ASSESSMENT OF VITAMIN D RECEPTORS IN ALOPECIA AREATA AND ANDROGENETIC ALOPECIA

Thesis

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Abstract

Background: Alopecia areata [AA] is a frequent autoimmune disease, the pathogenesis of which is still unknown. Androgenic alopecia [AGA] is a non cicatricial or potentially reversible type of patterned hair loss, in which genetic predisposition and hormonal factors play a role. Expression of vitamin D receptors (VDR) on keratinocytes is necessary for maintenance of the normal hair cycle specially anagen initiation. The relation between VDR and both AA and AGA represents an attractive area of research.

Purpose: Assessment of VDR in the skin and blood of AA and AGA patients, in order to evaluate their possible role in these hair diseases.

Patients and methods: This study recruited 20 patients with AA, 20 patients with AGA and 20 healthy controls. Blood samples and lesional scalp biopsies were taken from all participants for the detection of VDR levels. Serum ferritin and TSH were measured for all AGA patients and controls, in addition to serum free testosterone for females of both groups.

Results: Serum and tissue VDR levels were lower in AA as well as AGA patients when compared to controls, with highly significant difference (p=0.000). Serum and tissue VDRs were positively correlated in each group. Tissue VDR was significantly lower in female AA patients than males (p=0.046) though serum and tissue VDR levels were significantly higher in female AGA patients than males (p=0.004). Serum testosterone levels were significantly lower in female AGA patients than female controls (p=0.019). Serum ferritin levels were significantly lower in AGA patients than controls (p=0.000).

Conclusion: The current study suggests an important role for VDR in the pathogenesis of AA and AGA through documenting lower serum and tissue VDR levels in AA and AGA patients in comparison to the controls.

Key words: Alopecia areata, Androgenetic alopecia, vitamin D receptors.

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List of Abbreviations

Abbreviation	Meaning
$1,25(OH)_2D_3$	1,25-dihydroxy vitamin D3
17B-HSD	17-B-Hydroxysteroid dehydrogenase
1α,25(OH)2D	1-alpha-25 dihydroxyvitamin D
7-DHC	7-Dehydrocholesterol
AA	Alopecia areata
Act1	Actin1
ACTH	Adrenocorticotrophic hormone
ACTHR	Adrenocorticotropin receptor
AGA	Androgenetic alopecia
AIRE	autoimmune regulator
ALP	Alkaline phosphatase
ANA	Anti nuclear antibody
APECED	Autoimmune Polyendocrinopathy-candidiasis-ectodermal dystrophy
AR	Androgen receptor
AT	Alopecia totalis
AU	Alopecia universalis
BAFF	B cell-activating factor of the TNF family
BDNF	Brain derived neurotrophic factor
BMPRIA	BMP type IA receptor
BMPs	Bone morphogenetic proteins
CBC	Complete blood count
CD	Cluster of differentiation
CHD	Coronary heart disease
CL	Companion layer
COX-2	Cyclooxygenase-2
CRH	Corticotropin releasing hormone
CsA	Cyclosporine A
CXCL10	Chemokine 10
CXCL9	Chemokine 9
DBD	DNA binding domain
DCs	Dendritic cells

DHEA-S	**Dehydroepiandrosterone sulfate**
DHT	**Dihydrotestosterone**
Dkk1	**Dikkopf1**
DM	**Diabetes mellitus**
DP	**Dermal papilla**
DS	**Dermal sheath**
E2	**Estradiol**
ECM	**Extracellular matrix**
Eda	**Ectodysplasia**
Edar	**Ectodysplasia receptor**
EGF	**Epidermal growth factor**
FAK	**Focal adhesion kinase**
FDA	**Food and Drug Administration**
FGFs	**Fibroblast growth factors**
FLG	**Filaggrin**
FPHL	**Female pattern hair loss**
FS	**Follistatin**
FU	**Follicular unit**
GAGs	**Glycasaminoglycans**
Gsdma3	**Gasdermin gene3**
HF	**Hair follicle**
HGF	**Hepatocyte growth factor**
HLA	**Human leukocyte antigen**
Hoxc13	**Homeobox C13**
HPA	**Hypothalamic-pituitary-adrenal**
Hr	**Hairless gene**
HSP27	**Heat shock protein27**
IFN-γ	**Interferon-γ**
IGE	**Immunoglobulin E**
IGF-1	**Insulin-like growth factor-I**
IL	**Interleukin**
IL1ra	**Interleukin 1 receptor antagonist**
IOM	**Institute of medicine**
IP	**Immune privilege**

