

Geriatric Dermatoses in Egypt

Thesis

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Presented By

Walaa Abd El Hady Awwad
(M.B., B.Ch)

Supervised by

Prof. Dr. Mostafa Mokhtar Kamel
Professor of Dermatology, Andrology and Venereology
Faculty of Medicine – Ain Shams University

Dr. Nehal Mohamed Zu El Fakkar
Assistant Professor of Dermatology, Andrology and Venereology
Faculty of Medicine – Ain Shams University

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List of Abbreviations

5-FU	5-Fluorouracil
AHAs	Alpha hydroxy acids
AP-1	Activator protein-1
BCC	Basal cell carcinoma
BP	Bullous pemphigoid
C.minutissimum	Corynebacterium minutissimum
DEJ	Dermal-epidermal junction
GAGs	Glycosaminoglycans
HA	Hyaluronic acid
HCL	Hydrochloride
HD	Hemidesmosomes
HIV	Human immunodeficiency virus
HPV	Human papilloma virus
Ig	Immunoglobulin
KOH	Potassium hydroxide
MMPs	Matrix metalloproteinases
NSAIDs	Nonsteroidal anti-inflammatory drugs
PAS	Periodic acid-schiff
PDT	Photodynamic therapy
PHN	Postherpetic neuralgia
PUVA	Psoralen and ultraviolet A
ROS	Reactive oxygen species
SC	Stratum corneum
SCC	Squamous cell carcinoma
STD	Sexually transmitted disease
TEWL	Trans-epidermal water loss
TGF	Transforming growth factor
UV	Ultraviolet
UVA	Ultraviolet A
UVB	Ultraviolet B

Introduction

The gradual increase in the life expectancy in the last few decades has challenged many authors to study the incidence of geriatric dermatoses. The overall functions of skin, the body's largest organ, decrease with age. Decline is noted in cell replacement, sensory perception, thermal regulation, and chemical clearance. Decrease in sweat, sebum, and vitamin D production also occurs (*Beaurgard and Gilchrest, 1987*).

Alteration in skin appearance may be due to intrinsic or extrinsic factors. Intrinsic changes (true aging) occur with the passage of time. Extrinsic alterations, most commonly called photoaging, are primarily caused by ultraviolet exposure from sunlight. Chronic sun exposure is responsible for the appearance of irregular mottled pigmentation, lentigines (brown macules), coarse wrinkling and telangectasis (*Moschella, 2001*). Immune response is lessened, the incidence of neoplasms increases, and there is greater susceptibility to skin infections (*Theodosat, 2004*). Moreover, wounds heal more slowly due to a combination of decreased immune and inflammatory response, collagen degradation, and delayed replenishment of the vasculature (*Norman, 2008a*).

Other normal changes and potential implications of skin aging include; flattening of dermal-epidermal junction. This change may compromise communication and nutrient transfer between

skin layers, increase dermal separation that may cause increased blistering or tearing and decrease in epidermal filaggrin (a protein required to bind keratin filaments into macrofibrils) that contributes to dryness and flaking of skin (**Tezuka et al.,1994**). Decline of enzymatically active melanocytes (about 10% to 20% each decade) contributes to increased sensitivity to ultraviolet radiation. Decline of DNA repair in combination with loss of melanin, increases the risk of photo carcinogenesis (**Baumann, 2007**).

In addition, there is a decrease in vascular responsiveness contributing to impaired thermal regulation and skin pallor. Decrease in the subcutaneous fat and changes in its distribution may limit conduction of heat loss and decrease protective ability in bony areas such as Ischial Tuberosities. Furthermore, delayed recovery of stratum corneum's function as a barrier leads to systemic absorption of topical medication (**Roberts, 2001**).

Aim of the Work

The aim of this work is to study the incidence of different types of dermatological problems among Egyptian aged people.

Aging

1.1 Definition

Aging is an ongoing process. Normal aging involves inevitable changes related to physiologic processes occurring at certain stages of life (*Norman, 2003c*).

1.2 Types of Aging

There are two primary skin aging processes, intrinsic and extrinsic. Variations in individual genetic background are thought to govern intrinsic aging, which results as time passes. By definition, this form of aging is inevitable, thus, apparently not subject to manipulation through changes in human behaviour (*Baumann, 2007*).

Conversely, extrinsic aging is affected by factors originating externally that are introduced to the human body, such as smoking, excessive alcohol consumption, poor nutrition, and chronic exposure to the sun. This form of aging is not inevitable and represents premature skin aging. Of these external factors, sun exposure is considered to be the most significantly deleterious to the skin. Indeed, 80% of facial aging is believed to be due to chronic sun exposure [*Klingman and Klingman,1993; Uitto, 1997; Gilchrest,1998; Uitto et al.,1998; Norman,2008b*].

