and IV (Monestier et al. 2006). The incidence is high among caucasians, affecting 90% of individuals over 50 years of age (J P Ortonne 1990).

Clinically, solar lentigines are characterized by well-defined, dark-brown or tan macules with irregular borders, ranging in size from a few mm to over 1 cm. They are considered a sign of photoaging and usually do not fade with time (Bologna, Jorizzo, and Schaffer 2012).

It is without a doubt that UV radiation plays a role in the pathogenesis of SL. The exact mechanism by which UV induces pigmentation in SL is still under debate.

Watanabe proposed that chronic UV exposure leads to degeneration of basal cell keratinocytes. The damaged keratinocytes are then segregated to the upper dermis and later phagocytosed by poorly stimulated macrophages that lack proper migration and digestive abilities, resulting in the pigmentary changes noticed clinically. Moreover, upregulation of genes involved in the inflammatory response, melanin production, and fatty-acid metabolism suggest the mutagenic effect of repeated UV exposure in the pathogenesis of solar lentigines (Aoki et al. 2007).

On histopathologic examination, findings include hyperpigmentation of basal layer with elongation of rete ridges and a mild increase in melanocytes on a background of solar elastosis. (Byrom et al. 2016).

There are very few studies available in the literature evaluating the impact of lentigines and other facial hyperpigmentations besides melasma. One study evaluated the prevalence of pigmentary disorders and its impact on quality of life in 140 caucasian patients. Among those studied, 74.3% had the diagnosis of lentigo, of which 47.3% stated they they were self-conscious about their skin appearance (A. Taylor et al. 2008).

Several effective treatment modalities are available including tretinoin, cryotherapy, chemical peels, and/or laser therapy. The best therapeutic response is

typically seen with laser therapy (Ortonne et al. 2006). Although solar lentigines are benign, they are a sign of photodamage, which may indicate an increased risk for the development of skin cancers. Therefore, patient education about regular use of sunscreen and sunprotective measures are an important part of treatment.

2.4.4 Seborrheic Keratosis and Dermatosi Papulosa Nigra

Seborrheic Keratosis (SK) is a common benign skin tumor that affects both men and women. Prevalence increases with age. It presents as single or multiple well demarcated, skin-colored to hyperpigmented, “stuck-on” papules that are typically seen on the back, chest, and extremities. Despite commonly being located on sun covered areas, sun exposure may be associated with earlier onset and higher frequency of seborrheic keratosis (Yeatman, Kilkenny, and Marks 1997). Although the etiology is unknown, it appears to have a familial tendency with an autosomal dominant pattern of inheritance.

Dermatosi Papulosa Nigra (DPN) is a variant of SK that presents as small hyperpigmented smooth papules commonly observed in darker skin types, especially African Americans and Afro-Caribbeans. It is more common in women and rarely observed in children. DPNs have an earlier onset and may even appear during adolescence. Lesions typically increase with age. SK and DPN are mostly asymptomatic; however, they may become pruritic and irritated. Treatment is not required unless for

cosmetic reasons (Bologna, Jorizzo, and Schaffer 2012).

2.4.5 Lichen Planus Pigmentosus

Lichen planus pigmentosus (LPP) is a chronic acquired disorder of hyperpigmentation classified as a variant of lichen planus that usually occurs in young to middle aged darker skinned individuals, especially those of Indian, Latin American, and Middle Eastern descent (Al-Mutairi and El-Khalawany 2010).

LPP is characterized clinically by oval to round gray-brown macules that may coalesce into patches on sun-exposed areas, commonly the face and neck and/or flexures (lichen planus pigmentosus inversus). Lesions are usually symmetric but can present unilaterally. They are often asymptomatic but can occasionally be pruritic. In contrast with erythema dyschromicum perstans (EDP), there is no previous history of an erythematous border. Patients may present with classic lichen planus lesions in other areas, and mucosal involvement has been reported (Al-Mutairi and El-Khalawany 2010).

Although the pathogenesis remains unknown, application of topical photosensitizers, such as mustard and amla oils along with sun exposure are possible culprits (Kanwar et al. 2003). On histology, main features of LPP include epidermal atrophy, vacuolar degeneration of basal layers, melanin incontinence, and presence of dermal melanophages.

There were no studies evaluating health-related quality of life (HRQoL) in patients with LPP. The disease course is unpredictable with periods of remission and exacerbations. Treatment options include topical steroids, calcineurin inhibitors, skin lightening agents, and chemical peels. Treatment with low-fluence 1064 nm Q-switched neodymium-doped yttrium aluminum garnet laser in combination with tacrolimus (calcineurin inhibitor) has been reported (Vashi and Kundu 2013).

2.4.6 Maturation Hyperpigmentation

Maturation hyperpigmentation is a descriptive term that refers to darkening of sun-exposed and mature skin, occurring in those with darker skin tones, especially skin phototypes V and VI. This recently described, yet likely common acquired hyperpigmentation, was first reported by Dr. Melvin Alexander as an unusual pattern of facial hyperpigmentation, involving malar and zygomatic facial areas, which often had ill-defined borders with fading into the patients' natural skin color (N. Vashi, Kundu, and Larocca 2014).

Maturation hyperpigmentation is characterized clinically by darkening of the lateral forehead, temples, cheeks, and also dorsal hands and feet in areas of sun-exposure. Treatment options include the same principles as those used for both melasma and post-inflammatory hyperpigmentation including sun protective measures and topical lightening agents, antioxidants, microdermabrasion, chemical peels, and/or laser and light-based therapy (Vashi and Kundu 2013).

2.4.7 Acanthosis Nigricans

Acanthosis nigricans (AN) is a common acquired disorder characterized by symmetrical hyperchromic plaques with a velvety texture typically seen on the neck, axilla, infra-mammary folds, and groin. AN is more common in obese adults but may appear at any age. AN is estimated to affect 20% of the US population (Kong et al. 2010) and appears to have a higher prevalence in African American (13.3%) and Hispanic (5.5%) population (Gilkison and Stuart 1992).

The pathogenesis is not fully understood. The hypothetical mechanism is that elevated insulin concentrations stimulate the proliferation of keratinocytes by binding to insulin-like growth factor-1 receptors present on keratinocytes, resulting in the clinical and histological finding of hyperkeratosis and papillomatosis (Hermanns-Lê, Scheen, and Piérard 2004).

AN may be a cutaneous marker for internal disease including insulin resistance and polycystic ovary syndrome (PCOS). Rarely, development of extensive AN, including involvement of the oral mucosa and palms in non-obese individuals (N., J., and J. 2013), can be suggestive of an internal malignancy. The proposed pathogenesis of malignant acanthosis nigricans is tumor secretion of transforming growth factor α (TGF- α) in the circulation, which stimulates keratinocyte proliferation (Koyama et al. 1997).

The clinical presentation consists of darkening and thickening of skin of the

axilla, groin and nape of neck, and less so on the face and other flexural areas. There are 8 types, obesity-related or pseudo AN, syndromic, benign, malignant, acral, unilateral, secondary to medication, and multifactorial or mixed type (Puri 2011). Mutation in fibroblast growth factor receptor gene (FGFR), FGFR2, and FGFR3 has been associated with familial AN (Ichiyama et al. 2016).

Histology reveals hyperkeratosis, papillomatosis, a variable degree of acanthosis without increase in melanocyte density, and melanin deposition. The dark appearance is due to hyperkeratosis and not an increase in the melanotic component (Murphy-Chutorian, Han, and Cohen 2013).

There is no information on health-related quality of life and AN. The goal of therapy is to treat the underlying condition. Weight reduction may significantly improve obesity associated AN, and discontinuation of an offending drug may also help in medication related AN. Topical therapy includes keratolytic agents, tretinoin, and chemical peels.

2.4.8 Periorbital hyperpigmentation

Periorbital hyperpigmentation (POH), also known as “dark circles” by patients is a very common dermatological complaint that affects all skin types, although more common in darker-skinned individuals. There is limited data on prevalence of POH, one

study conducted in India estimates the prevalence to be 30.76%, being slightly more common in women than men (P. B. Sheth, Shah, and Dave 2014).

Etiopathogenesis is complex involving multiple factors. POH can be divided into primary and secondary types. Primary type, also called idiopathic cutaneous hyperchromia of the orbital region (ICHOR), refers to skin darkening around the eyes without any systemic or local cutaneous disorders. Usually this form has an early onset, being observed in childhood and may progress during life. It has been suggested that this could in fact be an extension of pigmentary demarcation lines rather than a distinct condition (Malakar et al. 2007).

Secondary type is called periorbital hyperpigmentation (POH). Secondary POH can appear as a result post-inflammatory hyperpigmentation due to atopy or allergic contact dermatitis, genetic background, increased skin pigmentation, hypervascularity, edema, and aging (Sarkar et al. 2014). The inheritance patterns of the genetic or constitutional form of POH is unclear, it may be autosomal dominant with different expression among family members (N. Vashi, Kundu, and Larocca 2014).

Individual face anatomy and the natural aging process contributes to a hollow and shadow appearance observed in older patients, due to the formation of a deeper tear trough and protrusion of infraorbital fat with aging. In addition, skin thinning, laxity, periorbital edema, and increased cutaneous vasculature may in combination worsen the

clinical appearance of the periorbital region (Alsaad and Mikhail 2013). Environment and lifestyle such as lack of sleep, sun exposure, nutritional status, drug intake, and hormonal causes are contributing factors for POH (Roberts 2014).

Huang et al. proposed a classification of dark circles based on clinical presentation and evaluation by wood's lamp and ultrasound. Dark eye circles were classified into 4 patterns: pigmented type, presenting as a brown hue without pink or bluish color; vascular type, appearing as a blue, pink or purple hue; structural type, appearing as a shadow due to face contour and disappears after front light illumination; and mixed type, which combines one or more of the described features. They found that the most common type was mixed (78%), followed by vascular (14%), pigmented (5%), and structural (3%) (Huang et al. 2014).

On histology, biopsy of lesional skin showed dermal melanocytes (Watanabe, Nakai, & Ohnishi, 2006), and larger blood vessels without hemosiderin deposition (Graziosi et al. 2013). POH may have a negative impact on patient quality of life. Patients complain of having a tired, sad, or stressed appearance. Treatment of periorbital hyperpigmentation is complex and therapy should be tailored to a patient's presentation and individual needs. Several treatment modalities have been reported, including hydroquinone, vitamin C, chemical peels, lasers, injection of autologous fat or hyaluronic acid fillers, with variable success (Roberts 2014).

2.4.9 Erythema Dyschromicum Perstans

Erythema dyschromicum perstans (EDP) or ashy dermatosis (dermatosis cinecienta) is a chronic asymptomatic disorder characterized by gray-brown macules and patches on both sun-exposed and sun protected areas of the trunk, arms, and face (Ramirez and Lopez Lino 1984). It usually affects young adults and children. Even though EDP can affect all racial and ethnic groups, it is more common in Latin American and Asian populations (Chang et al. 2015).

The etiology of EDP is unclear; however, a possible immune-mediated reaction to an unknown trigger in genetically susceptible patients has been proposed (Piquero-Martin et al. 1989). Reported triggers include medications (penicillin, benzodiazepines), radiographic oral contrast, pesticides, and infestations. It has been associated with endocrinopathies, vitiligo (Henderson, Tschén, and Schaefer 1988), and HIV. Additionally, in Mexican mestizo patients HLA-DR4 may be a risk factor (Correa et al. 2007).

EDP presents as relatively well-defined, blue-black to ash-gray macules and patches distributed symmetrically on the trunk, neck, upper extremities, and face. It may have a discrete, raised erythematous border. Mucosal involvement is uncommon (Vashi & Kundu, 2013).

Histologically, active lesions of EDP show vacuolar degeneration of the basal

layer, papillary dermal edema, and a lymphocytic infiltrate. Older or inactive lesions show pigment incontinence and dermal melanophages without inflammation (Chang et al. 2015).

There are many reported therapeutic options to treat EDP; however, most are ineffective. Topical lightening agents and steroids are usually not helpful. Oral medications such as corticosteroids, griseofulvin, isoniazid, and antimalarials have been reported. In two small case series, dapsone (Bahadir et al. 2004) and clofazimine showed good treatment response (Piquero-Martin et al. 1989). Tacrolimus 0.03% applied twice daily showed improvement in about 57% of patients in a prospective study with 13 subjects (Al-Mutairi and El-Khalawany 2010).

2.4.10 Exogenous Ochronosis

Exogenous Ochronosis (EO) is a rare and poorly understood cause of cutaneous hyperchromia. It is characterized by blue-black or black-brown macules coalescing into patches, distributed symmetrically over the infraorbital and zygomatic regions. The incidence of EO is unknown, with the majority of cases reports being from Africa (Burke and Maibach 1997) and only few reported in the United States. Aside from Africa, the worldwide incidence appears low. This could be attributed to under-reporting or misdiagnosis with clinically similar conditions (Tan 2010).

Although the reason for this feared hyperchromia remains elusive, it is believed that it results from prolonged use of topical agents that include hydroquinone, resorcinol, phenol, mercury, quinine injections, antimalarials, and /or picric acid. The most accepted hypothesis is that EO results from inhibition of the enzyme homogentisic acid oxidase (HGOA) by hydroquinone containing compounds, leading to accumulation of homogentisic acid, which is then polarized to form the ochronotic pigment deposited in the dermis (Ladizinski, Mistry, and Kundu 2011).

EO is characterized clinically by asymptomatic brown-gray or blue-gray lesions on sites of contact and sun exposure, most often of the face and neck and less often the extensor surfaces. Exogenous ochronosis can be classified into 3 clinical stages: (1) erythema and mild pigmentation; (2) hyperpigmentation, black colloid milium (“caviar-like” lesions), and scant atrophy; (3) papulo-nodular lesions, with or without inflammation (Dogliotti and Leibowitz 1979).

Histologically, exogenous ochronosis reveals the classically yellow-brown, banana shaped deposits in the papillary dermis with an overlying normal epidermis. In early stages, subtle changes including basophilia, homogenization, swelling of the collagen bundles, and altered texture and arrangement of elastic fibers similar to solar elastosis are observed (Chowdary, Mahalingam, and Vashi 2014). Late lesions may present with degeneration of ochronitic pigment forming a colloid millium (Findlay,

Morrison, and Simson 1975) and rarely formation of sarcoid-like granuloma has been reported (Dogliotti and Leibowitz 1979).

Dermoscopy and reflectance confocal microscopy are non-invasive tools that may be helpful to differentiate EO from other common hyperpigmentation disorders including melasma, especially in patients who prefer to avoid skin biopsy. Dermoscopy findings of EO include blue-gray amorphous areas obliterating follicular openings but not surrounding them, (Charlín et al. 2008) a diffuse brown background and small, thin annular brown-gray globules around the follicular openings may be observed. In contrast, melasma has a brown reticular pattern with a light brown background and follicular sparing (Gil et al. 2010).

The reflectance confocal microscopy (RCM) features of EO are well-defined, dark round to oval spaces located next to follicles and banana-shaped structures in the papillary dermis (Gil et al. 2010).

EO has notoriously been extremely difficult to treat with just few case reports illustrating treatment options of trichloroacetic acid, cryotherapy, retinoic acid, and low potency topical corticosteroids, and satisfactory options of dermabrasion, CO2 laser (Kanechorn-Na-Ayuthaya et al. 2013), chemical peels, q-switched laser (Bellew and Alster 2004), and intense pulsed light (IPL) (Gil et al. 2010). Results, overall, have typically not been uniform or consistently successful. Early diagnosis and patient

education regarding long term use of hydroquinone compounds and use of hydroquinone sparing agents are important measures in order to prevent this difficult to treat condition.

CHAPTER THREE: METHODOLOGY

3.1 Research Design

This is a cross-sectional study conducted to evaluate the impact of skin hyperpigmentation disorders on patients' health-related quality of life and patients' knowledge, attitudes, and practices towards skin hyperpigmentation disorders. The study was approved by the Boston University Institutional Review Board (IRB) under protocol number H-33375. This study aims to answer the following questions:

1. How does hyperpigmentation affect patients' quality of life and what are patients' knowledge, beliefs, and attitudes regarding these disorders?
2. Do assessments of clinical disease severity predict quality of life?
3. What are the factors associated with a higher impact on quality of life measures?
4. What are the factors associated with patients' knowledge of their diagnosis?

3.2 Sample

The study was conducted on 298 consenting adult patients with a skin hyperpigmentation disorder who sought dermatological care at Boston Medical Center (BMC) or East Boston Neighborhood Health Center (EBNHC) from February of 2015 to March of 2016. Subjects under the age of 18 and those unable or unwilling to complete the questionnaire were excluded. No identifying information was collected, and only 1 visit was required to complete the survey and the clinical examination. Inclusion criteria

can be found in appendix V.