IP-10	**Interferon inducible protein-10**
IRS	**Inner root sheath**
KGF	**Keratinocyte growth factor**
KOH	**Potassium hydroxide**
LBD	**Ligand binding domain**
LEF-1	**lymohocyte enhancer finding protein-1**
LRP5/6	**lipoprotein receptor related protein**
MCP-1	**Monocyte chemoattractant protein-1**
MED	**Minimal erythema dose**
MHC	**Major histocompatibility complex**
MIF	**Macrophage Migration Inhibitory Factor**
MIG	**Monokine induced by IFN-γ**
MSH	**Melanocyte stimulating hormone**
MX1	**Myxovirus resistance 1**
NCoR	**Nuclear co repressor**
NGF	**Nerve growth factor**
nVDR	**Nuclear vitamin D receptor**
ORS	**Outer-root sheath**
P75NTR	**P75 neurotrophin receptor**
PCO	**Poly cystic ovarian**
PDGF-A	**Platelet-derived growth factor-A**
PRL	**Prolactin**
PTH	**Parathyroid hormone**
PTPN22	**Protein tyrosine phosphatase, non-receptor type 22**
RANKL	**Receptor activator of nuclear factor kappa-B ligand**
RPR	**rapid plasma reagin**
RXR	**Retinoid X receptor**
SCID	**Severe combined immunodeficient**
SGK	**Serine/Threonine-protein kinase**
Shh	**Sonic hedgehog**
SLE	**Systemic lupus erythematous**
SMRT	**Silencing mediator of retinoic acid and thyroid receptor**
SNPs	**Single nucleotide polymorphisms**
SRC	**Steroid receptor activator complex**

TGF	**Transforming growth factor**
Th	**T helper**
TIBC	**Total iron-binding capacity**
TLR1/2	**Toll like receptor1/2**
TNF	**Tumor necrosis factor**
Tregs	**T regulatory cells**
TSH	**Thyroid-stimulating hormone**
UK	**United kingdom**
US	**United states**
UTR	**Untranslated region**
UVB	**Ultraviolet B**
VDBP	**Vitamin D-binding protein**
VDR	**Vitamin D receptor**
VDREs	**Vitamin D response elements**
VDRIP	**Vitamin D receptor interacting protein complex**
Δ5-3B-HSD	**3B-hydroxysteroid dehydrogenase/Δ5-4-isomerase**

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INTRODUCTION

Hair is a primary characteristic of mammals, and exerts a wide range of functions. In human society, hair is of enormous, psychosocial importance and many human diseases are associated with hair loss or less frequently with overabundance of hair ***(Schneider et al., 2009)***.

Hair follicle development takes place during fetal skin development and relies on tightly regulated ectodermal–mesodermal interactions. After birth, mature and actively growing HFs periodically regenerate by spontaneously undergoing repetitive cycles of growth ***(Schneider et al., 2009)***.

Alopecia areata is a frequent autoimmune disease with a life time risk of about 1.7% in the general population, including males and females across all ethnic groups ***(Hon and leung, 2011)***. It is a common cause of non cicatricial alopecia that occurs as a patchy, confluent or diffuse pattern ***(Hordinsky and Ericson, 2004)***. The commonest site affected is the scalp ***(Wasserman et al., 2007*)**.

The pathogenesis of AA is still unknown. In spite of the impressive progress, there is still a long way to go to completely understand the mechanisms of the disease and to identify AA-specific targets for treatment ***(Norris, 2004)***. Many factors such as genetic predisposition, autoimmunity, cytokines, chemokines and stress have been suggested as causes for AA ***(Firooz et al., 2005 &Alkhalifa et al., 2010)*.** Several studies have been done in the last few years to investigate the role of stem cells in AA ***(AL-Refu, 2012)***.

Androgenetic alopecia is a noncicatricial or potentially reversible type of patterned hair loss ***(Soni, 2009)***. It affects both sexes and all ethnic groups although the severity and frequency is greater in men and there are racial differences in prevalence***(Messenger, 2009)***.

The development of AGA depends on several factors including alteration of hair cycle dynamics, hair follicle miniaturization ***(Shweiger et al., 2010)***, genetic predisposition, presence of sufficient androgens, androgen receptors and androgen receptor co activators ***(Alsantali and Shapiro, 2009)***.

Vitamin D is a steroid hormone synthesized in the epidermal keratinocytes under influence of ultraviolet- B (UV-B) light (290-315 nm) or acquired in the diet and dietary supplements ***(Bouillon et al., 2008)***.

The active form of vitamin D, $1,25(OH)_2D_3$, has multiple effects on innate and adaptive immune responses through its varied effects on T and B lymphocytes, macrophages and dendritic cells (DCs), all of which express VDR ***(Kim et al., 2007& Adorini and Penna, 2008)***. As such, the impact of $1,25(OH)_2D_3$ and VDR on human physiology and disease are broad and there is wide interest in the role of this hormone and its receptors in many areas of medicine ***(Gorman et al., 2007)*.**

Vitamin D receptors are members of the nuclear hormone receptor super family that act as a ligand-inducible transcription factors regulating $1,25(OH)_2D_3$ - responsive genes ***(Reicharth et al., 1994)***. They are involved in regulating skin biology such as epidermal proliferation and differentiation and the hair growth cycle ***(Amor et al., 2012)***. Vitamin D receptors are strongly expressed in the key structures of human and murine hair follicles ***(Reicharth et al., 1994*)**. Studies demonstrated that