Exposed areas of the skin, typically the face, chest and extensor surfaces of the arms, display the majority of extrinsically aged skin, which results from the cumulative

effects of life-long ultraviolet(UV) rayes exposure. Rhytides, pigmented lesions (such as ephelides, lentigines, and patchy hyperpigmentation) and depigmented lesions (e.g. guttate hypomelanosis) are the clinical presentation of photo-aged skin. Losses in tone and elasticity are also observed in photo-aged skin, along with increased skin fragility, areas of purpura due to blood vessel weakness, and benign lesions (e.g. acrochordons, keratoses, and telangiectasia) (*Kohl et al., 2009*).

Skin that ages intrinsically is smooth and unblemished, and characterized by normal geometric patterns, with some exaggerated expression lines. Histologically, such skin shows epidermal and dermal atrophy, flattening of the epidermal rete ridges, as well as reduced numbers of fibroblasts and mast cells (*Roupe, 2001*). In addition, the number of collagen fibrils as well as the ratio of collagen III to collagen I increases(*Baumann, 2007*).

1.3 Mechanism of Aging

1.3.1 Intrinsic aging

Telomeres, the specialized structures found at the ends of eukaryotic chromosomes, are now believed to play an essential role in the intrinsic aging process at the cellular level. Intact telomeres are essential for extending the lifespan of cells (*Geserick and Blasco, 2006*).

During the process of aging, telomere length shortens. This telomeric erosion can be considered a gauge by which

aging can be measured, a veritable internal aging clock, and the basis for one of the presently favored theories on aging (*Boukamp, 2001*).

In one of the investigations of the progressive telomere shortening, researchers determined that the telomere shortening associated with aging is characterized by tissue-specific loss rates (*Nakamura et al., 2002*). Indeed, the natural, progressive shortening of telomeres may be one of the primary mechanisms of cellular aging in skin (*Roupe, 2001*). Telomeres and other cellular constituents also sustain low-grade oxidative damage as a result of aerobic cellular metabolism, which contributes to intrinsic aging (*Kosmadaki and Gilchrest, 2004*).

1.3.2 Extrinsic aging

Skin damage results from UV exposure through several mechanisms, including the formation of sunburn cells as well as thymine and pyrimidine dimers, collagenase production, and the induction of an inflammatory response. Sunburn cells, or UV-induced apoptotic cells, have long been used as markers to evaluate skin damage caused by sun exposure. Ultraviolet-induced apoptosis is mediated by caspase-3, high levels of which are thought to be good indicators of the presence of cellular apoptosis (*Yao et al., 2005*). Activation of apoptosis occurs in a pathway that involves caspase-7 (*Pinnel et al., 2005*).

Mast cells and macrophages are found in greater numbers in photo-aged skin and are also thought to be involved in the mechanism of photo aging (*Bosset et al., 2003*). Interestingly, telomeres do not appear to play a central role in extrinsic aging (*Sugimoto et al., 2006*).

The aging process is believed to be at least partially due to the formation and activity of free radicals, also known as reactive oxygen species (ROS). Free radicals are composed of oxygen molecules with an unpaired electron and are affected by several exogenous and endogenous factors, including UV exposure, pollution, stress, smoking and normal metabolic processes. Furthermore, some evidences suggest that free radicals induce alterations in gene expression pathways, which in turn contribute to the degradation of collagen and the accumulation of elastin that occurs in photo-aged skin. Anti-oxidants neutralize free radicals by supplying another electron, delivering an electron pair to an oxygen molecule and stabilizing it (*Scharffetter-Kochanek et al., 2000*).

1.4 Aging Changes

1.4.1 Histological changes

1.4.1.1 Epidermis

There is general agreement that the thickness of the stratum corneum does not change with age. In a study comparing the effects of intrinsic and extrinsic aging,

histopathological examination of 83 biopsies from sun-exposed and protected skin in healthy volunteers aged 6–84 years revealed epidermal thickness to be constant across the decades in both sun-exposed and -protected skin, with the thickness found to be greater in sun-exposed skin (*El-Domyati et al., 2002*). In another study, the spinous layer of wrinkles was shown to be thinner at the base than at the flanks, in addition, fewer keratohyalin granules are present in the wrinkles’ base when compared to the flanks (*Contet-Audonneau et al., 1999*).