Eligible patients who spoke English, Spanish, or Portuguese were verbally asked if they were willing to participate in a onetime questionnaire about their skin disorder. Patients who expressed willingness to participate received a detailed informed consent (Appendix I) explaining the study.

3.3 Data Collection

Information about patients were collected in two parts; a self-administered survey and a clinical examination performed by a trained dermatologist. For the first part, those who agreed to participate after reading the informed consent were given the survey — a paper-based questionnaire — in their preferred language. A study member was available to answer questions related to the survey during the entire duration needed to complete the survey, and at times helped patients with poor reading skills to complete the survey. The self-administered survey comprised 3 domains. The first domain collected information about demographic characteristics such as age, gender, country of birth, primary language spoken, occupation, race/ethnicity, marital status, and educational level. The second domain incorporated 22 non-validated multiple-choice questions regarding patients' knowledge about etiology, use of sunscreen, and sun protective behaviors. Patients were also asked if family members had a similar condition, and about their feelings towards their skin condition, skin health practices, and previous treatments. The third domain included the following quality of life measurement tools: *the Dermatology Life Quality Index (DLQI)*, and *the Skin Discoloration Impact Evaluation*

Questionnaire (SDIEQ). The two measurement tools are detailed in appendix IV and V, respectively.

The DLQI is the first validated dermatology-specific health-related quality of life questionnaire (Finlay and Khan 1994). It is composed of 10 questions covering 6 different domains of quality of life, including symptoms and feelings related to daily activities, leisure, work and school, personal relationships, and treatment over the past week. Subjects were asked to tick a box that best described their answer. The response to each question ranged on a Likert scale from 0= not at all, 1= a little, 2= a lot, to 3= very much. Total score ranges from 0 (no impairment of quality of life) to 30 (maximum impairment). To translate DLQI to a more practical clinical interpretation about patients view of overall impairment on skin-related quality of life, the 5 DLQI bands score proposed by Hongbo et al. were used. DLQI scores 0 to 1=no effect on patient's life, DLQI scores 2 to 5=small effect on patient's life; DLQI scores 6 to 10=moderate effect on patient's life; DLQI scores 11 to 20=very large effect on patient's life; DLQI scores 21 to 30=extremely large effect on patient's life (Hongbo et al. 2005).

The SDIEQ is a five-item, non-validated, brief health-related quality of life questionnaire (A. Taylor et al. 2008). It is composed of five items graded on a Likert scale from 0= not at all, 1= a little, 2= a lot to 3= very much. A total score ranges from 0 (no impairment of quality of life) to 15 (maximum impairment) (Appendix V). (A. Taylor et al. 2008) (Balkrishnan et al. 2003).

After completing the survey, a physician trained in dermatology proceeded with a

clinical examination and further diagnostic processes. In addition to the structured dermatological clinical examination, careful collection and documentation of information was performed in two subdomains: a general information subdomain including diagnosis, skin type, and visit type, and a diagnosis-specific subdomain. The diagnosis specific subdomain was performed for patients with melasma and post acne hyperpigmentation. For those diagnosed with melasma, the modified *Melasma Area Severity Index (MASI)*, a reliable and validated tool, was used (Appendix VI) [(Kimbrough-Green et al. 1994)]. A total MASI score was obtained along with a clinical determination of melasma pattern. The MASI score is calculated by a subjective assessment of three factors: area (A) of involvement, darkness (D) and homogeneity (H). The area of involvement of the forehead, right malar region, left malar region and chin corresponding, respectively, to 30%, 30%, 30% and 10% of total face. Each of these four areas is given a numeric value of 0 to 6 (0= no involvement; 1= < 10 %; 2=10–29%; 3=30–49%; 4= 50–69%; 5= 70–89% and 6= 90–100%). Darkness and homogeneity are rated on a scale from 0 to 4 (0= absent; 1= slight; 2=mild; 3=marked; 4=maximum). The total score ranges from 0 to 48. Recent literature by Pandya et al. has suggested the elimination of the homogeneity assessment which was followed in this study (Pandya et al. 2011). Hence, modified MASI score was calculated as follows: forehead 0.3 (D)(A) + right malar 0.3 (D)(A) + left malar 0.3 (D)(A) + chin 0.1 (D)(A). To increase the validity of our clinical evaluation, wood's light examination was performed to help identify the possible location of pigment deposition. In epidermal melasma, lesions are enhanced with wood's light, whereas in dermal melasma, lesions are not. When some areas are enhanced and other are

not, a mixed appearance is noted. Often times, wood light examination does not help distinguish lesion from normal especially in darker skin types, and this pattern is known as indeterminate or inapparent (N. P. Sanchez et al. 1981).

For patients that were diagnosed with post-acne hyperpigmentation, based on clinical examination and history, the *Post Acne Hyperpigmentation Index (PAHPI)* (Appendix VII) was calculated. The PAHPI is a validated scoring method developed by Savory et al. It measures the clinical severity of post-inflammatory hyperpigmentation from acne. It consists of three domains: size, intensity, and number of lesions. Each variable is assigned different weights, with lesion size and darkness being assigned higher weights. The sum of the three variables ranges from 6 to 22 (Savory et al., 2014). For all other disorders of hyperpigmentation, the body location and body surface area was obtained. No additional scoring method was used for any other diagnosis.

3.4 Statistical Analysis

Study data were collected and managed using Research Electronic Data Capture (REDCap) tool (Harris et al. 2009). REDCap is a secure, web-based application designed to support data capture for research studies. Data entry was performed by co-investigator Mayra Buainain de Castro Maymone. Excel sheets were generated through REDCap and exported to STATA. Statistical analyses were performed using STATA/SE 13.0.

Descriptive statistics for general demographic, clinical characteristics, and general attitudes and knowledge regarding hyperpigmentation disorders were generated and are reported in separate tables. Given that PIH and melasma were the 2 most common diagnoses, a new variable for diagnosis was constructed to reflect those diagnosed with PIH, melasma, and those with other hyperpigmentation disorders, being grouped under one category. For purposes of this thesis, “other hyperpigmentation disorders” refers to diagnoses other than PIH or melasma found in this sample. Chi-square and Fisher exact tests were used to examine significant differences pertaining to descriptive characteristics as broken down by the three categories of diagnosis: PIH, melasma, and others.

A correlation matrix was calculated for the association between measures of quality of life, and measures of disease severity was assessed using Spearman rho correlation. DLQI score, MASI, PIH, and SDIEQ scores were mathematically transformed to resemble a normal distribution.

A bivariate analysis with one-way analysis of variance and post-hoc test was performed to describe the magnitude of hyperpigmentation disorders as broken down by PIH, melasma, and others on patients’ quality of life as measured by DLQI. Mean scores for DLQI for every respondent was generated by dividing the total score by the number of questions for descriptive purposes, while the effect of the total DLQI was modeled in the bivariate model. The DLQI total scores were transformed arithmetically to closely resemble a normal distribution and satisfy the assumption for ANOVA.

Two multivariate models were constructed: a logistic multinomial regression and a multiple regression model. A logistic multinomial regression was performed to determine factors associated with higher odds of patients' knowledge of their actual diagnosis as determined by the clinician. Patient's knowledge of their diagnosis variable was constructed by using information from both the self-administered survey and the clinical examination. Those patients whose reported diagnosis matched the clinical diagnosis made by the dermatologist were coded as "yes", while those who did not were coded as "no". The model was adjusted to the following confounders: level of education (coded into three categories; lower/elementary school or middle school, high school diploma, and college or graduate degree), age (coded in two categories; younger or equal to 45 years of age and older than 45), visit type (coded in two categories; first visit or a follow-up visit), disease duration (coded in three categories; those who had their condition for up to 12 months, for up to 5 years, and for up to 15 years or longer), and use of sunscreen (coded in three categories; currently using sunscreen, not using sunscreen, and those who do not know). The second model was a multiple regression model performed to determine factors associated with higher DLQI scores. The model was adjusted to the following potential confounders: clinical diagnosis, disease duration, visit type, age, use of sunscreen, and accurate knowledge of the diagnosis. Gender was not included as a confounding factor because given the gender imbalance in the dataset, the results would likely be skewed away from the null. We also did not include race, language, and skin-type as all of these were found to highly correlate with each other and education. Controlling variables in our model was done based on a "stepwise"

method as there is very limited prior information from the literature. We kept the variables that made up the cut point of (0.1) significance level in the model. We then rearranged the order of introducing these variables to the model and chose to perform a “forced entry” regression method, as the stepwise regression method is not recommended due to its many limitations (Field 2009). We inserted the variables in the model based on our theory of their relative contribution on patients’ quality of life. We chose to include education rather than race or language because we were interested in making inferences about modifiable attributes for patients and for informing policies. All assumptions for logistic and multiple regression were examined. To meet the assumptions, DLQI scores were converted to square roots to closely resemble a normal distribution and predictors that were found to be associated were removed from the model.

CHAPTER FOUR: RESULTS

4.1 Descriptive Statistics

4.1.1 Socio-demographic characteristics of study participants

A total of 298 patients completed the questionnaire. The mean age was 41 years (SD \pm 12.39). The majority of patients was female (268, 90%) and identified themselves as white (121, 50%) and Hispanic (140, 51%). Two hundred and thirteen (72 %) of patients were not U.S. born, and the top five countries of origin were U.S., El Salvador, Colombia, Dominican Republic, and Guatemala. The reported primary language spoken was English in (119, 41%), followed by Spanish 113 (39%) and Portuguese (30, 10.3%). Most of the patients were single (142, 48.8%), employed (197, 70.68%), and had a high school diploma (95, 32.8%), this being the most common highest level of education. Detailed demographic characteristics are presented in Table 4.

Characteristic	n	(%)
Age		
(18–25)	26	(08.72%)
(26–35)	87	(29.19%)
(36–45)	82	(27.52%)
(46–55)	63	(21.14%)
(≥ 56)	40	(13.42%)
Gender		
Female	268	(89.58%)
Male	30	(10.42 %)
Race (n=238)*		
White	121	(50.48%)
African American	92	(38.66%)
Asian	23	(09.66%)
Native American	2	(00.84%)
Ethnicity (n= 274)*		
Hispanic or Latino	140	(51.09%)
Not Hispanic or Latino	134	(48.91%)
Marital status (n=291)*		
Single	142	(48.80%)
Married	104	(35.74%)
Separated	10	(03.44%)
Widowed	8	(02.75%)
Divorced	15	(05.15%)
Living in common law	12	(04.12%)
Occupation (n=278)		
Working	197	(70.68%)
Not working	81	(29.14%)
Education (n=291)		
Lower/elementary school	28	(09.62%)
Middle school	40	(13.75%)
High school	95	(32.65%)
College	72	(25.34%)
Graduate school	54	(18.56%)

* Sample size may vary due to missing data.

Table 4. Basic demographic characteristic of the study population (n=298)

4.1.2 Basic clinical characteristic

Among those diagnosed with a disorder of hyperpigmentation, melasma was the most common diagnosis, affecting 50% of patients, followed by post-inflammatory hyperpigmentation (33%), lentigines (7.4%), dermatosis papulosa nigra (3.4%), seborrheic keratosis (3.4%), and lichen planus pigmentosus (2.7%). The frequency of various hyperpigmentation disorders diagnosed in the study participants can be found in Table 5.

Table 5. Diagnosis of hyperpigmentation conditions among study participants.

Diagnosis (n=298)	n (%)
Melasma	149 (50%)
Post-inflammatory hyperpigmentation PIH due to acne	99 (33.2%) 51 (51%)
Lentigines	22 (7.4%)
Dermatosis papulosa nigra	10 (3.4%)
Seborrheic keratosis	10 (3.4%)
Lichen planus pigmentosus	8 (2.7%)
Maturational hyperpigmentation	7 (2.4%)
Acanthosis nigricans	6 (2.0%)
Periorbital hyperpigmentation	5 (1.7%)
Erythema dyschromicum perstans	3 (0.1%)
Macular amyloidosis	2 (0.7%)
Exogenous Ochronosis	1 (0.3%)
Drug induced hyperpigmentation	1 (0.3%)
Melanocytic nevi	1 (0.3%)
Nevus of Ota	1 (0.3%)

Basic clinical characteristics are presented in Table 6.

The most common Fitzpatrick skin phototypes were III and IV (38.6% and 29.5%, respectively). Patients with Fitzpatrick skin phototypes IV were more likely to be diagnosed with melasma ($p=0.003$), while those with skin phototypes V and VI were more likely to be diagnosed with PIH ($p=0.001$ & 0.004 , respectively). Patients diagnosed with melasma were more likely to have the disorder for up to 5 years and those with PIH were more likely to have it for >10 years ($p=0.037$ and 0.046 , respectively).

Among those patients diagnosed with melasma (50%), the most common clinical pattern was centrofacial (49%), followed by malar (26.9%), combined (22.1%), and body (1%). Wood's light evaluation was performed in 99 patients; the most common pattern was mixed 59 (59.6%), followed by epidermal 42 (42.4%), inapparent 2 (2%), and dermal 1 (1.1%). The mean modified MASI score was 5.3 (SD \pm 3.46). Use of birth control was reported by 151 patients, and the most common methods were oral contraceptives (62.3%), Mirena/Skyla® IUD (13.9%), Copper IUD (12.6%), Depo-Provera® (7.9%), etonogestrel implant -Implanon® (6.6%). Ninety-seven (47.5%) of those who were diagnosed with melasma were found to be currently using birth control while 56 (27.45%) and 51 (25%) among those who were diagnosed with PIH and other hyperpigmentation disorders, respectively. This was found to be statistically significant at p value 0.042. There was no significant association between use of thyroid medication and the development of any type of hyperpigmentation disorder evaluated in our study.

Table 6. Basic clinical characteristics of the study population

Attribute	n^o (%)	Melasma Mean /n(%)	PIH Mean /n(%)	p value[⊗]
Skin type (n=295*)				
I	0	0	0	-
II	16 (05.42%)	6 (85.71)	1 (14.29)	0.243
III	87 (29.49%)	45 (64.29)	25 (35.71)	0.188
IV	114 (38.64%)	64 (69.57)	28 (30.43)	0.003
V	52 (17.63%)	10 (27.03)	27 (72.97)	0.000
VI	26 (08.81%)	4 (23.53)	13 (76.47)	0.004
Duration of symptoms (n=241*)				
Up to 1 year	16 (06.64)	12 (46.15)	14 (53.85)	0.323
Up to 5 years	101 (41.91)	47 (64.38)	26 (35.62)	0.037
Up to 10 years	56 (23.24)	25 (56.82)	19 (43.18)	0.787
> 10 years	20 (08.30)	14 (40.00)	21 (60.00)	0.046
DLQI(n=282*)				
No effect	55 (19.50)	12 (37.50)	20 (62.50)	0.501
Small effect	89 (31.56)	36 (57.14)	27 (42.86)	0.990
Moderate effect	72 (25.53)	35 (58.33)	25 (41.67)	0.816
Very large effect	63 (22.34)	29 (53.70)	25 (46.30)	0.562
Extreme effect	3 (01.06)	1 (33.33)	2 (66.67)	0.578
SDIEQ(n=202)				
Small impact	98 (32.89)	36 (58.06)	26 (41.94)	0.772
Medium impact	63 (21.14)	26 (50.98)	25 (49.02)	0.313
High impact	41 (13.76)	23 (62.16)	14 (37.84)	0.437

* Denominators might differ due to missing data.

⊗ Generated through either chi-square test or fisher exact test whenever appropriate.

o Other causes of hyperpigmentation are included in total n size calculation but not in chi-square or Fisher exact tests; therefore, numbers might not add up to total n.

Post-inflammatory hyperpigmentation was the second most common diagnosis, affecting 99 patients. Among those diagnosed with PIH, 51 patients had PIH related to acne. In order to assess the severity of post-inflammatory hyperpigmentation, we used the PAHPI score developed by Savory et al. The mean PAHPI score was 10.32 (SD \pm 3.34). We arbitrarily assigned cut off points for the obtained results that ranged from a minimum of 6 to a maximum of 22 points: 6–10=very mild, 11–14=mild, 15–18=moderate, and 19–22=severe post-inflammatory hyperpigmentation (PIH). Most patients were found to have very mild to mild disease severity.

