Evaluation of Serum Vitamin D Level in Vitiligo Patients with and without Autoimmune Diseases

Thesis

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Summary

Vitiligo is an acquired skin disorder caused by the disappearance of pigment cells from the epidermis that gives rise to well defined white patches which are often symmetrically distributed. It occurs worldwide in about 0.1-2% of different population and it occurs as frequently in males as it does in females. The cause is unknown, but might involve genetic factors, autoimmunity, neurologic factors, toxic metabolites, and lack of melanocyte growth factors.

Vitiligo reflects a systemic process that has important implications beyond the skin. These include other autoimmune diseases and ocular and neurological abnormalities. Vitiligo is commonly associated with systemic autoimmune conditions, including hypothyroidism and hyperthyroidism, diabetes mellitus, and Sjogren's syndrome.

In our study, we aimed to evaluate serum vitamin D levels in vitiligo patients with and without autoimmune diseases in comparison to healthy controls.

Vitamin D is a secosteroid hormone that regulates the growth and differentiation of multiple cell types, and displays immunoregulatory and anti-inflammatory properties. In the skin calcitriol regulates the growth of epidermal cells by inhibiting proliferation and inducing terminal differentiation of keratinocytes, and enhances immunosuppressive and anti-inflammatory pathways.

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List of Abbreviations

AD	:	Atopic dermatitis
ADCC	:	Antibody-dependent cell cytotoxicity
AISL	:	Autoimmune susceptibility locus
AMPs	:	Antimicrobial peptides
ANA	:	Antinuclear antibody
ANOVA	:	Analysis of Variance
Anti TG	:	Antithyroglobulin antibody
Anti TPO	:	Antithyroid peroxidase antibody
APC	:	Antigen presenting cell
B	:	Regression coefficient
BSA	:	Body surface area
CAT	:	Catalase gene
COMT	:	Catechol-O-methyl transferase
CMV	:	Cytomegalovirus
CPDs	:	Cyclobutane pyrimidine dimers
CPM	:	Count per minute
CTLA-4	:	Cytotoxic lymphocyte antigen 4
DBP	:	Vitamin D binding protein
DCs	:	Dendritic cells
EBV	:	Epstein-Barr virus
FGF	:	Ffibroblast growth factors
FOXP1	:	Forkhead box P1 gene
H2O2	:	Hydrogen peroxide
HBD	:	Human beta-defensin
HCV	:	Hepatitis C virus
HIV	:	Human immunodeficiency virus
HLA	:	Human Leukocyte Antigen
HS	:	Highly significant
IBD	:	Inflammatory bowel disease
IFN-γ	:	Interferon gamma
IKP	:	Isomorphic Koebner phenomenon
IL-1	:	Interleukin-1
IU	:	International units
kDa	:	Kilo dalton
MARRS	:	Membrane associated rapid response steroid binding
MAP	:	Mitogen-activated protein
MCHR1	:	Melanin-concentrating hormone receptor 1
MHC	:	Major histocompatibility
MS	:	Multiple sclerosis
MYG1	:	Melanocyte proliferating gene 1
N	:	Number
NK	:	Natural killer

List of Abbreviations (Cont.)

NO	:	Nitric oxide
NS	:	Non significant
NSV	:	Non-segmental vitiligo
P	:	Propability value
PTH	:	Parathyroid hormone
PTHrP	:	Parathyroid hormone-related peptides
PUVA	:	Psoralen and ultraviolet rays
r	:	Correlation coefficient
RA	:	Rheumatoid arthritis
Raf	:	Rapidly growing fibrosarcoma
RIA	:	Radioimmunoassay
S	:	Significant
SD	:	Standard deviation
SLE	:	Systemic lupus erythematosus
SPF	:	Sunburn protective factor
TCR	:	T-cell receptors
Th1	:	T helper 1
TNF-α	:	Tumor necrosis factor-alpha
Treg	:	Regulatory T cells
TRP	:	Tyrosinase-related protein
TSH	:	Thyroid stimulating hormone
TYR	:	Tyrosinase
UK	:	United Kingdom
UV	:	ultraviolet light
VDR	:	Vitamin D receptor
VKH	:	Vogt-Koyanagi-Harada
1α,25(OH)2D3 1,25(OH)2D3	:	Calcitriol(1,25-dihydroxy-vitamin D3 , 1α,25-dihydroxyvitamin D3)
1α-OHase or CYP27B1	:	1α hydroxylase or cytochrome P450 protein
4-TBP	:	4-tertiary butylphenol
7DHC	:	7-dehydrocholesterol
24-OHase or CYP24A1	:	24-hydroxylase
25(OH)D	:	25-hydroxyvitamin D
%=	:	Percentage

