Relationship between Serum 25–Hydroxyvitamin D_3 Level and Severity of Atopic Dermatitis

Thesis

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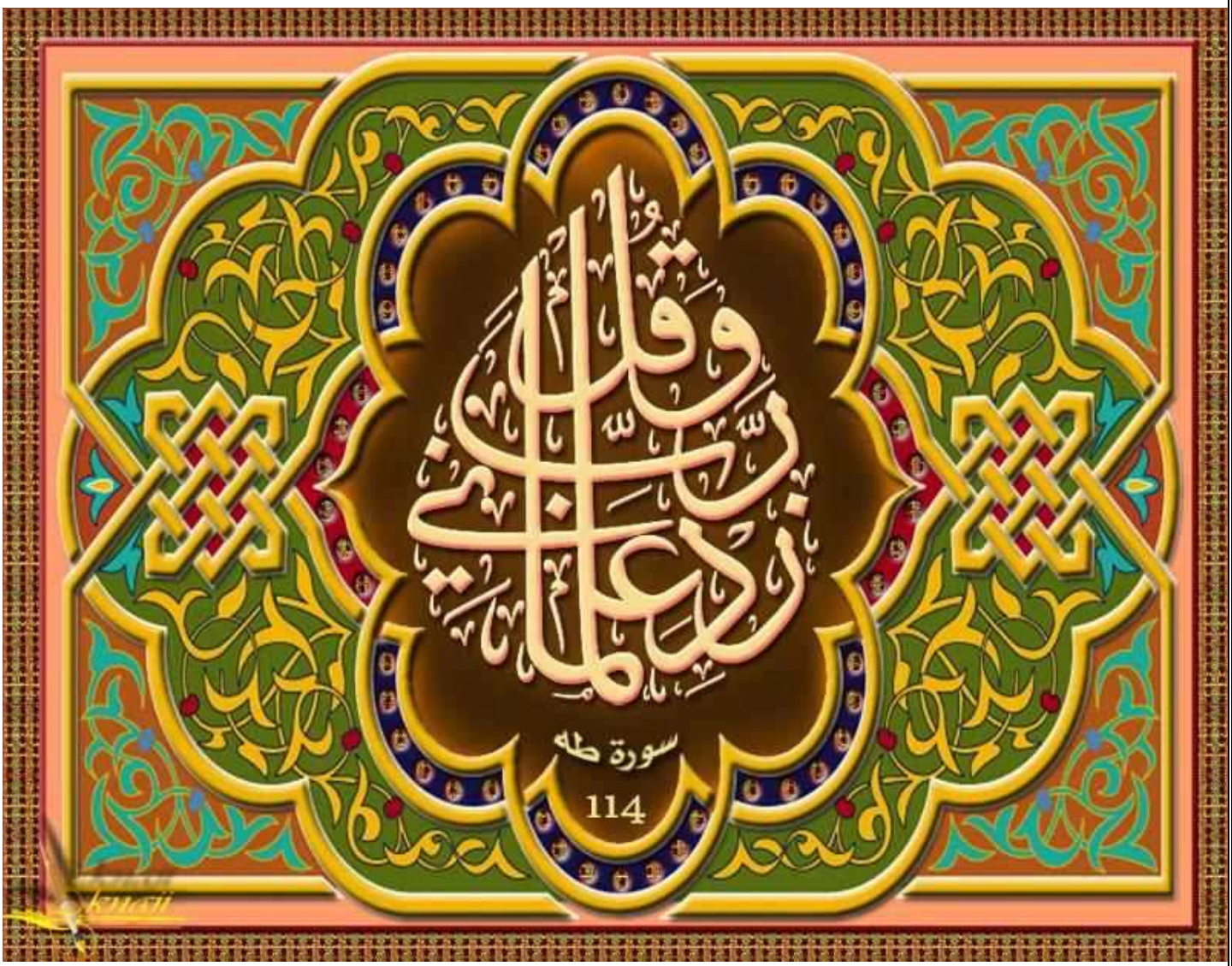
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TABLE OF CONTENTS