The overall mean DLQI was 6.56 (SD \pm 5.35), minimum and maximum ranges were 0 to 24. The mean total DLQI in those diagnosed with PIH was 7.89 (SD \pm 0.61), melasma 6.75 (SD \pm 0.45), and other hyperpigmentation disorders 4.5 (SD \pm 0.55). Overall, 31.5% and 25.5% of patients reported small and moderate effects on quality of life, respectively. No significant difference between groups was found when comparing DLQI score bands (Table 6 and 8). The mean total score obtained in the 5-question Skin Discoloration Impact Evaluation questionnaire (SDIEQ) questionnaire was 6.36 ± 4.59 , minimum and maximum ranges are 0 to 15. Overall, most patients reported a small impact (98, 32.8%) and moderate impact (63, 21.1%) on their quality of life (Table 6).

4.1.3 Patients' knowledge, attitudes and practices among survey participants

Patients' beliefs, knowledge, attitudes, and practices regarding predisposing factors, such as sun awareness, previous treatment, monthly expenditure on over-the-

counter skin products, and best person to treat their skin condition are described in detail in Table 7.

4.1.4 Patients' knowledge of predisposing factors

Our analyses demonstrated that patients diagnosed with melasma were significantly more likely to attribute the cause of brown spots to the sun (59.74%, $p < 0.001$) and hormones (58.73%, $p < 0.001$) when compared with those with PIH and other skin hyperpigmentation disorders (Table 7). Patients diagnosed with PIH were more likely to attribute the brown spots to acne (68%, $p < 0.001$). There was no statistically significant difference among those that attributed the cause of brown spots to genetic, race, or family history (Table 7).

4.1.5 Patients' behavior regarding sun protection and sun awareness

Most patients 201 (69.01%) reported using lotion, cream, and/or skin products containing sunscreen. More than half of the patients did not know if their sunscreen was broad spectrum. More patients with melasma used sunscreen 107 (53.23%) when compared with those with PIH (46, 22.89%) and other hyperpigmentation disorders (48, 23.88%). In contrast, those diagnosed with PIH used sunscreen less (44, 51.76%) when compared with patients diagnosed with melasma and other hyperpigmentation disorders. There was a significant difference between groups difference for this comparison ($p < 0.001$) (Table 5).

Table 7. General description of patients' beliefs, attitudes, and knowledge about hyperpigmentation conditions

Attribute	n (%)	Melasma Mean /n(%)	PIH Mean /n%	Other Mean /n%	p value
Attributed cause of brown spots^s					
Sun	77 (26.19)	46 (59.74)	10 (12.99)	21 (27.27)	0.000
Genetic	75 (26.04)	27 (36.00)	25 (33.33)	23 (30.67)	0.079
Hormones	63 (22.42)	37 (58.73)	15 (23.81)	11 (17.46)	0.000
Acne spots/rash	91 (32.04)	18 (19.78)	62 (68.13)	11 (12.09)	0.000
Race	102 (34.34)	35 (34.31)	41 (40.20)	26 (25.49)	0.107
Family history	104 (35.25)	39 (37.50)	35 (33.65)	30 (28.85)	0.610
Currently using sunscreen (n=291)*					
Yes	201 (69.01)	107 (53.23)	46 (22.89)	48 (23.88)	0.000
No	85 (26.02)	17 (20.00)	44 (51.76)	24 (28.24)	
I don't know	5 (01.70)	2 (40.00)	3 (60.00)	0 (0.00)	
Sun Protection Factor (SPF) (n=210)*					
10- 20	24 (11.43)	7 (29.17)	7 (29.17)	10 (41.67)	0.008
21-50	102 (48.57)	51 (50.00)	31 (30.39)	20 (19.61)	
50-100	38 (18.10)	26 (68.42)	2 (5.26)	10 (26.32)	
>100	12 (05.71)	9 (75.00)	2 (16.67)	1 (8.33)	
Don't know	34 (16.19)	19 (55.88)	7 (20.59)	8 (23.53)	
Frequency of sunscreen application (n= 209)*					
Every 2 hours	17 (08.13)	10 (58.82)	3 (17.65)	4 (23.53)	0.008
2 to 3 times a day	108 (51.67)	64 (59.26)	17 (15.74)	27 (25.00)	
One time a day	28 (13.40)	15 (53.57)	7 (25.00)	6 (21.43)	
Occasionally / almost never	56 (26.79)	19 (33.93)	25 (44.64)	12 (21.43)	
Broad spectrum (n=100)*					
Yes	39 (39.00)	17 (43.59)	15 (38.46)	7 (17.95)	0.653
No	5 (05.00)	2 (40.00)	2 (40.00)	1 (20.00)	
Don't know	56 (56.00)	27 (48.21)	14 (25.00)	15 (26.79)	
Sun-protective measures: wear a hat (n=287)*					
Rarely or never	147 (51.22)	65 (44.22)	49 (33.33)	33 (22.45)	0.092
Sometimes	83 (28.92)	37 (44.58)	31 (37.35)	15 (18.07)	
Usually	30 (10.45)	9 (30.00)	8 (26.67)	13 (43.33)	
Always	27 (09.41)	15 (55.56)	5 (18.52)	7 (25.93)	
Sun-protective measures: seek shade (n=291)*					
Rarely or never	82 (28.18)	26 (31.71)	34 (41.46)	22 (26.83)	0.000
Sometimes	114 (39.18)	52 (45.61)	42 (36.84)	20 (17.54)	
Usually	68 (23.37)	35 (51.47)	14 (20.59)	19 (27.94)	
Always	27 (9.28)	14 (51.85)	4 (14.81)	9 (33.33)	

First notice of the dark spot made (n=295)*

By patient	286 (96.9)	126 (44.06)	89 (31.12)	71 (24.83)	0.754
By doctor	6 (02.00)	2 (33.33)	2 (33.33)	2 (33.33)	
By others	3 (01.00)	1 (33.33)	2 (66.67)	0	

Patient first used resources for help (n=293)*

Internet	37 (12.60)	9 (24.32)	21 (56.76)	7 (18.92)	0.002
Friend	32 (10.90)	17 (53.12)	7 (21.88)	8 (25.00)	0.392
Doctor	195 (66.60)	94 (48.21)	53 (27.18)	48 (24.62)	0.036
Family member	24 (08.20)	7 (29.17)	13 (54.17)	4 (16.67)	0.067
Other	13 (04.40)	3 (23.08)	5 (38.46)	5 (38.46)	0.236

Previous knowledge about hyperpigmentation disorders[§] (n=296)*

Post-inflammatory hyperpigmentation	78 (27.18)	17 (21.79)	49 (62.82)	12 (15.38)	0.000
Melasma	76 (26.21)	43 (56.58)	19 (25.00)	14 (18.42)	0.027
Lentigo/sun spots	119 (41.90)	50 (42.02)	38 (31.93)	31 (26.05)	0.942
Freckles	179 (61.72)	78 (43.58)	60 (33.52)	41 (22.91)	0.513
Moles/nevi	154 (54.61)	54 (35.06)	59 (38.31)	41 (26.62)	0.018

Use of OTC lightening creams (n=292)*

Yes	147 (50.30)	79 (53.74)	48 (32.65)	20 (13.61)	0.000
No	138 (47.30)	43 (31.16)	46 (33.33)	49 (35.51)	
Don't know	7 (02.40)	5 (43.49)	0 (00.00)	2 (28.57)	

Monthly spending on OTC (n=277)*

\$0	107 (38.63)	32 (29.91)	38 (35.51)	37 (34.58)	0.001
<\$50	132 (47.65)	63 (47.73)	40 (30.30)	29 (21.97)	
≥\$50	27 (09.75)	19 (70.37)	7 (25.93)	1 (03.70)	
> \$100	11 (03.97)	7 (63.64)	3 (27.27)	1 (09.09)	

Where products were obtained (n=285)*

US pharmacy	149 (50.00)	69 (46.31)	55 (36.91)	25 (16.78)	0.006
Abroad	25 (08.39)	18 (72.00)	3 (12.00)	4 (16.00)	0.012
Community store	17 (05.70)	9 (52.94)	5 (29.41)	3 (17.65)	0.812
Friend	16 (05.37)	11 (68.75)	4 (25.00)	1 (06.25)	0.092
Not applicable/ other	96 (32.21)	26 (27.08)	32 (33.33)	38 (39.58)	0.000

Products obtained with prescription (n=298)*

Yes	147 (49.80)	86 (58.50)	40 (27.21)	21 (14.29)	0.000
No	146 (49.50)	43 (29.45)	52 (35.62)	51 (34.93)	

Products tried[§]

Hydroquinone	124	68 (54.84)	37 (29.84)	19 (15.32)	0.000
Kojic acid	14	3 (21.43)	8 (57.14)	3 (21.43)	0.120
Azelaic acid	11	5 (45.45)	6 (54.55)	0 (00.00)	0.033
Tri-luma	40	28 (70.00)	5 (12.50)	7 (17.50)	0.000
Antioxidants	3	0 (00.00)	2 (66.67)	1 (33.33)	0.400
Steroid cream	18	3 (16.67)	8 (44.44)	7 (38.89)	0.115

Use of birth control (n=298)*					
Yes	204 (68.46)	97 (47.55)	56 (27.45)	51 (25.00)	0.042
No	94 (31.54)	33 (35.11)	39 (41.49)	22 (23.40)	
Thyroid medication (n=257)*					
Yes	20 (07.80)	6 (30.00)	5 (25.00)	9 (45.00)	0.291
No	228 (88.70)	102 (44.74)	72 (31.58)	54 (23.68)	
Don't know	9 (03.50)	3 (33.33)	4 (44.44)	2 (22.22)	
Family member with same condition (n=)*					
Yes	104 (35.30)	39 (37.50)	35 (33.65)	30 (28.85)	0.603
No	157 (53.20)	73 (46.50)	49 (31.21)	35 (22.29)	
Don't know	34 (11.50)	16 (47.06)	11 (32.35)	7 (20.59)	
How much condition bothered participants (n=298)*					
Very much	162 (54.36)	78 (48.15)	54 (33.33)	30 (54.36)	0.233
A lot	92 (30.87)	35 (38.04)	27 (29.35)	30 (32.61)	
A little	35 (11.74)	13 (37.14)	12 (34.29)	10(28.57)	
Not at all	9 (03.02)	4 (44.44)	2 (22.22)	3 (33.33)	
Patient belief about who best to treat their condition (n=292)*					
Primary care doctor	2 (00.07)	2 (100.00)	0 (00.00)	0 (00.00)	0.356
Dermatologist	283 (96.90)	123 (43.46)	91 (32.16)	69 (24.38)	
Aesthetician	1 (00.03)	0 (0.00)	0 (0.00)	1 (100.00)	
Friend who has same condition	1 (00.03)	0 (0.00)	1 (100.00)	0 (0.00)	
Other	5 (01.07)	1 (20.00)	2 (40.00)	2 (40.00)	

§ Attributes are not mutually exclusive; therefore, total percentages were not generated.

* Denominators might differ due to missing data.

□ Generated through either chi-square test, fisher exact test, or t-test when appropriate.

▫ Fisher-exact test value was not possible to generate due to small sample size.

A total of 102 (48.6%) patients reported use of sunscreen with sun protection factor (SPF) 21 to 50. We found that those with melasma used the recommended SPF of 21–50 more often than those diagnosed with PIH and others ($p < 0.008$). Moreover, those diagnosed with melasma applied sunscreen 2 to 3 times a day more often than those with PIH and others. The comparison between groups was significant at $p < 0.001$.

During peak hours, between 10am to 4pm, most patients 182 (65%) and 165 (57.5%) reported staying outside for 1 hour or less on weekdays and weekends, respectively. When outdoors, more than half of patients rarely or never wore a hat 147 (51.2%) and only 27 (9.3%) reported always and 68 (23.4%) usually seeking shade. More patients with PIH reported rarely or never seeking shade when compared with patients with other hyperpigmentation disorders. More patients with melasma reported usually and always seeking shade ($p < 0.001$).

4.1.6 Patients' beliefs, attitudes and practices towards skin hyperpigmentation

The skin hyperpigmentation was self-perceived by the vast majority (286, 97%) of patients. The predominant source of information used by patients to gain knowledge about their skin condition was the medical doctor. Interestingly, the internet was shown to be the first resource used by those diagnosed with PIH when compared with other groups ($p < 0.002$), whereas those diagnosed with melasma were more likely to seek medical help ($p < 0.036$) (Table 7). The vast majority (238, 96.9%) of patients reported that the best person to treat their dark spot(s) is the dermatologist. No significant difference was found between melasma, PIH, and other groups.

To assess general knowledge about common hyperpigmentation conditions, patients were asked if they had ever heard of post-inflammatory hyperpigmentation, melasma, lentigo or sun spots, freckles, and moles or nevi. Sixty-seven percent of patients have previously heard of freckles, 54.61% moles/nevi, and 41.90 % of lentigo/sunspots. Those diagnosed with PIH (62.82%) were significantly more likely to have prior knowledge of their condition than those with melasma (21.79%) and other hyperpigmentation disorders (15.38%) at $p < 0.001$. Similarly, those diagnosed with melasma (56.58%) were more likely to have heard of the condition “melasma” when compared with PIH (25%) and other hyperpigmentation disorders (18.3%) at $p < 0.027$. The use of over-the-counter lightening creams was reported by 147 (50.30%) of patients. Those with melasma (53%) were more likely to try an over-the-counter lightning cream when compared with PIH (32%) and others (18%). Those with other hyperpigmentation disorders were less likely to try over-the-counter creams when compared with the other two groups, which was significant at $p < 0.001$.

The average monthly expenditure on skin lightning products reported by most patients (47.65%) was less than 50 dollars. Those with melasma were more likely to spend \geq \$50 (70.31%) on skin products compared with those with PIH (25.93%) and other hyperpigmentation (3.70%), respectively ($p < 0.001$). Nearly half of products tried by patients were obtained with a prescription (147, 49.80%) from a pharmacy in the United States (149, 50%). Only 10% of patients obtained the products from overseas/abroad. Those diagnosed with melasma (72%) obtained products from abroad

more frequently compared with those diagnosed with PIH (12%) and other hyperpigmentation disorders (16%) ($p < 0.012$). Patients with melasma (58.50%) were more likely to be prescribed a lightening product compared with PIH (27.21) and others (14.29) ($P < 0.001$).

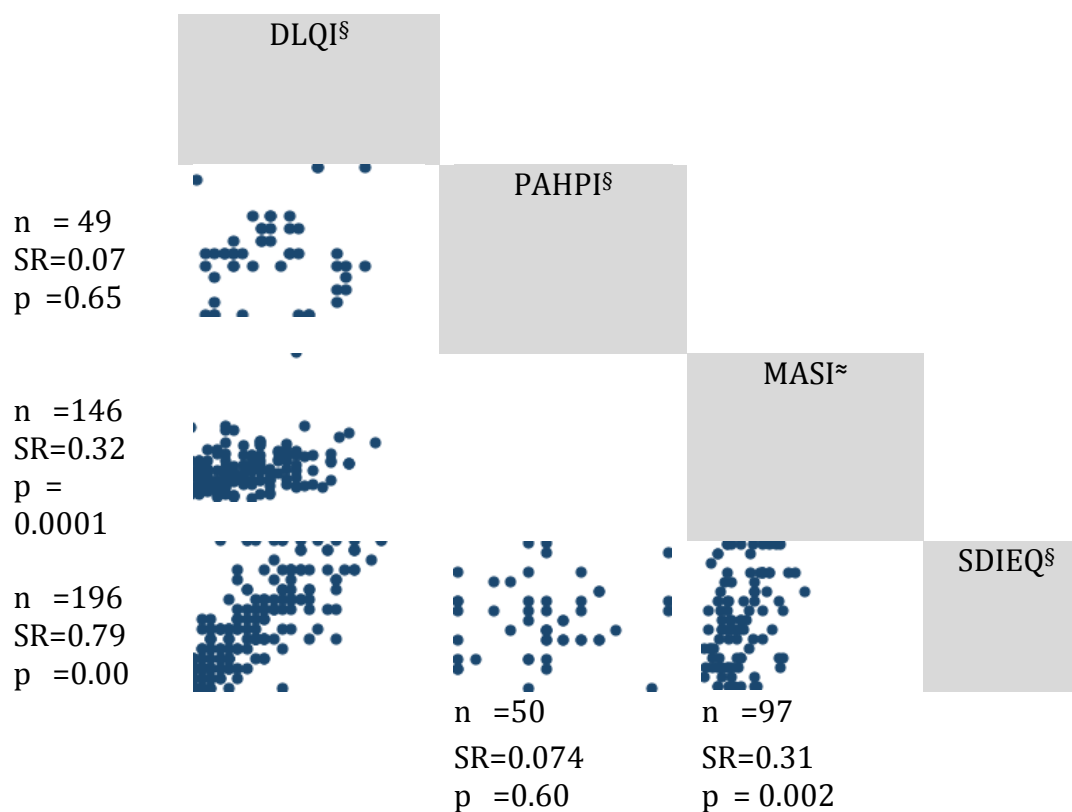
Hydroquinone had reported use by 43.15% of patients, 31.5% of which reported improvement of hyperpigmentation. The average time of hydroquinone use was less than 3 months in 48.4%, followed by 3 to 5 months in 21.4% of patients. About 30% of patients used hydroquinone for periods longer than 6 months. Patients with melasma were more likely to be prescribed hydroquinone (54.85%) compared to those with PIH (29.84%) and other hyperpigmentation disorders (15.32%). Those with melasma were more likely to have tried triple combination cream (specifically Tri-luma®) (28, 70%) than those with PIH (5, 12.5%) and others (7, 17.5%) ($P < 0.001$). Almost two thirds of patients reported that they do not have a favorite brand of skin care products for their hyperpigmentation disorder. The use of birth control was reported by 52.75% of patients. Those diagnosed with melasma (47.55%) were found to be significantly more likely to use birth control compared with PIH (27.45%) and other hyperpigmentation disorders (25%) at $p < 0.042$ (Table 7). When questioned if they have ever tried skin lightening cream containing kojic acid, azelaic acid, antioxidants, and steroids, only a small percentage responded yes (5%, 4%, 9%, and 6.6% respectively), and the vast majority answered no or don't know.