Introduction

Vitiligo is an acquired skin disorder caused by the disappearance of pigment cells from the epidermis that gives rise to well defined white patches which are often symmetrically distributed. It occurs worldwide in about 0.1-2% of the population and it occurs as frequently in males as it does in females. The cause is unknown, but might involve genetic factors, autoimmunity, neurologic factors, toxic metabolites, and lack of melanocyte growth factors ***(Njoo and Westerhof, 2001).***

Vitiligo is commonly associated with systemic autoimmune conditions, including hypothyroidism and hyperthyroidism, diabetes mellitus, and Sjogren's syndrome. Many autoimmune conditions have been found to be associated with reduced vitamin D levels, including rheumatoid arthritis (RA), diabetes mellitus, and multiple sclerosis (MS). However, little is known about the association between vitiligo and reduced vitamin D levels ***(Sehgal et al., 1976; Niepomniszcze and Amad, 2001; Montes et al., 2003; Adorini and Penna, 2008).***

Vitamin D_3 can be obtained through the diet, but it is mainly biosynthesized from 7-dehydrocholesterol (7DHC) in skin exposed to ultraviolet (UV) light. Vitamin D_3 is hydroxylated in the liver to produce 25 hydroxy vitamin D_3 ($25(OH)D_3$), a reliable indicator of vitamin D status, and is further hydroxylated in the kidney to form the active hormone calcitriol ($1,25(OH)_2D_3$). $1,25(OH)_2D_3$, the biologically active form of vitamin D_3, is a secosteroid hormone that regulates the growth and differentiation

of multiple cell types, and displays immunoregulatory and anti-inflammatory properties. Cells involved in innate and adaptive immune responses including macrophages, dendritic cells, T cells and B cells express the vitamin D receptor (VDR), and can both produce and respond to $1,25(OH)_2D_3$. The net effect of the vitamin D system on the immune response is an enhancement of innate immunity coupled with multifaceted regulation of adaptive immunity ***(Adorini and Penna, 2008).***

Aim of the work

The aim of this work is to evaluate serum levels of vitamin D in vitiligo patients with and without autoimmune diseases.

Vitiligo

1.1. Definition

Vitiligo is divided into segmental and non-segmental forms. “Generalized vitiligo or non-segmental vitiligo (NSV) is an acquired chronic pigmentation disorder characterized by white patches, often symmetrical, which usually increases in size with time, corresponding to a substantial loss of functioning epidermal and sometimes hair follicle melanocytes” while “Segmental vitiligo is an acquired chronic pigmentation disorder characterized by white patches with a unilateral distribution that may totally or partially match a dermatome, but not necessarily. Other distribution patterns can be encountered that cross several dermatomes, or correspond to large areas delineated by Blaschko’s lines” ***(Taïeb and Picardo, 2007).***

1.2. Nomenclature and Historical Background

Vitiligo was observed very early in history, and most ancient civilizations and religions had some type of reference about lack of pigmentation ***(Lahiri, 2009).***

Vitiligo is cited in many ancient writings. Indian literature dating to 1500 to 1000 BC refers to the word Kilas (“Kil” means white, “as” means to cast or throw away) and

palita ("pal" implies gray, old, and aged), referring to white patches on the skin ***(Singh et al., 1974).***