In aged skin, the intersection of the epidermis and dermis, known as the dermal–epidermal junction (DEJ), is known to be flattened with a correspondingly diminished connecting surface area which may lead to more shear-type injuries and bullae formation (*Fenske and Lober, 1986*). In a study of the abdominal skin, DEJ surface area was shown to be reduced from 2.64 mm² in subjects aged 21–40 year to 1.90 mm² in subjects aged 61–80. It is thought that such a loss of DEJ surface area may contribute to the increased fragility of the skin associated with age and may also lead to reduced nutrient transfer between the dermal and epidermal layers (*Baumann, 2007*).

1.4.1.2 Dermis

Aging changes affect the three primary structural components of the dermis, collagen, elastin and glycosaminoglycans. Approximately 20% of dermal thickness disappears as people become older. Aged dermis has been shown through

structural examination to be relatively acellular and avascular (*Fenske and Lober, 1986*). Changes in collagen production and the development of fragmented elastic fibers also characterize normal aged dermis. Dermis that is also photo-aged exhibits disorganized collagen fibrils and the accumulation of abnormal elastin- containing material (*El-Domyati et al., 2002*).

Collagen

It is the primary structural component of the dermis and the most abundant protein found in humans. Collagen is responsible for conferring strength and support to human skin. Over time, the structural proteins and main components of the skin deteriorate, resulting in the cutaneous signs of aging (*Fenske and Lober, 1986*).

Seventy percent of the dry skin mass is composed of collagen (*Gniadecka et al., 1998*). In aged skin, collagen is characterized by thickened fibrils, organized in rope-like bundles, that appear to be in disarray in comparison to the pattern observed in younger skin (*Baumann, 2007*).

The ratio of collagen types found in human skin also changes with age. In young skin, collagen I constitutes 80% and collagen III constitutes about 15% of total skin collagen; in older skin, the ratio of Type III to Type I collagen has been shown to increase, due, significantly, to an appreciable loss of collagen I (*Oikarinen, 1990*). In addition, the overall collagen content per unit area of skin surface is known to decline

approximately 1% per year. In irradiated skin, collagen I levels have been shown to be reduced by 59% (*Fisher et al.,1997*), this reduction was found to be linked to the extent of photo damage (*Griffiths et al.,1993*).

An integral constituent of the DEJ, collagen IV imparts a structural framework for other molecules and plays a key role in maintaining mechanical stability. No significant differences have been found in collagen IV levels in sun-exposed skin compared to unexposed skin, but significantly lower levels of collagen IV have been identified at the base of wrinkles in comparison to the flanks of the same wrinkles. The mechanical stability of the DEJ may be adversely affected by this loss of collagen IV, thereby contributing to wrinkles formation (*Contet-Audonneau et al.,1999*).

Collagen VII is the primary constituent in anchoring fibrils that attach the basement membrane zone to the underlying papillary dermis. A significantly lower number of anchoring fibrils were identified in patients with chronically sun-exposed skin in comparison to normal controls. It was theorized by the researchers that wrinkles may form as a result of a weakened bond between the dermis and epidermis, due to anchoring fibrils degradation. Such a loss of collagen VII is more marked in the base of the wrinkles (as seen with collagen IV) (*Baumann, 2007*).

It is known that UVR exposure significantly up-regulates the synthesis of several types of collagen-degrading enzymes

known as matrix metalloproteinases (MMPs). First, UV exposure leads to an increase in the amount of the transcription factors c-jun and c-fos. The other transcription factors involved in this mechanistic chain are already abundant without UV exposure. Activator protein-1 (AP-1) is then formed by the combination of c-jun and c-fos. In turn, AP-1 activates the MMPs genes, which stimulate the production of collagenase, gelatinase and stromelysin. Collagen degradation is mediated by AP-1 activation and by inhibition of transforming growth factor (TGF) β signaling (*Rittie and Fisher, 2002*).

Research in humans has shown that within hours of UVB exposure, MMPs, specifically collagenase and gelatinase, are produced. Multiple exposures to UVB induce a sustained induction of MMPs. Given that collagenase attacks and degrades collagen, long-term elevations in the levels of collagenase and other MMPs likely yield the disorganized and clumped collagen identified in photo-aged skin (*Fisher et al.,1997*).

Notably, these MMPs may represent the mechanism through which collagen I level decline in response to UV exposure. By characterizing the wide-ranging effects of UV in activating cell surface growth factor and cytokine receptors, researchers have been able to ascertain that skin aging (extrinsic and intrinsic) is marked by elevated AP-1 activity and MMPs expression, inhibited TGF β signaling, as well as reduced