4.2 Correlation

4.2.1 Correlation between quality of life measures and clinical disease severity measures.

To crudely validate SDIEQ against DLQI and to understand how measures of quality of life relate to the actual clinical severity of the disease, a correlation matrix was constructed among DLQI, SDIEQ, PAHI, and MASI. SDIEQ demonstrated a strong correlation with DLQI (spearman's rho coefficient 0.79, $p < 0.001$), while PAHI correlated weakly with both DLQI (spearman's rho coefficient 0.07, $p = 0.65$) and SDIEQ (spearman's rho coefficient 0.074, $p = 0.6$ value). MASI had a weak but significant correlation with DLQI (spearman's rho coefficient 0.32, $p < 0.001$) and SDIEQ (spearman's rho coefficient 0.31, $p < 0.002$ value). See Figure 1.

Figure 1. Correlation between quality of life scores and clinical disease severity scores.



SR= Spearman's rho coefficient

[≈] Score was converted to log to approximate normality.

[§] Score was converted to square roots to approximate normality.

4.3 Bivariate Analysis

4.3.1 Association between DLQI score and clinical diagnosis

In order to examine the association between DLQI and clinical diagnosis, a bivariate analysis was performed, and a positive association was found between the overall DLQI (square roots) and melasma versus others ($p=0.003$) and PIH versus others ($p<0.001$).

The results suggest that patients with PIH have significantly worse quality of life than those with other hyperpigmentation disorders and those with melasma have significantly worse quality of life than those with other hyperpigmentation disorders. (Table 8).

Table 8. Bivariate Analysis for the association between DLQI score and clinical diagnosis

Attribute	n (%)	Mean /n(%)
Melasma	121	6.75*
PIH	91	7.89**
Others	70	4.5

* $p < 0.05$ for the comparison melasma vs. others

** $p < 0.05$ for the comparison PIH vs. others

4.3.1 Association between DLQI score and clinical diagnosis

In order to examine the association between DLQI and clinical diagnosis, a bivariate analysis was performed, and a positive association was found between the overall DLQI (square roots) of melasma versus others ($p=0.003$) and PIH versus others ($p < 0.001$). Interestingly, in our study population, patients with PIH have significantly worse DLQI than patients with melasma ($p < 0.005$) (Table 8).

4.4 Multivariate Models

4.4.1 Factors Associated with Patient Knowledge of Their Diagnosis (Table 6)

In a logistic regression analysis performed to study factors associated with higher

likelihood of patients' knowledge of their diagnosis, a higher level of education, younger age, longer duration of having the condition, and current use of sunscreen were found to have 2.4, 2, 3.7, and 2.4 significantly higher odds of diagnosis knowledge. Results can be seen in Table 9. Those with college degrees were 2.4 times more likely to know their diagnosis compared with those with middle school education or less ($p=0.05$). Those younger than 45 years were 2.1 times more likely to know their diagnosis compared with those with 45 years or older ($P=0.04$). A higher likelihood of knowing the diagnosis was observed among those with disease duration up to 5 years compared with those with 1 year or less ($P=0.03$). Those that used sunscreen were 2.4 times more likely to know the diagnosis compared with those that did not use sunscreen ($P=0.02$). Surprisingly, visit type (first visit vs. follow-up) was not shown to be statistically different in evaluating for diagnosis recognition (Table 9).

Table 9. Factors associated with higher odds of patients' knowledge of their diagnosis.

Dependent Variables	N (%)	Odds ratio^s	p value	Confidence Interval
Level of education				
Middle school diploma or less (<i>reference</i>)	68 (23.37)			
High school diploma	95 (32.65)	0.87	0.78	(0.31, 2.38)
College or graduate degree	128 (43.99)	2.48	0.05	(0.97, 6.31)
Age				
>45 years old (<i>reference</i>)	103 (34.56)			
≤45 year	195 (65.44)	2.15	0.04	(1.05, 4.43)
Visit type				
First visit (<i>reference</i>)	122 (46.04)			
Second visit	143 (53.96)	0.87	0.69	(0.45, 1.68)
Duration				
Up to 1 year (<i>reference</i>)	40 (16.60)			
Up to 5 years	101 (41.91)	3.72	0.03	(1.14, 12.07)
≥ 15 years	100 (41.49)	3.12	0.06	(0.95, 10.28)
Use of Sunscreen				
No (<i>reference</i>)	85 (29.72)			
Yes	201 (70.28)	2.44	0.02	(1.12, 5.33)

4.4.2 Factors Associated with DLQI scores

The type of hyperpigmentation disorder and disease duration were both factors associated with a change in DLQI scores. Those with melasma have an increase of 0.62 in DLQI score in comparison with those with other hyperpigmentation disorders ($p < 0.002$). Similarly, those diagnosed with PIH have an increase of 0.98 in DLQI score compared with reference group ($p < 0.001$) (Table 10).

Table 10. Factors associated with DLQI scores.

Dependent Variables	Change in DLQI score[§]	p value	Confidence Interval
Hyperpigmentation disorder			
Other hyperpigmentation disorder (<i>reference</i>)			
Melasma	0.62	0.002	(0.220,1.01)
PIH	0.98	0.000	(0.53,1.43)
Duration			
Up to 1 year (<i>reference</i>)			
Up to 5 years	-0.44	0.049	(-0.88, -0.01)
≥ 15 years	-0.55	0.017	(0.95, 10.28)
Level of education			
Middle school diploma or less (<i>reference</i>)			
High school diploma	-0.019	0.93	(-0.44, 0.40)
College or graduate degree	-0.14	0.54	(-0.56, 0.29)
Visit type			
First visit (<i>reference</i>)			
Second visit	0.87	0.69	(0.45, 1.68)
Age			
>45 years old (<i>reference</i>)			
≤45 year	0.18	0.327	(-0.18, 0.55)
Use of Sunscreen			
No (<i>reference</i>)			
Yes	0.21	0.24	(-0.14, 0.57)
Knowledge of the diagnosis			
No (<i>reference</i>)			
Yes	0.12	0.51	(-0.25, 0.5)

[§]DLQI total scores were transformed to square roots of total scores to approach normal distribution.

CHAPTER FIVE: DISCUSSION

Although disorders of hyperpigmentation are often benign conditions that do not impair physical health, they are commonplace in clinical practice and can carry adverse psychological outcomes for patients (S. J. Kang et al. 2014). Despite the fact that there are numerous studies evaluating quality of life in melasma patients (Pawaskar et al. 2007) (Ikino et al. 2015) (Pichardo et al. 2009), little is known about the effect of other common and uncommon hyperpigmentation disorders on quality of life (A. Taylor et al. 2008). Health related quality of life is defined as individuals' self- perception of their position in life (WHOQOL, 1993), which can vary according to culture and value system. It is a concept that captures the effect of a certain disease on a person's life as perceived by that person (Chen 2012).

For example, males and females may react differently to having a skin hyperpigmentation disorder. Although these disorders affect both genders, the frequency of women (70%) who seek ambulatory care for dyschromia is much higher than men (30%) [(S. J. Kang et al. 2014)], and the impact of these disorders on female patients' quality of life is higher, regardless of the specific diagnosis (Tejada et al. 2011) (D Hexasel, Arellano, and Rendon 2006) (Linthorst Homan et al. 2009). This could be why females constituted the majority (90%) of our sample. Additionally, we observed a higher frequency of melasma cases, a common hyperpigmentation disorder in females [(Grimes 2009)], which might have also contributed to the higher number of females in our sample.

The majority of our study population identified themselves as being Hispanic and/or Latinos. The higher number of Hispanics in this sample can be explained by the location of recruitment sites, which included a tertiary care center that cares for the underserved and a community health center located in East Boston, where the self-reported Hispanic or Latino rate is 52.8%, compared to the national average of 17.4% Hispanics living in US.

Among hyperpigmentation disorders, melasma and PIH were the most common. The majority of those diagnosed with melasma were of Fitzpatrick skin phototype IV. This finding is consistent with the literature, melasma being more common in Fitzpatrick skin types III to IV (V. M. Sheth and Pandya 2011a). To complement clinical evaluation, wood's light examination was performed to help identify the possible location of pigment deposition. As this examination is quite subjective, it remains unclear if this distinction has a true correlation with histological pigment depth and other clinical significance to treatment. In a study by Grimes et al. using wood's light to evaluate pigment depth in patients skin types IV to VI, histological evidence of dermal melanin was found in wood's light enhanced lesions that are consistent with epidermal melasma, moreover histological evidence of melanin was observed in the epidermis and dermis of all subjects (Grimes, Yamada, and Bhawan 2005).

The second most common diagnosis in this sample was post-inflammatory hyperpigmentation, which, in agreement with previous literature, was more common

among those with skin types V–VI (Savory et al. 2014), with disease duration of longer than 10 years. The effect of these two most common hyperpigmentation disorders on quality of life was compared to all other hyperpigmentation disorders. The magnitude of effect of all hyperpigmentation disorders on quality of life as measured by mean DLQI was 6.5 ± 5.3 . Broken down, the DLQI mean for PIH and melasma was 7.89 and 6.75, respectively. It may be the case that the conditions classified as others in our setting might generally be perceived as more common types of hyperpigmentation disorders and therefore are associated with higher quality of life measurements. Overall, it has been noted that quality of life by definition is highly subjective and might not relate to disease severity (Jayaprakasam et al. 2002) (Balkrishnan et al. 2003). Therefore, the significantly lower quality of life for patients with melasma and PIH can still bring contextual understanding to the effect of these disorders on patients' quality of life.

The mean DLQI for melasma reported in previous studies ranged from 4.5 (Harumi and Goh 2016), 7.3 (Leeyaphan et al. 2011) to 7.5 (Pichardo et al. 2009), and this is comparable to mean DLQI for melasma (6.75) obtained in our study. Only one study evaluating DLQI and PIH was found in the literature, and mean DLQI was 8.4 (Joshi et al. 2009), this is slightly higher than our mean of 7.89. In comparison to other dermatological conditions in the literature, the mean DLQI for the total sample was higher than non-melanoma skin cancer (NMSC) 2.4 (Rhee et al. 2004), vitiligo 4.9 (Krüger and Schallreuter 2015), erythema of rosacea 6.2 (Bewley et al. 2016), acne scars 5 (Chuah and Goh 2015), and lower than atopic dermatitis 8.5 (Beikert et al. 2014),

pemphigus vulgaris and foliaceus 10.2 (Sung, Roh, and Kim 2015), and psoriasis 12.74 (Kouris et al. 2016).

Although physicians use clinical disease severity as an important tool in decision making and evaluation of treatment efficacy, it has been shown that interpretation of HRQoL based on disease severity may be clinically unreliable (Jayaprakasam et al. 2002). This is because — as discussed before — perception of HRQoL is highly subjective and is confounded by many other factors (Chen 2012). To explore this aspect in our sample, the relationship between clinical severity and patient-reported quality of life for those who received a diagnosis with melasma and PIH was evaluated.

The modified MASI score was used to evaluate melasma severity and mean score was 5.3 ± 3.46 . This was much lower compared with those reported by Dominguez et al (mean score 10) [(Dominguez et al. 2006)], and Freitag et al. (mean 10.6 ± 6) [(Freitag et al. 2008)], suggesting that our patient population had milder disease severity. A possible explanation may be that patients had better access to health care and sought treatment early or they may have had prior treatment.

Moreover, MASI had a weak, although significant, correlation with DLQI scores (spearman's rho coefficient 0.32, $p < 0.001$) and SDIEQ (spearman's rho coefficient 0.31, $p < 0.002$ value) corroborating with other studies that clinical severity may not be the only

criteria used by patients to assess disease burden (Balkrishnan et al. 2003) (Dominguez et al. 2006).

For PIH, the novel PAHPI total score was used (mean $10.32 \pm SD 3.3$) and most patients were classified as having very mild to mild disease severity. Although scores were very mild to mild, the mean DLQI (7.89) was significantly higher when compared with patients with other hyperpigmentation disorders, suggesting that although they may have had mild disease, it still significantly impacts their quality of life. PAHPI, which also correlated weakly with the quality of life measurements, DLQI and SDIEQ (spearman's rho coefficient 0.07, $p = 0.65$) (spearman's rho coefficient 0.074, $p = 0.6$ value).

In the absence of a specific health-related quality of life instrument (HRQoL) for skin hyperpigmentation, we used the *Skin Discoloration Impact Evaluation Questionnaire* (SDIEQ) created by Balkrishnan et al., and the validated but not disease specific questionnaire developed by Finlay et al., *Dermatology Quality of Life Index* (DLQI) (Finlay and Khan 1994). Although the DLQI is a reliable and easy to use HRQoL questionnaire, many questions focus on physical limitations and places less value on psychological impact of skin diseases (Nijsten 2012), making it better to assess inflammatory diseases but not ideal for conditions with a greater psychological impact such as hyperpigmentation disorders. On the other hand, the *Skin Discoloration Impact Evaluation Questionnaire* (SDIEQ) is a brief questionnaire whose questions focus mostly

on patients' feelings, experiences, effort placed on hiding discoloration, and effect on leisure and social activities. The SDIEQ could be a practical and short replacement for the DLQI; however, it is not validated for use in hyperpigmentation disorders. We aimed to assess how the two questionnaires correlated with each other in an attempt to roughly validate the SDIEQ. We found a strong correlation between the DLQI and SDIEQ (spearman rho of 0.79 $p=0.00$), which suggests that SDIEQ scores can acceptably reflect DLQI scores; however, further validation studies with more vigorous methodology are required to find out possible cut-off values for the SDIEQ that can accurately reflect patients' quality of life.

The two factors in our study that were significantly associated with DLQI are type of hyperpigmentation disorder and disease duration. One study with a much smaller sample size of 112 patients using different statistical analyses but similar categorization of disease duration demonstrated that patients with melasma for longer periods had significantly higher Spanish-language Melasma Quality of Life (Sp-MELASQoL). Of note, these patients also had higher MASI (Dominguez et al. 2006). In contrast, we found that longer disease duration was associated with lower DLQI and better health-related quality of life (HRQoL). The reason for this discrepancy and that our patient population feels that their skin condition is less of a burden over time needs to be further investigated. No correlation was found between DLQI and years of education, age, visit type, and use of sunscreen.

A large amount of patient (69%) reported that they did not know their diagnosis, the remaining of those patients reported they knew their diagnosis; however, only 30% actually had the correct diagnosis. Therefore, out of our total sample population, only 30% knew their diagnosis correctly. Multiple factors including poor health literacy, language barriers, and discordant diagnosis could be involved. On the other hand, most patients who knew their diagnosis had accurate perception (knowledge) regarding predisposing factors and generally adopted sun protective behaviors with 69% reporting using sunscreen. Of note, overall, few adopted other important sun protective measures such as seeking shade and wearing hats. The reported rate for sunscreen use in this study was similar to that reported for patients with multiple primary melanoma (70%) [(Warren et al. 2015)]. However, our study sample rate of sunscreen use was found to be not only be much higher than rates reported among the general population, 15% in men and 30% in women (Holman et al. 2015) but also higher than rates among those with photosensitivity disorders, at about 50% among patients with cutaneous lupus erythematosus (Vilá et al. 1999), and among patients with cutaneous malignancies such as single primary melanoma with 45–57% reporting sunscreen use. This raises the questions about motivational factors behind the use of sunscreen. A possible explanation might be related to the Hawthorn bias (Parsons 1974), in which respondents tend to modify or improve aspects of their behaviors when they are aware of being observed. Another explanation of this finding may be the gender imbalance in this study sample with 90% being female and that females are more likely to use sunscreen and other forms of sun protection than males (Altsitsiadis et al. 2012). Moreover, patients in this study

were presenting to a tertiary dermatological care center and this may have selected a more health conscious population. Patients who attributed their hyperpigmentation disorder to the sun were more likely to use and reapply the recommended SPF. This finding suggests that educating patients regarding their condition could possibly lead to increased compliance with sun protective measures.