The name vitiligo was first used by the famous Roman physician Celsus at the second century AD in his medical classic "De Medicina". The word vitiligo has often been said to have derived from "vitium" (defect or blemish) rather than "vitellus" meaning calf ***(Panda, 2005).***

In the Holy Koran, the word "baras", meaning white skin, is used to describe a condition that Jesus cured ***(Sharque, 1984).***

1.3. Epidemiology

Vitiligo is the most prevalent pigmentary disorder that occurs worldwide with an incidence rate of between 0.1% and 2% ***(Alkahateeb et al., 2003; Daneshpazhooh et al., 2006 and Torello et al., 2008)*** irrespective of age, race ***(Moretti et al., 2006 and Torello et al., 2008)*** ethnic origin or skin color ***(Whitton et al., 2008).*** The prevalence has been reported as high as 4% in some South Asian, Mexican and United States populations ***(Parsad et al., 2003; Sehgal and Srivastava, 2007).***

Almost half of the patients present before the age of 20 years, and nearly 70–80% before the age of 30 years. Adults and children of both sexes are equally affected, although larger number of females consult the doctor probably due to the

greater psycho–social perceived impact of the disease ***(Sehgal and Srivastava, 2007).***

1.4. Genetics

Genetic risk for vitiligo is well supported by multiple lines of evidence. Vitiligo is frequently associated with familial clustering ***(Mehta et al., 1973; Carnevale et al., 1980; Goudie et al., 1983; Hafez et al., 1983; Das et al., 1985; Majumder et al., 1993 and Alkhateeb et al., 2003)*** and 20% to 30% of patients with vitiligo have positive family history ***(Passeron and Ortonne, 2005).*** In addition, segregation analysis suggested that vitiligo is a multifactorial and polygenic disorder that likely results from multiple genetic and environmental factors ***(Arcos-Burgos et al., 2002; Alkhateeb et al., 2003; Zhang et al., 2004 and Sun et al., 2006).***

There may in fact be two coexisting modes of inheritance for vitiligo depending on age of onset. In patients with early onset vitiligo (before the age of 30 years), vitiligo inheritance most closely followed a dominant mode of inheritance with incomplete penetration. However, a predisposition to vitiligo resulting from a recessive genotype and exposure to certain environmental triggers appeared to explain the inheritance pattern of late onset vitiligo (after 30 years of age) ***(Huggins et al., 2005).***

Several Human Leukocyte Antigen (HLA) studies have been performed which showed sporadic association between vitiligo and certain HLA groups. Linkage and association studies have provided strong support for vitiligo susceptibility genes on chromosomes 1p31, 7q, 8p and 17p13 in Caucasian population and 4q13-q21, 6p21-p22-q27 and 22q12 in Chinese population ***(Nath et al., 2001; Alkhateeb et al., 2002; Spritz et al., 2004; Chen et al., 2005; Liang et al., 2007 and Quan et al., 2010).***

Chromosome 1p31 has been found to be associated to a highly significant degree with generalized vitiligo in North American and United Kingdom (UK) whites. It is termed the autoimmune susceptibility locus (AISL), and it is responsible for susceptibility to autoimmunity, particularly vitiligo, whereas the presence of other genes (e.g., the major histocompatibility (MHC) locus on chromosome 6), combined with exposure to extrinsic or intrinsic factors, may mediate the occurrence of Hashimoto's thyroiditis in individuals who are AISL susceptible. This is the reason for the increased prevalence of Hashimoto's thyroiditis in patients with vitiligo, and it seems to be genetically determined ***(Alkhateeb et al., 2002 and Alkhateeb et al., 2003).***

Catechol-O-methyl transferase (COMT) is an enzyme that plays a major role in the metabolism of toxic or biologically active drugs, neurotransmitters and metabolites. One such metabolite, O-quinones, can be formed during melanin synthesis in the absence of adequate COMT activity. A functional single-nucleotide polymorphism in the COMT gene was found to be associated