Regarding patients' beliefs, attitudes, and practices towards skin hyperpigmentation, the vast majority of patients (97%) trusted dermatologist expertise to treat their skin disorder. Most patients reported that they were the first to notice their skin lesions (self-perceived), and those with melasma and other hyperpigmentation disorders reported the medical doctor as the first source of information. Those with post-inflammatory hyperpigmentation notably used the internet as the first source of information. About half of the patients in this study reported the use of over-the-counter skin (OTC) lightening products, and this behavior was more common among patients with melasma. The prevalence of skin lightening use varies worldwide, ranging from 26% in West Africa (Del Giudice and Yves 2002) to 60% in Jordan (Hamed et al. 2010), and 80% in African descendants living in Paris (Petit et al. 2006). In our study, 31% of patients that used prescription hydroquinone for treatment of their hyperpigmentation reported improvement. Hydroquinone use is popular among patients with hyperpigmentation disorders (Nordlund, Grimes, and Ortonne 2006), and its reported improvement versus placebo in a clinical trial was around 40% (Ennes, Paschoalick, and Alchorne 2000). Of note, about 30% of patients in our study who reported using

prescription strength hydroquinone used it for longer than 5 months. Therefore, it is important to educate patients about the side effects of long term use of hydroquinone containing products including allergic contact dermatitis, hyperpigmentation, nail discoloration, and exogenous ochronosis among others (Ladizinski, Mistry, and Kundu 2011). Given the widespread use of skin lightening products, it is important that dermatologists discuss in detail the amount and location to apply the cream and treatment duration. Patient should be aware that although effective, hydroquinone-containing products should be used for short amount of time and other agents are available for maintenance therapy.

Although both melasma and PIH treatments are quite similar being based upon sun protection and topical agents as first line therapy, many more melasma patients than PIH patients were prescribed hydroquinone and triple combination cream. This could be interpreted in different ways, treating physicians may not be aware of the importance of early treatment of PIH in darker skin types, as the condition may fade with time or simply patients are not familiar or do not discuss treatment options with their physician. Coinciding with this, monthly expenditure with skin lightening products was higher in patients diagnosed with melasma. Also, melasma patients were significantly more likely to obtain products from abroad. We hypothesize that this could be due to higher medication cost in U.S. pharmacies, additionally most of our sample was non-US born and likely have access to medications from their home countries. Of note, patients were not always aware of the ingredients in their lightening creams, and only few reported they

had tried kojic acid (5%), hydroquinone (43.1%), azelaic acid (4%), antioxidants (9.1%), and steroids (6.6%).

Hormonal contraceptives are associated with triggering and worsening of melasma (J P Ortonne et al. 2009). We found that the use of birth control methods (47.5%) was significantly higher in our melasma patients, and the percentage was comparable to the reported rates of hormonal contraception (53%) by Ortonne et al. (J P Ortonne et al. 2009). This is likely attributed to the majority of patients being of reproductive age, yet as hormonal contraception is a possible melasma trigger it is important to counsel patients case by case regarding non-hormonal birth control options.

When patient's knowledge about their disease is not adequate this is likely to result in poor treatment compliance (J. Lin et al. 2008). We found factors of a higher level of education, younger age, longer duration of having the condition, and current use of sunscreen to have 2.4, 2, 3.7, and 2.4 significantly higher odds of knowing their diagnosis. The significant association with sunscreen ($p < 0.02$) suggests that appropriate knowledge and understanding of one's skin disorder plays an important role in treatment compliance. Additionally, age younger than 45 years old was associated with a higher odds of diagnosis knowledge. This could possibly be explained by younger patients being more concerned by their skin appearance and therefore seeking information and/or medical help sooner than older patients. Therefore, patients 45 years or older with less

years of formal education and those newly diagnosed may benefit from appropriate education and counseling time by their treating physician.

Limitations

Although our sample was racially and ethnically diverse, our results may not be fully generalizable given our recruitment sites that provide care for an underserved population and one that is located in a primarily Hispanic area. Our results from DLQI and SIEDQ may be overestimated as these patients were seeking dermatologic treatment in a center specialized in ethnic skin. Furthermore, this study is based mostly on self-reported information, which is subject to recall bias. Another limitation was the use of DLQI to assess the impact of melasma on QoL, in spite high correlation with *Melasma Quality of Life* (MELASQoL) scale. Because of this, emotional and psychosocial aspects may have been neglected. Also patients unwilling to complete our survey were excluded, which was 17 correlating to 5.7% of patients questioned. Due to sample gender disparity, we did not include gender in the multivariate analysis and this is factor related to quality of life.

CHAPTER SIX: CONCLUSION

The effect of hyperpigmentation disorders on patients' quality of life is not negligible and was found to be higher for those complaining of melasma and PIH in this study. Furthermore, the magnitude of effect on their quality of life was not correlated with the clinical severity. This signifies the importance of using a holistic approach that seeks to explore, acknowledge, and find ways to mitigate the difficulties inflicted by hyperpigmentation disorders on patients' life, regardless of the clinical severity. Extra care should be taken regarding eliciting discussion with patients complaining of melasma and PIH, and those who had the disease for less than one year, given the significantly higher impact on their perceived quality of life found in this study. We found that patients' who are younger, who use sunscreen more, who had the disease longer, and who had higher years of education are more likely to know their diagnosis. Patient's knowledge of the diagnosis is associated with better compliance (J. Lin et al. 2008); therefore, making sure that the patient is aware of his/her diagnosis should be a priority during every medical encounter. Although all patients should be educated about their diagnosis, more time should be spent educating those who had high school education or less, those who use sunscreen less, and who are older than 45 years of age about their disease. Given the percentage of those who were not aware of their diagnosis (69%), a review of the methods of communication between dermatologists and patients are needed. One of the reasons for patients' failure to know their diagnosis might be attributed to language barriers (Partida 2007), use of education-level inappropriate language, or a language that is heavily infiltrated with scientific/medical jargon . Further

studies are needed to examine specific factors associated with patients' failure to know their dermatological diagnosis to mitigate this problem and create a more patient-centered approach. An overwhelming 97% of patients view the dermatologist as the best person to treat their condition, so it is our responsibility to accurately diagnose, treat, and counsel patients while not underestimating the impact of skin hyperpigmentation on patients' daily life.

APPENDIX

APPENDIX I. Informed consent

RESEARCH CONSENT FORM

Title of Project: Skin Hyperpigmentation Questionnaire

Principal Investigator: Neelam Vashi

Background

You are being asked to participate in a research study because you have: skin hyperpigmentation (dark/brown spots) on your face or body.

The study will involve a onetime questionnaire survey with questions aimed at learning more about your knowledge and the effects of your skin condition has had on your life. Your participation in this study will only be for the day that you fill out the survey. Please read the information carefully. If you have questions please ask the investigator or study staff. You should only complete this survey when you feel completely informed. If you read any words that are not clear to you, please ask the Principal investigator or study personal to explain them to you.

Purpose

This is a research study to find out more about your attitudes and the impact of your skin condition in your life. You will be one of approximately 200–300 subjects to be asked to participate in this study.

The research will take place at the following location(s): BMC and EBNHC

After you agree to be in this study, a study investigator will provide you with the survey

form to be completed in one sitting. The survey will consist of 32 questions related to your current perception of your health and skin condition. You may skip any questions that make you feel uncomfortable. Survey completion will take approximately 15 minutes total. This survey will be anonymous and there will be no questions that will ask for any identifying information.

Right to Refuse or Withdraw

Taking part in this study is voluntary. You have the right to refuse to take part in this study. If you decide to be in the study and then change your mind, you can withdraw from the research. Your participation is completely up to you.

Subject's Rights

By consenting to participate in this study you do not waive any of your legal rights.

Giving consent means that you have heard or read the information about this study and that you agree to participate. You will be given a copy of this form to keep.

You may obtain further information about your rights as a research subject by calling the Office of the Institutional Review Board of Boston University Medical Center at 617-638-7207. The investigator or a member of the research team will try to answer all of your questions. If you have questions or concerns at any time, contact the PI, Dr. Neelam Vashi and Co-investigator: Mayra Maymone at (857) 206-3895.

APPENDIX II. Inclusion and exclusion criteria

Inclusion criteria

1. Individuals 18 years or older
2. Individuals referred to dermatology for any hyperpigmentation disorder
3. Individuals willing and able to answer the questionnaire in English, Portuguese, or Spanish.

Exclusion criteria

1. Individuals who do not speak English, Portuguese, or Spanish
2. Any patient who cannot give consent due to intellectual disability

APPENDIX III. Non-validated skin questionnaire

Skin Hyperpigmentation Questionnaire

Have you taken this survey before? Yes No → END SURVEY IF “YES”

Age: _____ years

Gender: Female Male

Were you born in the USA: Yes No → Country of Origin (specify): _____

Primary language spoken: English Spanish Portuguese French
 Other (specify): _____

Race (*check all that apply*): White Black or African American
 Asian American Indian or Alaska Native Native
 Hawaiian or other Pacific Islander

Ethnicity: Hispanic or Latino Not Hispanic or Latino

Job/occupation: Not working Working → Occupation:

Marital Status: Single Married Separated Widowed
 Living in common law Divorced

Education (highest): Lower/elementary school Middle school High school
 diploma
 College degree Graduate school

We would like to know more about you and your skin care.

Please check the box that best describes your answer.

1. Where do you have dark/brown spots? (*check all that apply*) Face Body

↳ **How long** have you had dark/brown spots?

1–6 months 7–12 months 1–5 years 5–10 years 10–15 years >15 years

2. Do you think the dark/brown spots are due to the sun? Yes No I don't know
 If not from the sun, what do you think they are from? _____

3. Do you think the dark/brown spots are caused by

a. Your genetic background? Yes No I don't know

- b. Pregnancy or hormones? Yes No I don't know
- c. Previous acne spots or rash? Yes No I don't know
- 4.** Are you currently using a lotion, cream, or sunscreen with Sun Protection Factor (SPF)? Yes No I don't know
- ↳ If **YES**, what Sun Protection Factor (SPF) are you using?
 10–20 21–50 51–100 >100 I don't know
- ↳ If **YES**, how often do you re-apply sunscreen?
 Every 2 hours 3 x day 2 x day 1 x day Occasionally
 Almost never
- ↳ If **YES**, is your sunscreen broad spectrum?
 Yes No I don't know
- 5.** On average, how many hours are you in the sun between 10 am – 4 pm?
- ↳ Weekends: 1 or less 2 3 4 5 6
- ↳ Weekdays: 1 or less 2 3 4 5 6
- 6.** When you are outdoors in the sun, how often do you do each of the following?
- ↳ Wear a hat: Rarely or never Sometimes Usually Always
- ↳ Stay in shade or under umbrella: Rarely or never Sometimes Usually
 Always
- 7.** Do you think your ethnicity or racial background makes you more prone to have dark spots?
 Yes No I don't know
- 8.** Do any of your family members have the same skin condition?
 Yes No I don't know
- 9.** How much do the dark/brown spots bother you?
 Very much A lot A little Not at all
- 10.** What is the name/diagnosis of your brown spots?

- 1 Post-Inflammatory Hyperpigmentation
 2 Melasma
 3 Solar Lentigo/sun spots
 4 Freckles
 5 Moles/nevi
 6 Other: _____
 7 I don't know

11. Have you ever heard of the following before?

- Post-Inflammatory Hyperpigmentation? 1 Yes 2 No
 → Melasma? 1 Yes 2 No
 → Solar Lentigo/sun spots? 1 Yes 2 No
 → Freckles? 1 Yes 2 No
 → Moles/nevi? 1 Yes 2 No

12. Did you first notice the dark/brown spots or did your doctor?

- 1 Me 2 The doctor 3 Other: _____

13. Where did you first go for help for your dark/brown spots?

- 1 Internet 2 Friend 3 Doctor 4 Family member
 5 Other: _____

14. Have you ever tried any over-the-counter lightening creams? (*include all the products you remember*)

1 Yes 2 No 3 I don't know

→ If **YES**, what product have you tried? _____

Did it help lighten the dark/brown spots?

1 Yes 2 No 3 I don't know

→ If **YES**, what product have you tried? _____

Did it help lighten the dark/brown spots?

1 Yes 2 No 3 I don't know

→ If **YES**, what product have you tried? _____

Did it help lighten the dark/brown spots?

1 Yes 2 No 3 I don't know

→ If **YES**, what product have you tried? _____

Did it help lighten the dark/brown spots?

1 Yes 2 No 3 I don't know

15. How much do you think you spend monthly on “over-the-counter” products to help your dark/brown spots? 1 \$0 2 < \$30 3 \$30–50 4 \$50–100 5 > \$100

16. Do you believe that the more expensive medicines/products help lighten your dark/brown spots more? 1 Yes 2 No 3 I don't know

17. Where did you get the cream that helped your dark/brown spots? (*check all that apply*)

1 US pharmacy 2 Abroad/home country 3 Community/neighbourhood store
4 Got from a friend 5 Not relevant 5 Other: _____

18. Have you ever used a prescription product to help lighten your dark/brown spots?

1 Yes 2 No 3 I don't know

→ If **YES**, did you consult a doctor/physician to obtain the product?

1 Yes 2 No 3 I don't know

19. Have you ever used a product containing any of the following?

a. Hydroquinone? Yes No I don't know

If **YES**, did the dark/brown spots become lighter? Yes No I don't know

If **YES**, what is the longest amount of time that you used it for?

< 3 months 3–5 months 6–12 months

1–5 years 5–10 years >10 years

b. Kojic Acid? Yes No I don't know

If **YES**, did the dark/brown spots become lighter? Yes No I don't know

c. Azelaic Acid? Yes No I don't know

If **YES**, did the dark/brown spots become lighter? Yes No I don't know

d. Tri-luma? Yes No I don't know

If **YES**, did the dark/brown spots become lighter? Yes No I don't know

e. Antioxidants? Yes No I don't know

If **YES**, did the dark/brown spots become lighter? Yes No I don't know

f. Steroid cream? Yes No I don't know

If **YES**, did the dark/brown spots become lighter? Yes No I don't know

20. Do you have a personal brand of products that you feel is better to treat dark/brown spots?

Yes No I don't know

↳ If **YES**, please write the name and/or brand: _____

21. Have you ever used any of the following?

a. Birth control? Yes No I don't know

If yes, what type do you use?

Copper IUD Oral contraceptive Mirena/skyla IUD

Depo-shot Implanon Other: _____

b. Thyroid medication? Yes No I don't know

22. Do you think that the best person to help treat your skin condition is:

- ₁ Primary care doctor ₂ Dermatologist ₃ Aesthetician
₄ Friend who has the same skin condition ₅ Other:

To be completed by MD

Date:

Study Number:

Diagnosis:

Skin type: I II III IV V VIFirst visit ₁ or Follow-up visit from: BMC/EBNC ₃ Outside Dermatology**BSA:****Body site:****MASI modified score:**Melasma pattern: Centro-facial Malar Mandibular Combined Body site:Wood's light: Epidermal Dermal Mixed Inapparent

Forehead:

Left Malar + Right malar:

Chin:

Modified MASI score: Forehead 0.3 (D) Area + right malar 0.3 (D)Area + left malar 0.3 (D)A + chin 0.1 (D)A.

Area

0=no involvement

1=<10%

2=10–29%

3=30–49%

4=50–69%

5=70–89%

6=90–100%

Darkness

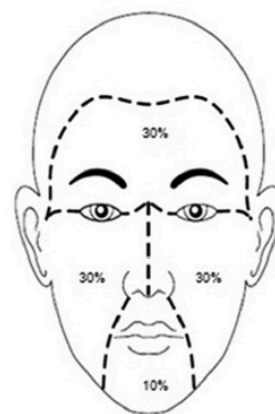
0=normal skin color

1=barely visible

2=mild hyperpigmentation;

3=moderate

4=severe



Scoring the postacne hyperpigmentation index

Weighted score (S)	Median lesion size
2	<3 mm
4	3–6 mm
6	7–10 mm
8	>10 mm

Weighted score (I)	Median lesion intensity
3	Slightly darker than surrounding skin
6	Moderately darker than surrounding skin
9	Significantly darker than surrounding skin

Weighted score (N)	No. of lesions
1	1–15
2	16–30
3	31–45
4	46–60
5	>60

Total postacne hyperpigmentation index = S + I + N; score range: 6–22.

APPENDIX IV. DLQI

DERMATOLOGY LIFE QUALITY INDEX**DLQI SCORE**

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please tick ⇒ one box for each question.

1. Over the last week, how **itchy, sore, painful** or **stinging** has your skin been?
 3 Very much 2 A lot 1 A little 0 Not at all 0 Not relevant
2. Over the last week, how **embarrassed** or **self-conscious** have you been because of your skin?
 3 Very much 2 A lot 1 A little 0 Not at all 0 Not relevant
3. Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **garden**?
 3 Very much 2 A lot 1 A little 0 Not at all 0 Not relevant
4. Over the last week, how much has your skin influenced the **clothes** you wear?
 3 Very much 2 A lot 1 A little 0 Not at all 0 Not relevant
5. Over the last week, how much has your skin affected any **social** or **leisure** activities?
 3 Very much 2 A lot 1 A little 0 Not at all 0 Not relevant
6. Over the last week, how much has your skin made it difficult for you to do any **sport**?
 3 Very much 2 A lot 1 A little 0 Not at all 0 Not relevant
7. Over the last week, has your skin prevented you from **working** or **studying**?
 3 Yes 0 No 0 Not relevant
 ↳ If "No", over the last week how much has your skin been a problem at **work** or **studying**? 2 A lot 1 A little 0 Not at all
8. Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?
 3 Very much 2 A lot 1 A little 0 Not at all 0 Not relevant
9. Over the last week, how much has your skin caused any **sexual difficulties**?

3 Very much 2 A lot 1 A little 0 Not at all 0 Not relevant

10. Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?

3 Very much 2 A lot 1 A little 0 Not at all 0 Not relevant

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APPENDIX V. Skin Discoloration Impact Evaluation Questionnaire (SDIEQ)

Skin Discoloration Impact Evaluation Questionnaire

Q1. Over the last week, how **embarrassed** or **self-conscious** have you been because of your skin?

3 Very much 2 A lot 1 A little 0 Not at all 0 Not relevant

Q2. Over the last week, how much have **people focused** on your **skin discoloration** rather than on what you are saying or doing?

3 Very much 2 A lot 1 A little 0 Not at all 0 Not relevant

Q3. Over the last week, how much the discoloration made you **feel unattractive** from others?

3 Very much 2 A lot 1 A little 0 Not at all 0 Not relevant

Q4. Over the last week, how much **efforts** have you **put into hiding** your skin discoloration from other?

3 Very much 2 A lot 1 A little 0 Not at all 0 Not relevant

Q5. Over the last week, how much has your skin affected any of **your social or leisure activities**?

3 Very much 2 A lot 1 A little 0 Not at all 0 Not relevant

BIBLIOGRAPHY

- Abad-Casintahan, Flordeliz, Steven Kim Weng Chow, Chee Leok Goh, Raj Kubba, Nobukazu Hayashi, Nopadon Noppakun, JoAnn See, Dae Hun Suh, Li Hong Flora Xiang, and Sewon Kang. 2016. "Frequency and Characteristics of Acne-Related Post-Inflammatory Hyperpigmentation." *Journal of Dermatology*, January. doi:10.1111/1346-8138.13263.
- Adameyko, Igor, Francois Lallemand, Jorge B. Aquino, Jorge A. Pereira, Piotr Topilko, Thomas Müller, Nicolas Fritz, et al. 2009. "Schwann Cell Precursors from Nerve Innervation Are a Cellular Origin of Melanocytes in Skin." *Cell* 139 (2): 366–379. doi:10.1016/j.cell.2009.07.049.
- Al-Mutairi, N., and M. El-Khalawany. 2010. "Clinicopathological Characteristics of Lichen Planus Pigmentosus and Its Response to Tacrolimus Ointment: An Open Label, Non-Randomized, Prospective Study." *Journal of the European Academy of Dermatology and Venereology* 24 (5): 535–540. doi:10.1111/j.1468-3083.2009.03460.x.
- Alexis, Andrew F., Amanda B. Sergay, and Susan C. Taylor. 2007. "Common Dermatologic Disorders in Skin of Color: A Comparative Practice Survey." *Cutis* 80 (5): 387–394. <http://www.ncbi.nlm.nih.gov/pubmed/18189024>.
- Alsaad, Salman M S, and Maryann Mikhail. 2013. "Periocular Hyperpigmentation: A Review of Etiology and Current Treatment Options." *Journal of Drugs in Dermatology* 12 (2): 154–157.
- Altsitsiadis, E., T. Undheim, E. De Vries, B. Hinrichs, E. Stockfleth, and M. Trakatelli. 2012. "Health Literacy, Sunscreen and Sunbed Use: An Uneasy Association." *British Journal of Dermatology* 167 (Suppl. 2): 14–21. doi:10.1111/j.1365-2133.2012.11082.x.
- Aoki, H., O. Moro, H. Tagami, and J. Kishimoto. 2007. "Gene Expression Profiling Analysis of Solar Lentigo in Relation to Immunohistochemical Characteristics." *British Journal of Dermatology* 156 (6): 1214–1223. doi:10.1111/j.1365-2133.2007.07830.x.
- Bahadir, Sevgi, Ümit Çobanoğlu, Gülseren Çimsit, Savas Yayli, and Köksal Alpay. 2004. "Erythema Dyschromicum Perstans: Response to Dapsone Therapy." *International Journal of Dermatology* 43 (3): 220–222. doi:10.1111/j.1365-4632.2004.01984.x.
- Balkrishnan, R, A J McMichael, F T Camacho, F Saltzberg, T S Housman, S Grummer, S R Feldman, and M-M Chren. 2003. "Development and Validation of a Health-

- Related Quality of Life Instrument for Women with Melasma.” *British Journal of Dermatology* 149 (3): 572–577. doi:5419 [pii].
- Beikert, F. C., A. K. Langenbruch, M. A. Radtke, T. Kornek, S. Purwins, and M. Augustin. 2014. “Willingness to Pay and Quality of Life in Patients with Atopic Dermatitis.” *Archives of Dermatological Research* 306 (3): 279–286. doi:10.1007/s00403-013-1402-1.
- Bellew, Supriya G, and Tina S Alster. 2004. “Treatment of Exogenous Ochronosis with a Q-Switched Alexandrite (755 Nm) Laser.” *Dermatologic Surgery* 30 (4 Pt 1): 555–558. doi:10.1111/j.1524-4725.2004.30177.x.
- Bertolotto, Corine, Patricia Abbe, Timothy J. Hemesath, Karine Bille, David E. Fisher, Jean Paul Ortonne, and Robert Ballotti. 1998. “Microphthalmia Gene Product as a Signal Transducer in cAMP-Induced Differentiation of Melanocytes.” *Journal of Cell Biology* 142 (3): 827–835. doi:10.1083/jcb.142.3.827.
- Bewley, Anthony, Joseph Fowler, Helmut Schöfer, Nabil Kerrouche, and Vincent Rives. 2016. “Erythema of Rosacea Impairs Health-Related Quality of Life: Results of a Meta-Analysis.” *Dermatology and Therapy* 6 (2): 237–247. doi:10.1007/s13555-016-0106-9.
- Bolognia, Jean L., Joseph L. Jorizzo, and Julie V. Schaffer. 2012. *Dermatology*. 3rd ed. Elsevier Health Sciences. doi:9780723435716.
- Burke, Pa, and Hi Maibach. 1997. “Exogenous Ochronosis.” *Journal of Dermatological Treatment* 8 (1): 21–26. doi:10.3109/09546639709160504.
- Byrom, Lisa, Sarah Barksdale, David Weedon, and Jim Muir. 2016. “Unstable Solar Lentigo: A Defined Separate Entity.” *Australasian Journal of Dermatology*, February. doi:10.1111/ajd.12447.
- Castanedo-Cazares, Juan Pablo, Diana Hernandez-Blanco, Blanca Carlos-Ortega, Cornelia Fuentes-Ahumada, and Bertha Torres-Álvarez. 2014. “Near-Visible Light and UV Photoprotection in the Treatment of Melasma: A Double-Blind Randomized Trial.” *Photodermatology, Photoimmunology and Photomedicine* 30 (1): 35–42. doi:10.1111/phpp.12086.
- Chang, Sung Eun, Hyun Woo Kim, Jae Min Shin, Ji Hyun Lee, Jung Im Na, Mi Ryung Roh, Jong Hee Lee, Ga Young Lee, and Joo Yeon Ko. 2015. “Clinical and Histological Aspect of Erythema Dyschromicum Perstans in Korea: A Review of 68 Cases.” *Journal of Dermatology* 42 (11): 1053–57. doi:10.1111/1346-8138.13002.
- Charlín, Raúl, Carlos B. Barcaui, Bernard Kawa Kac, Deborah Brazuna Soares, Rosa Rabello-fonseca, and Luna Azulay-abulafia. 2008. “Hydroquinone-Induced

- Exogenous Ochronosis: A Report of Four Cases and Usefulness of Dermoscopy.” *International Journal of Dermatology* 47 (1): 19–23. doi:10.1111/j.1365-4632.2007.03351.x.
- Chen, Suephy C. 2012. “Health-Related Quality of Life in Dermatology: Introduction and Overview.” *Dermatologic Clinics* 30(2): 205-208, xiii. doi:10.1016/j.det.2011.12.001.
- Chowdary, Sandhya, Meera Mahalingam, and Neelam A. Vashi. 2014. “Reading Between the Layers.” *American Journal of Dermatopathology* 36 (12): 989–991. doi:10.1097/DAD.000000000000142.
- Chuah, Sai Yee, and Chee Leok Goh. 2015. “The Impact of Post-Acne Scars on the Quality of Life Among Young Adults in Singapore.” *Journal of Cutaneous and Aesthetic Surgery* 8 (3): 153–158. doi:10.4103/0974-2077.167272.
- Correa, Marisol Carrillo, Elisa Vega Memije, Gilberto Vargas-Alarcón, Roberto Arenas Guzmán, Florencia Rosetti, Victor Acuña-Alonzo, Nonantzin Martínez-Rodríguez, and Julio Granados. 2007. “HLA-DR Association with the Genetic Susceptibility to Develop Ashy Dermatitis in Mexican Mestizo Patients.” *Journal of the American Academy of Dermatology* 56 (4): 617–620. doi:10.1016/j.jaad.2006.08.062.
- Davis, Erica C, and Valerie D Callender. 2010. “Postinflammatory Hyperpigmentation: A Review of the Epidemiology, Clinical Features, and Treatment Options in Skin of Color.” *Journal of Clinical and Aesthetic Dermatology* 3 (7): 20–31.
- Del Giudice, Pascal, and Pinier Yves. 2002. “The Widespread Use of Skin Lightening Creams in Senegal: A Persistent Public Health Problem in West Africa.” *International Journal of Dermatology*, 41:69–72. doi:10.1046/j.1365-4362.2002.01335.x.
- Dogliotti, M, and M Leibowitz. 1979. “Granulomatous Ochronosis – a Cosmetic-Induced Skin Disorder in Blacks.” *South African Medical Journal = Suid-Afrikaanse Tydskrif Vir Geneeskunde* 56 (19): 757–760.
- Dominguez, Arturo R, Rajesh Balkrishnan, Allison R Ellzey, and Amit G Pandya. 2006. “Melasma in Latina Patients: Cross-Cultural Adaptation and Validation of a Quality-of-Life Questionnaire in Spanish Language.” *Journal of the American Academy of Dermatology* 55 (1): 59–66. doi:10.1016/j.jaad.2006.01.049.
- Dunwell, Patricia, and Arlene Rose. 2003. “Study of the Skin Disease Spectrum Occurring in an Afro-Caribbean Population.” *International Journal of Dermatology*, 42: 287–289. doi:10.1046/j.1365-4362.2003.01358.x.

- Ennes, SBP, RC Paschoalick, and M Mota De Avelar Alchorne. 2000. "A Double-Blind, Comparative, Placebo-Controlled Study of the Efficacy and Tolerability of 4% Hydroquinone as a Depigmenting Agent in Melasma." *Journal of Dermatological Treatment* 11 (3): 173–179. doi:10.1080/09546630050517333.
- Field, Andy. 2009. *Discovering Statistics Using SPSS. Statistics*. Vol. 58.
- Findlay, G H, J G Morrison, and I W Simson. 1975. "Exogenous Ochronosis and Pigmented Colloid Milium from Hydroquinone Bleaching Creams." *British Journal of Dermatology* 93 (6): 613–622. <http://www.ncbi.nlm.nih.gov/pubmed/1220808>.
- Finlay, a Y, and G K Khan. 1994. "Dermatology Life Quality Index (DLQI) – a Simple Practical Measure for Routine Clinical Use." *Clinical and Experimental Dermatology* 19 (3): 210–216. doi:10.1111/j.1365-2230.1994.tb01167.x.
- Freitag, Fernanda M., T. F. Cestari, L. R. Leopoldo, P. Paludo, and J. C. Boza. 2008. "Effect of Melasma on Quality of Life in a Sample of Women Living in Southern Brazil." *Journal of the European Academy of Dermatology and Venereology*. doi:10.1111/j.1468-3083.2007.02472.x.
- Gil, Inmaculada, Sonia Segura, Estela Martínez-Escala, Josep Lloreta, Susana Puig, Mariano Vélez, Ramón M Pujol, and Josep E Herrero-González. 2010. "Dermoscopic and Reflectance Confocal Microscopic Features of Exogenous Ochronosis." *Archives of Dermatology* 146 (9): 1021–1025. doi:10.1001/archdermatol.2010.205.
- Gilchrest, B A, T B Fitzpatrick, R R Anderson, and J A Parrish. 1977. "Localization of Malanin Pigmentation in the Skin with Wood's Lamp." *British Journal of Dermatology* 96 (3): 245–248. doi:10.1111/j.1365-2133.1977.tb06132.x.
- Gilkison, C, and C A Stuart. 1992. "Assessment of Patients with Acanthosis Nigricans Skin Lesion for Hyperinsulinemia, Insulin Resistance and Diabetes Risk." *Nurse Practitioner* 17 (2): 26, 28, 37 passim. <http://www.ncbi.nlm.nih.gov/pubmed/1542462>.
- Goh, C. L., and C. N. Dlova. 1999. "A Retrospective Study on the Clinical Presentation and Treatment Outcome of Melasma in a Tertiary Dermatological Referral Centre in Singapore." *Singapore Medical Journal* 40 (7): 455–458.
- Graziosi, Antonio Carmo, Marina Rodrigues Quaresma, Nilceo Schwery Michalany, and Lydia Masako Ferreira. 2013. "Cutaneous Idiopathic Hyperchromia of the Orbital Region (CIHOR): A Histopathological Study." *Aesthetic Plastic Surgery* 37 (2): 434–438. doi:10.1007/s00266-012-0048-2.

- Grimes, Pearl E, Nanaka Yamada, and Jag Bhawan. 2005. "Light Microscopic, Immunohistochemical, and Ultrastructural Alterations in Patients with Melasma." *American Journal of Dermatopathology* 27 (2): 96–101. doi:10.1097/01.dad.0000154419.18653.2e.
- Grimes, Pearl E. 2009. "Management of Hyperpigmentation in Darker Racial Ethnic Groups." *Seminars in Cutaneous Medicine and Surgery* 28 (2): 77–85. doi:10.1016/j.sder.2009.04.001.
- Halder, Rebat M., Maithily A. Nandedkar, and Kenneth W. Neal. 2003. "Pigmentary Disorders in Ethnic Skin." *Dermatologic Clinics* 21 (4): 617–628, vii. doi:10.1016/S0733-8635(03)00083-4.
- Hamed, Saja H., Reema Tayyem, Nisreen Nimer, and Hatim S. AlKhatib. 2010. "Skin-Lightening Practice among Women Living in Jordan: Prevalence, Determinants, and User's Awareness." *International Journal of Dermatology* 49 (4): 414–420. doi:10.1111/j.1365-4632.2010.04463.x.
- Harris, Paul A., Robert Taylor, Robert Thielke, Jonathon Payne, Nathaniel Gonzalez, and Jose G. Conde. 2009. "Research Electronic Data Capture (REDCap)-A Metadata-Driven Methodology and Workflow Process for Providing Translational Research Informatics Support." *Journal of Biomedical Informatics* 42 (2): 377–381. doi:10.1016/j.jbi.2008.08.010.
- Harumi, Ochi, and Chee Leok Goh. 2016. "The Effect of Melasma on the Quality of Life in a Sample of Women Living in Singapore." *Journal of Clinical and Aesthetic Dermatology*. 9 (1): 21–24.
- Henderson, C D, J A Tschen, and D G Schaefer. 1988. "Simultaneously Active Lesions of Vitiligo and Erythema Dyschromicum Perstans." *Archives of Dermatology* 124 (8): 1258–1260. doi:10.1001/archderm.1988.01670080070022.
- Hermanns-Lê, Trinh, André Scheen, and Gérald E Piérard. 2004. "Acanthosis Nigricans Associated with Insulin Resistance : Pathophysiology and Management." *American Journal of Clinical Dermatology* 5 (3): 199–203. <http://www.ncbi.nlm.nih.gov/pubmed/15186199>.
- Hexsel, D, I Arellano, and M Rendon. 2006. "Ethnic Considerations in the Treatment of Hispanic and Latin-American Patients with Hyperpigmentation." *British Journal of Dermatology* 156 Suppl (December): 7–12. doi:10.1111/j.1365-2133.2006.07589.x.
- Hexsel, Doris, David Lacerda, Andrea S Cavalcante, Carlos A Machado Filho, Célia Luiza P V Kalil, Eloísa L Ayres, Luna Azulay-Abulafia, et al. 2013. "Epidemiology of Melasma in Brazilian Patients: A Multicenter Study." *International Journal of Dermatology* 53(4):440–444. doi:10.1111/j.1365-4632.2012.05748.x.

- Holman, Dawn M., Zahava Berkowitz, Gery P. Guy, Nikki A. Hawkins, Mona Saraiya, and Meg Watson. 2015. "Patterns of Sunscreen Use on the Face and Other Exposed Skin among US Adults." *Journal of the American Academy of Dermatology* 73 (1): 83–92. doi:10.1016/j.jaad.2015.02.1112.
- Hongbo, Yan, Charles L. Thomas, Michael A. Harrison, M. Sam Salek, and Andrew Y. Finlay. 2005. "Translating the Science of Quality of Life into Practice: What Do Dermatology Life Quality Index Scores Mean?" *Journal of Investigative Dermatology* 125 (4): 659–664. doi:10.1111/j.0022-202X.2005.23621.x.
- Huang, Yau-Li, Shyue-Luen Chang, Lih Ma, Mei-Ching Lee, and Sindy Hu. 2014. "Clinical Analysis and Classification of Dark Eye Circle." *International Journal of Dermatology* 53 (2): 164–170. doi:10.1111/j.1365-4632.2012.05701.x.
- Ichiyama, S., Y. Funasaka, Y. Otsuka, R. Takayama, S. Kawana, H. Saeki, and A. Kubo. 2016. "Effective Treatment by Glycolic Acid Peeling for Cutaneous Manifestation of Familial Generalized Acanthosis Nigricans Caused by FGFR3 Mutation." *Journal of the European Academy of Dermatology and Venereology* 30 (3): 442–445. doi:10.1111/jdv.13580.
- Ikino, Juliana Kida, Daniel Holthausen Nunes, Vanessa Priscilla Martins da Silva, Tania Silvia Fröde, and Mariana Mazzochi Sens. 2015. "Melasma and Assessment of the Quality of Life in Brazilian Women." *Anais Brasileiros de Dermatologia* 90 (2): 196–200. doi:10.1590/abd1806-4841.20152771.
- Jablonski, Nina G. 2004. "The Evolution of Human Skin and Skin Color." *Annual Review of Anthropology* 33 (1): 585–623. doi:10.1146/annurev.anthro.33.070203.143955.
- Jang, Y H, J Y Lee, H Y Kang, E-S Lee, and Y C Kim. 2010. "Oestrogen and Progesterone Receptor Expression in Melasma: An Immunohistochemical Analysis." *Journal of the European Academy of Dermatology and Venereology* 24: 1312–1316. doi:10.1111/j.1468-3083.2010.03638.x.
- Jayaprakasam, A., A. Darvay, G. Osborne, and D. McGibbon. 2002. "Comparison of Assessments of Severity and Quality of Life in Cutaneous Disease." *Clinical and Experimental Dermatology* 27 (4): 306–308. doi:10.1046/j.1365-2230.2002.01025.x.
- Joshi, Smita S., Susan L. Boone, Murad Alam, Simon Yoo, Lucile White, Alfred Rademaker, Irene Helenowski, Dennis P. West, and Roopal V. Kundu. 2009. "Effectiveness, Safety, and Effect on Quality of Life of Topical Salicylic Acid Peels for Treatment of Postinflammatory Hyperpigmentation in Dark Skin." *Dermatologic Surgery* 35 (4): 638–644. doi:10.1111/j.1524-4725.2009.01103.x.

- Kanechorn-Na-Ayuthaya, Pinyapat, Nucha Niumphradit, Kobkul Aunhachoke, Artit Nakakes, Rangsit Sittiwangkul, and Chutika Srisuttiyakorn. 2013. "Effect of Combination of 1064 Nm Q-Switched Nd:YAG and Fractional Carbon Dioxide Lasers for Treating Exogenous Ochronosis." *Journal of Cosmetic and Laser Therapy* 15 (1): 42–45. doi:10.3109/14764172.2012.748198.
- Kang, H. Y., J. S. Hwang, J. Y. Lee, J. H. Ahn, J. Y. Kim, E. S. Lee, and W. H. Kang. 2006. "The Dermal Stem Cell Factor and c-Kit Are Overexpressed in Melasma." *British Journal of Dermatology* 154 (6): 1094–1099. doi:10.1111/j.1365-2133.2006.07179.x.
- Kang, Hee Young, Itaru Suzuki, Dong Jun Lee, Jaehyun Ha, Pascale Reiniche, Jérôme Aubert, Sophie Deret, Didier Zugaj, Johannes J Voegel, and Jean-Paul Ortonne. 2011. "Transcriptional Profiling Shows Altered Expression of Wnt Pathway- and Lipid Metabolism-Related Genes as Well as Melanogenesis-Related Genes in Melasma." *Journal of Investigative Dermatology* 131: 1692–1700. doi:10.1038/jid.2011.109.
- Kang, Stephanie J, Scott A Davis, Steven R Feldman, and Amy J McMichael. 2014. "Dyschromia in Skin of Color." *Journal of Drugs in Dermatology* 13 (4): 401–406.
- Kang, W. H., K. H. Yoon, E. S. Lee, J. Kim, K. B. Lee, H. Yim, S. Sohn, and S. Im. 2002. "Melasma: Histopathological Characteristics in 56 Korean Patients." *British Journal of Dermatology* 146 (2): 228–237. doi:10.1046/j.0007-0963.2001.04556.x.
- Kanwar, A. J., S. Dogra, S. Handa, D. Parsad, and B. D. Radotra. 2003. "A Study of 124 Indian Patients with Lichen Planus Pigmentosus." *Clinical and Experimental Dermatology* 28 (5): 481–485. doi:10.1046/j.1365-2230.2003.01367.x.
- Kim, En Hyung, You Chan Kim, Eun So Lee, and Hee Young Kang. 2007. "The Vascular Characteristics of Melasma." *Journal of Dermatological Science* 46 (2): 111–116. doi:10.1016/j.jdermsci.2007.01.009.
- Kimbrough-Green, C K, C E Griffiths, L J Finkel, T A Hamilton, S M Bulengo-Ransby, C N Ellis, and J J Voorhees. 1994. "Topical Retinoic Acid (Tretinoin) for Melasma in Black Patients. A Vehicle-Controlled Clinical Trial." *Archives of Dermatology*. 130 (6): 727–733. doi:10.1001/archderm.1994.01690060057005.
- Kong, Alberta S, Robert L Williams, Robert Rhyne, Virginia Urias-Sandoval, Gina Cardinali, Nancy F Weller, Betty Skipper, et al. 2010. "Acanthosis Nigricans: High Prevalence and Association with Diabetes in a Practice-Based Research Network Consortium – A PRImary Care Multi-Ethnic Network (PRIME Net) Study." *Journal of the American Board of Family Medicine* 23 (4): 476–485. doi:10.3122/jabfm.2010.04.090221.

- Kouris, Anargyros, Christos Christodoulou, Vasiliki Efstathiou, Revekka Tsatovidou, Evangelia Torlidi-Kordera, Eftychia Zouridaki, and George Kontochristopoulos. 2016. "Comparative Study of Quality of Life and Psychosocial Characteristics in Patients with Psoriasis and Leg Ulcers." *Wound Repair and Regeneration* 24 (2): 443-446. doi:10.1111/wrr.12416.
- Koyama, Shohei, Kazuho Ikeda, Mikio Sato, Ken Shibahara, Kyoko Yuhara, Hisayuki Fukutomi, Kiyoshi Fukunaga, et al. 1997. "Transforming Growth Factor-Alpha (TGF α)-Producing Gastric Carcinoma with Acanthosis Nigricans: An Endocrine Effect of TGF α In the Pathogenesis of Cutaneous Paraneoplastic Syndrome and Epithelial Hyperplasia of the Esophagus." *Journal of Gastroenterology* 32 (1): 71-77. doi:10.1007/BF01213299.
- Krüger, C, and K Schallreuter. 2015. "Stigmatisation, Avoidance Behaviour and Difficulties in Coping Are Common Among Adult Patients with Vitiligo." *Acta Dermato Venereologica* 95 (5): 553-558. doi:10.2340/00015555-1981.
- Ladizinski, Barry, Nisha Mistry, and Roopal V Kundu. 2011. "Widespread Use of Toxic Skin Lightening Compounds: Medical and Psychosocial Aspects." *Dermatologic Clinics* 29 (1): 111-123. doi:10.1016/j.det.2010.08.010.
- Lee, Ai Young. 2014. "An Updated Review of Melasma Pathogenesis." *Dermatologica Sinica* 32 (4): 233-239. doi:10.1016/j.dsi.2014.09.006.
- . 2015. "Recent Progress in Melasma Pathogenesis." *Pigment Cell and Melanoma Research* 28 (6): 648-660. doi:10.1111/pcmr.12404.
- Leeyaphan, Charussri, Rungsima Wanitphakdeedecha, Woraphong Manuskiatti, and Kanokvalai Kulthanan. 2011. "Measuring Melasma Patients' Quality of Life Using Willingness to Pay and Time Trade-off Methods in Thai Population." *BMC Dermatology* 11 (1): 16. doi:10.1186/1471-5945-11-16.
- Lehraiki, Abdelali, Patricia Abbe, Michael Cerezo, Florian Rouaud, Claire Regazzetti, Bérengère Chignon-Sicard, Thierry Passeron, Corine Bertolotto, Robert Ballotti, and Stéphane Rocchi. 2014. "Inhibition of Melanogenesis by the Antidiabetic Metformin." *Journal of Investigative Dermatology* 134: 2589-2597. doi:10.1038/jid.2014.202.
- Lieberman R, Moy L. 2008. "Estrogen Receptor Expression in Melasma: Results from Facial Skin of Affected Patients." *Journal of Drugs in Dermatology* 7 (5): 463-465.
- Lin, Jennifer Y, and David E Fisher. 2007. "Melanocyte Biology and Skin Pigmentation." *Nature* 445 (7130): 843-50. doi:10.1038/nature05660.

- Lin, Jing, Grant Edward Sklar, Vernon Min Sen Oh, and Shu Chuen Li. 2008. "Factors Affecting Therapeutic Compliance: A Review from the Patient's Perspective." *Therapeutics and Clinical Risk Management* 4 (1): 269–286.
- Linthorst Homan, May W., Phyllis I. Spuls, John de Korte, Jan D. Bos, Mirjam A. Sprangers, and J. P W van der Veen. 2009. "The Burden of Vitiligo: Patient Characteristics Associated with Quality of Life." *Journal of the American Academy of Dermatology* 61 (3): 411–420. doi:10.1016/j.jaad.2009.03.022.
- Malakar, Subrata, Koushik Lahiri, Uttam Banerjee, S Mondal, and S Sarangi. 2007. "Periorbital Melanosis Is an Extension of Pigmentary Demarcation Line-F on Face." *Indian Journal of Dermatology, Venereology and Leprology* 73 (5): 323. doi:10.4103/0378-6323.34009.
- Matsui, Mary S., Michael J. Petris, Yoko Niki, Nevena Karaman-Jurukovska, Neelam Muizzuddin, Masamitsu Ichihashi, and Daniel B. Yarosh. 2015. "Omeprazole, a Gastric Proton Pump Inhibitor, Inhibits Melanogenesis by Blocking ATP7A Trafficking." *Journal of Investigative Dermatology* 135 (3): 834–841. doi:10.1038/jid.2014.461.
- Monestier, S., C. Gaudy, J. Gouvernet, M.A. Richard, and J.J. Grob. 2006. "Multiple Senile Lentigos of the Face, a Skin Ageing Pattern Resulting from a Life Excess of Intermittent Sun Exposure in Dark-Skinned Caucasians: A Case-Control Study." *British Journal of Dermatology* 154 (3): 438–444. doi:10.1111/j.1365-2133.2005.06996.x.
- Murphy-Chutorian, Blair, George Han, and Steven R. Cohen. 2013. "Dermatologic Manifestations of Diabetes Mellitus." *Endocrinology and Metabolism Clinics of North America* 42 (4): 869–898. doi:10.1016/j.ecl.2013.07.004.
- N., Vojackova, Hercogova J., and Fialova J. 2013. "Acanthosis Nigricans as Paraneoplastic of Internal Malignancy." *Journal of the American Academy of Dermatology* 68 (4): AB137.
<http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L70997629> \n <http://dx.doi.org/10.1016/j.jaad.2012.12.567> \n <http://sfx.library.uu.nl/utrecht?sid=EMBASE&issn=01909622&id=doi:10.1016/j.jaad.2012.12.567&atitle=Acanthosis+nigricans+as+>.
- Nijsten, Tamar. 2012. "Dermatology Life Quality Index: Time to Move Forward." *Journal of Investigative Dermatology* 132 (1): 11–13. doi:10.1038/jid.2011.354.
- Noh, Tai Kyung, Seok Joo Choi, Bo Young Chung, Jin Soo Kang, Jong Hee Lee, Mi Woo Lee, and Sung Eun Chang. 2014. "Inflammatory Features of Melasma Lesions in Asian Skin." *Journal of Dermatology* 41(9):788–794. doi:10.1111/1346-8138.12573.

- Nordlund, J J, T F Cestari, H Chan, and W Westerhof. 2006. "Confusions about Colour: A Classification of Discolorations of the Skin." *British Journal of Dermatology* 156 Suppl: 3–6. doi:10.1111/j.1365-2133.2006.07588.x.
- Nordlund, J J, P E Grimes, and J P Ortonne. 2006. "The Safety of Hydroquinone." *Journal of the European Academy of Dermatology and Venereology* 20 (7): 781–787. doi:10.1111/j.1468-3083.2006.01670.x.
- Ortonne, J P. 1990. "Pigmentary Changes of the Ageing Skin." *British Journal of Dermatology* 122 Suppl (April): 21–28. doi:10.1111/j.1365-2133.1990.tb16121.x.
- Ortonne, J P, I Arellano, M Berneburg, T Cestari, H Chan, P Grimes, D Hexsel, et al. 2009. "A Global Survey of the Role of Ultraviolet Radiation and Hormonal Influences in the Development of Melasma." *Journal of the European Academy of Dermatology and Venereology* 23 (11): 1254–1262. doi:10.1111/j.1468-3083.2009.03295.x.
- Ortonne, Jean Paul, Amit G. Pandya, Harvey Lui, and Doris Hexsel. 2006. "Treatment of Solar Lentigines." *Journal of the American Academy of Dermatology* 54 (5 Suppl. 2). doi:10.1016/j.jaad.2005.12.043.
- Pandya, Amit G., Linda S. Hynan, Rafia Bhore, Fransell Copeland Riley, Ian L. Guevara, Pearl Grimes, James J. Nordlund, et al. 2011. "Reliability Assessment and Validation of the Melasma Area and Severity Index (MASI) and a New Modified MASI Scoring Method." *Journal of the American Academy of Dermatology* 64 (1): 78–83.e2. doi:10.1016/j.jaad.2009.10.051.
- Parsons, H.M. 1974. "What Happened at Hawthorne." *Science* 183: 922–931. <http://www.praxiom.com/iso-definition.htm>.
- Partida, Yolanda. 2007. "Language Barriers and the Patient Encounter." *Virtual Mentor* 9 (8): 566–571. doi:10.1001/virtualmentor.2007.9.8.msoc1-0708.
- Passeron, T. 2013. "Melasma Pathogenesis and Influencing Factors - An Overview of the Latest Research." *Journal of the European Academy of Dermatology and Venereology* 27 (Suppl. 1): 5–6. doi:10.1111/jdv.12049.
- Pawaskar, Manjiri D, Parth Parikh, Tania Markowski, Amy J McMichael, Steven R Feldman, and Rajesh Balkrishnan. 2007. "Melasma and Its Impact on Health-Related Quality of Life in Hispanic Women." *Journal of Dermatological Treatment* 18 (1): 5–9. doi:10.1080/09546630601028778.
- Petit, Antoine, Cécile Cohen-Ludmann, Philippe Clevenbergh, Jean François Bergmann, and Louis Dubertret. 2006. "Skin Lightening and Its Complications among African people Living in Paris." *Journal of the American Academy of Dermatology* 55 (5):

873–878. doi:10.1016/j.jaad.2006.05.044.

- Pichardo, Rita, Quirina Vallejos, Steven R. Feldman, Mark R. Schulz, Amit Verma, Sara A. Quandt, and Thomas A. Arcury. 2009. “The Prevalence of Melasma and Its Association with Quality of Life in Adult Male Latino Migrant Workers.” *International Journal of Dermatology* 48 (1): 22–26. doi:10.1111/j.1365-4632.2009.03778.x.
- Piquero-Martin, J, R Perez-Alfonzo, V Abrusci, L Briceno, A Gross, W Mosca, F Tapia, and J Convit. 1989. “Clinical Trial with Clofazimine for Treating Erythema Dyschromicum Perstans. Evaluation of Cell-Mediated Immunity.” *International Journal of Dermatology* 28 (3): 198–200.
- Puri, Neerja. 2011. “A Study of Pathogenesis of Acanthosis Nigricans and Its Clinical Implications.” *Indian Journal of Dermatology* 56 (6): 678. doi:10.4103/0019-5154.91828.
- Ramirez, O, and D G Lopez Lino. 1984. “[Current Status of Ashy Dermatitis. Synonym- Erythema Dyschromicum Perstans].” *Medicina Cutánea Ibero-Latino-Americana* 12 (1): 11–18. <http://www.ncbi.nlm.nih.gov/pubmed/6376975>.
- Rawlings, A V. 2006. “Ethnic Skin Types: Are There Differences in Skin Structure and Function?” *International Journal of Cosmetic Science* 28 (2): 79–93. doi:10.1111/j.1467-2494.2006.00302.x.
- Rhee, John S, B Alex Matthews, Marcy Neuburg, Timothy L Smith, Mary L Burzynski, and Ann B Nattinger. 2004. “Skin Cancer and Quality of Life: Assessment with the Dermatology Life Quality Index.” *Dermatologic Surgery* 30 (4 Pt 1): 525–529. doi:10.1111/j.1524-4725.2004.30169.x.
- Roberts, Wendy E. 2014. “Periorbital Hyperpigmentation: Review of Etiology, Medical Evaluation, and Aesthetic Treatment.” *Journal of Drugs in Dermatology* 13 (4): 472–482. <http://www.ncbi.nlm.nih.gov/pubmed/24719068>.
- Sanchez, Miguel R. 2003. “Cutaneous Diseases in Latinos.” *Dermatologic Clinics* 21 (4): 689–697. doi:10.1016/S0733-8635(03)00087-1.
- Sanchez, N. P., M. A. Pathak, S. Sato, T. B. Fitzpatrick, J. L. Sanchez, and M. C. Mihm. 1981. “Melasma: A Clinical, Light Microscopic, Ultrastructural, and Immunofluorescence Study.” *Journal of the American Academy of Dermatology* 4 (6): 698–710. doi:10.1016/S0190-9622(81)70071-9.
- Sarkar, Rashmi, Pooja Arora, Vijay Kumar Garg, Sidharth Sonthalia, and Narendra Gokhale. 2014. “Melasma Update.” *Indian Dermatology Online Journal* 5 (4): 426–435. doi:10.4103/2229-5178.142484.

- Savory, Stephanie A, Nnenna G Agim, Rui Mao, Shayna Peter, Casey Wang, Gerardo Maldonado, Jessica Bearden Dietert, et al. 2014. "Reliability Assessment and Validation of the Postacne Hyperpigmentation Index (PAHPI), a New Instrument to Measure Postinflammatory Hyperpigmentation from Acne Vulgaris." *Journal of the American Academy of Dermatology* 70 (1): 108–114. doi:10.1016/j.jaad.2013.09.017.
- Sheth, Pratik B, Hiral A Shah, and Jayendra N Dave. 2014. "Periorbital Hyperpigmentation: A Study of Its Prevalence, Common Causative Factors and Its Association with Personal Habits and Other Disorders." *Indian Journal of Dermatology* 59 (2): 151–157. doi:10.4103/0019-5154.127675.
- Sheth, Vaneeta M, and Amit G Pandya. 2011a. "Melasma: A Comprehensive Update: Part I." *Journal of the American Academy of Dermatology* 65 (4): 689–697; quiz 698. doi:10.1016/j.jaad.2010.12.046.
- Sheth, Vaneeta M., and Amit G. Pandya. 2011b. "Melasma: A Comprehensive Update." *Journal of the American Academy of Dermatology* 65 (4): 699–714. doi:10.1016/j.jaad.2011.06.001.
- Shin, Jung U., Jihun Park, Sang Ho Oh, and Ju Hee Lee. 2013. "Oral Tranexamic Acid Enhances the Efficacy of Low-Fluence 1064-Nm Quality-Switched Neodymium-Doped Yttrium Aluminum Garnet Laser Treatment for Melasma in Koreans: A Randomized, Prospective Trial." *Dermatologic Surgery* 39 (3 Pt 1): 435–442. doi:10.1111/dsu.12060.
- Sung, Jae Yong, Mi Ryung Roh, and Soo-Chan Kim. 2015. "Quality of Life Assessment in Korean Patients with Pemphigus." *Annals of Dermatology* 27 (5): 492–498. doi:10.5021/ad.2015.27.5.492.
- Tamega, A. De A, L. D B Miot, C. Bonfietti, T. C. Gige, M. E A Marques, and H. A. Miot. 2013. "Clinical Patterns and Epidemiological Characteristics of Facial Melasma in Brazilian Women." *Journal of the European Academy of Dermatology and Venereology* 27 (2): 151–156. doi:10.1111/j.1468-3083.2011.04430.x.
- Tan, Siak-Khim. 2010. "Exogenous Ochronosis – a Diagnostic Challenge." *Journal of Cosmetic Dermatology* 9 (4): 313–317. doi:10.1111/j.1473-2165.2010.00529.x.
- Taylor, Anne, Manjiri Pawaskar, Sarah L Taylor, Rajesh Balkrishnan, and Steven R Feldman. 2008. "Prevalence of Pigmentary Disorders and Their Impact on Quality of Life: A Prospective Cohort Study." *Journal of Cosmetic Dermatology* 7 (3): 164–168. doi:10.1111/j.1473-2165.2008.00384.x.
- Taylor, Susan C. 2002. "Skin of Color: Biology, Structure, Function, and Implications for Dermatologic Disease." *Journal of the American Academy of Dermatology* 46 (2

III): 41–62. doi:10.1067/mjd.2002.120790.

Tejada, Cs Caroline Dos Santos, Raúl Andrés Mendoza-Sassi, Hiram Larangeira De Almeida, Paulo Neves Figueiredo, Victor Felipe Dos Santos Tejada, Santos Tejada, Hiram Larangeira, De Almeida Jr, Victor Felipe, and Hiram Larangeira De Almeida Jr. 2011. “Impact on the Quality of Life of Dermatological Patients in Southern Brazil.” *Anais Brasileiros de Dermatologia* 86 (6): 1113–1121. doi:S0365-05962011000600008 [pii].

Tomita, Yasushi, Kazuhisa Maeda, and Hachiro Tagami. 1989. “Mechanisms for Hyperpigmentation in Postinflammatory Pigmentation, Urticaria Pigmentosa and Sunburn.” *Dermatology* 179: 49–53. doi:10.1159/000248449.

Vashi, Neelam A., and R. V. Kundu. 2013. “Facial Hyperpigmentation: Causes and Treatment.” *British Journal of Dermatology* 69 (Suppl. 3): 41–56. doi:10.1111/bjd.12536.

Vashi, NeelamA, RoopalV Kundu, and CeciliaA Larocca. 2014. “Physiologic Pigmentation: Molecular Mechanisms and Clinical Diversity.” *Pigment International* 1 (2): 44. doi:10.4103/2349-5847.147039.

Vilá, L. M., A. M. Mayor, A. H. Valentín, S. I. Rodríguez, M. L. Reyes, E. Acosta, and S. Vilá 1999. “Association of Sunlight Exposure and Photoprotection Measures with Clinical Outcome in Systemic Lupus Erythematosus.” *Puerto Rico Health Sciences Journal* 18 (2): 89–94.

Warren, Matthew, Erin McMeniman, Agnieszka Adams, and Brian De’Ambrosio. 2015. “Skin Protection Behaviour and Sex Differences in Melanoma Location in Patients with Multiple Primary Melanomas.” *Australasian Journal of Dermatology*, July. doi:10.1111/ajd.12373.

Watanabe, Shinichi, Kenji Nakai, and Takamitsu Ohnishi. 2006. “Condition Known as ‘Dark Rings Under the Eyes’ in the Japanese Population Is a Kind of Dermal Melanocytosis Which Can Be Successfully Treatedby Q-Switched Ruby Laser.” *Dermatologic Surgery* 32 (6): 785–789. doi:10.1111/j.1524-4725.2006.32161.x.

Wilmer, Erin N, Cheryl J Gustafson, Christine S Ahn, Scott A Davis, Steven R Feldman, and William W Huang. 2014. “Most Common Dermatologic Conditions Encountered by Dermatologists and Nondermatologists.” *Cutis* 94 (6): 285–292. <http://www.ncbi.nlm.nih.gov/pubmed/25566569>.

Wu, Xin-gang, Ai-e Xu, Xiu-zu Song, Jun-hui Zheng, Ping Wang, and Hong Shen. 2010. “Clinical, Pathologic, and Ultrastructural Studies of Progressive Macular Hypomelanosis.” *International Journal of Dermatology* 49 (10): 1127–1132. doi:10.1111/j.1365-4632.2010.04492.x.

Yamaguchi, Yuji, and Vincent J Hearing. 2009. "Physiological Factors That Regulate Skin Pigmentation." *BioFactors* 35 (2): 193–199. doi:10.1002/biof.29.

———. 2014. "Melanocytes and Their Diseases." *Cold Spring Harbor Perspectives in Medicine* 4 (5): a017046–a017046. doi:10.1101/cshperspect.a017046.

Yeatman, J M, M Kilkeny, and R Marks. 1997. "The Prevalence of Seborrhoeic Keratoses in an Australian Population: Does Exposure to Sunlight Play a Part in Their Frequency?" *British Journal of Dermatology* 137: 411–414.

CURRICULUM VITAE

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Education

- **Boston University School of Medicine** - Doctor of Science in Dermatology, September 2016
- **Boston University School of Medicine** - Master of Science in Dermatology, 2012–2014 Clinic-based rotation in Dermatology
- **Instituto de Pesquisas Médicas (IPEMED)** - Specialization in Dermatology, 2011–2012
- **Anhaguera Uniderp School of Medicine** - Medical Doctor, 2004–2010
- **Uniderp Dental School** - Doctor of Dental surgery, 1999–2003

Professional experience

- Intern in dermatology, clinic based rotation, full-time student 2012–2016
- Prefeitura Municipal de Campo Grande PMCG, Primary care center at Campo Grande 20h/week, 2010–2012.
- SAMU Campo Grande, emergency medical regulator 8h/week, 2011–2012.

Relevant Course Works and Skills

1. Masters in Dermatology

- Structure and function of skin
- Basic Dermatology
- Sex transmitted disease and AIDS
- Clinical Pathological Correlation
- Clinical Dermatology
- Cutaneous Microbiology
- Photobiology
- Dermatology surgery
- Good clinical Practice in Clinical
- Biostatistics

2. Doctorate in Dermatology

- Dissertation: IRB submission and survey questionnaire with 330 subjects recruited
- Clinical Dermatology

Presentation and publications

1. **Maymone M**, Vashi NA. Progressive Macular Hypomelanosis. In P. B. Love, R. V. Kundu (Eds.), *Clinical Cases in Skin of Color: Adnexal, Inflammation, Infections, and Pigmentary Disorders* (first edition). London: Springer, ISBN 978-3-319-22391-9, November, 2015.
2. Vashi NA, **Maymone M**. Approach and Resources. In N. A. Vashi (Ed.), *Beauty and Body Dysmorphic Disorder: A Clinician's Guide* (first edition). New York: Springer Science + Business Media LLC, ISBN 978-3319178660, September, 2015.
3. Vashi NA, **Maymone M**, Kundu RV. Aging differences in ethnic skin. *J Clin Aesthet Dermatol*. 2016;9(1):31–38.
4. **Maymone M**, Gan S, and Bigby M. (2014). “Evaluating the Strength of Clinical Recommendations in the Medical Literature: GRADE, SORT, and AGREE.” *The Journal of Investigative Dermatology* 134 (10): e25. doi:10.1038/jid.2014.335.
5. **Maymone M**, Ho J, Vashi NA, Bhawan J, Generalized Dowling-Degos disease with a dyschromatosis universalis hereditaria-like phenotype. (2015). New England Dermatological Society, Boston University School of Medicine.
6. **Maymone M**, Markova A, Vashi NA, Goldberg L. (2014). Facial papules in frontal fibrosing alopecia. New England Dermatological Society, Boston University School of Medicine.
7. Larrocca C, Lam C, **Maymone M**. (2013). Diffuse Cutaneous Sarcoidosis, New England Dermatological Society, Boston University School of Medicine.
8. **Maymone M**, Rattanasirivilai P, Gan S, Miller D. Rickettsialpox. (2012). New England Dermatological Society, Boston University School of Medicine.
9. **Maymone M** et. al. (2010) Xeroderma Pigmentososo. *Congresso Médico Científico Internacional Brasil/ Itália*.
10. **Maymone M**. (2010). Ictiose Histrix. *VI Jornada Acadêmica de Medicina da Uniderp*, Campo Grande. 2010. v.2. p.20 – 20.

11. **Maymone M.** (2010). Abscesso Orbitário Unilateral Decorrente Se Sinusite Aguda Em Neonato Com 24 Dias De Vida. *VI Jornada Acadêmica de Medicina da Uniderp*, Campo Grande. v.2. p.18 – 18.

12. **Maymone M.** (2010). Aneurisma De Jugular Externa. VIII Jornada Médica da Santa Casa-Dr. William Maksoud, 2010, Campo Grande. Aneurisma De Jugular Externa.v.2. p.23 – 23.

Oral presentations

1. **Maymone M**, Vashi NA. Repigmentation of facial hypomelanosis with non-ablative fractionated laser. (2016). Oral presentation at 36th Annual Conference of the American Society for Laser Medicine and Surgery, Boston, 2016. Boston, MA.
2. **Maymone M**, Vashi NA. Skin Hyperpigmentation Disorders: Associations and Impact on Health-Related Quality of Life: Doctoral dissertation defense. Boston University Dermatology department.
3. Maymone M, Sacht G (2010). Ictiose Histrix. *VI Jornada Academica de Medicina da Uniderp*, Campo Grande. 2010. v.2. p.20 – 20.

Poster Presentations

1. Maymone M, Vashi NA, Kundu. (2016). Maturation Hyperpigmentation: A distinct entity. (2016). 12th Annual Skin of Color Scientific Symposium, Washington DC, 2016.
2. Maymone, Mayra Buainain de Castro Maymone, Vashi, Neelam. Effective treatment of exogenous ochronosis with Q-switched alexandrite laser. 2016. Poster presentation at 36th Annual Conference of the American Society for Laser Medicine and Surgery, Boston, 2016.
3. Maymone M, Vashi NA. Repigmentation of facial hypomelanosis with non-ablative fractionated laser. (2016). Poster presentation at 36th Annual Conference of the American Society for Laser Medicine and Surgery, Boston, 2016. Boston, MA.

Work in progress

1. Skin Hyperpigmentation Disorders: Associations and Impact on Health-Related Quality of Life: Doctoral dissertation.

2. Comparing the Efficacy of Combined Glycolic Acid and Salicylic Acid versus Glycolic Acid Peel Alone in the Treatment of Melasma: A Split Face Study
3. Barriers of Dermatological care at Boston Medical Center.

Languages

- Mother language: Brazilian Portuguese
- Fluent in English
- Spanish fluent spoken

Computer Skills

- Microsoft, Excel, and PowerPoint
- Epic Medical Records
- Ability to perform data entry and quality monitoring

Other Skills

- Highly motivated and hard-working
- Excellent organizational skills

Personal Life

Married and mother of two girls. Enjoy reading, movies and ice skating.