Title	Page No.
1. INTRODUCTION	**1**
2. AIM OF THR WORK	**4**
3. REVIEW OF LITERATURE	
3.1 Vitamin D	
3.1.1 Physiology of vitamin D	**5**
3.1.2 Sources of vitamin D	**5**
3.1.3 Vitamin D metabolism	**6**
3.1.4 Vitamin D action	**11**
3.1.5 Vitamin D and climate	**14**
3.1.6 Reference intakes for vitamin D	**15**
3.1.7 Vitamin D deficiency	**16**
3.2 Atopic Dermatitis	
3.2.1 Prevelance	**27**
3.2.2 “Atopic march” and “Atopic triad”	**28**
3.2.3 Histopathology	**29**
3.2.4 Atopy as a systemic disease	**29**
3.2.5 Pathogenisis	**30**
3.2.6 Other factors contributing to flare of atopic dermatitis	**48**
3.2.7 Mechanism of pruritus	**52**
3.2.8 Clinical features	**53**
3.2.9 Diagnostic criteria	**54**
3.2.10 Pharmacological and vascular abnormalities	**57**
3.2.11 Associated disorders	**57**
3.2.12 Scoring of AD	**58**
3.2.13 Diagnosis	**61**
3.2.14 Severity and activity markers	**61**
3.2.15 Differantial dignosis	**62**
3.2.16 Course of Atopic dermatitis	**62**
3.2.17 Complications	**63**
3.3 Vitamin D and Atopic deramtitis	
3.3.1 Role of vitamin D in normal skin	**65**
3.3.2 Role of vitamin D in atopic dermatitis	**68**
4. PATIENTS AND METHODS	**74**
5. RESULTS	**81**
6. DISCUSSION	**118**
7. SUMMARY	**131**
8. CONCLUSION AND RECOMMENDATIONS	**133**
9. APPENDICES	**135**
10. REFERENCES	**137**
11. ARABIC SUMMARY	**158**

LIST OF TABLES

No	Title	Page
Table 1	Dietary sources of vitamin D	6
Table 2	Recommended Dietary Allowances (RDAs) for Vitamin D	16
Table 3	Biochemical changes that characterize early, moderate, and severe vitamin D deficiency	22
Table 4	Diagnostic criteria of AD	55
Table 5	The UK refinement of Hanifin and Rajka diagnostic criteria of AD	56
Table 6	Age and sex of the patients and controls among group 1A and 2A	82
Table 7	Associated other atopic manifestations among cases of group 1A	83
Table 8	Family history and history of food allergy in cases of group 1A	84
Table 9	Severity according to SCORAD in patients of group 1 A	85
Table 10	Relationship between mean SCORAD index and atopic triad in group 1 A	86
Table 11	Comparison between group 1 A and group 2 A 25 OH Vitamin D Level	87
Table 12	Relation between severity of AD and vitamin D levels among in group 1 A	89
Table 13	Relationship between 25 OH Vit D Level and atopic triad in group 1 A	91
Table 14	Correlation between severity of AD and SCORAD with 25 OH Vitamin D	92
Table 15	Age and sex of the patients and controls among group 1B and 2B	93
Table 16	Associated other atopic manifestations among cases of group 1 B	95
Table 17	Family history and history of food allergy and rickets in cases of group 1B	96
Table 18	Severity according to SCORAD in patients of group 1 B	97
Table 19	Relationship between mean SCORAD index and atopic triad in group 1B	98
Table 20	Comparison between group 1 B and group 2 B (25 OH Vitamin D Level)	99
Table 21	Relation between severity of AD and vitamin D levels among group 1 B	101
Table 22	Relation between 25 OH Vitamin D Level and atopic triad in group1 B	103
Table 23	Correlation between severity of AD and SCORAD with 25OH Vit D level in group 1B	104
Table 24	Comparison between age and sex in group 1A and group 1B	105
Table 25	Associated atopic manifestations among the patients of group 1A and group 1B	107
Table 26	Severity of AD and SCORAD index among the patients of group 1A and group 1B	108
Table 27	Relationship between SCORAD index and atopic triad in patients of group 1A and 1B	110
Table 28	Comparison between the patients of group 1A and 1B according to (vitamin D level)	111
Table 29	Relation between both severity of AD and vit D levels in the patients of group 1A and 1B	112
Table 30	Relationship between mean vit D level and atopic triad in the patients of group 1A and 1B	114

LIST OF FIGURES

No	Title	Page
Figure 1	Synthesis and metabolism of vitamin D in the regulation of calcium, phosphorus	7
Figure 2	Pathway of vitamin D synthesis	8
Figure 3	Vitamin D sources, metabolism, mechanism of action and biological functions	8
Figure 4	Dietary vitamin D (A) and calcium (B) leading to reduced bone resorption	12
Figure 5	Radiographs for rickets	21
Figure 6	Mechanism of innate and adaptive immune reponse to vitamin D	26
Figure 7	The Th1–Th2 Paradigm and Its Role in Allergy	33
Figure 8	Immunologic pathways in AD	36
Figure 9	The structure of the epidermal barrier located in the lower part of the stratum corneum	44
Figure 10	"Outside-inside-outside" model of AD.	47
Figure 11	Eczema vaccinatum	63
Figure 12	Eczema herpeticum	64
Figure 13	Molluscum contagiosum in AD patients	64
Figure 14	Staphylococcus colonization in AD	64
Figure 15	Role of vitamin D in the skin	72
Figure 16	SCORAD evaluation form	77
Figure 17	25-hydroxyvitamin D ELISA Kit	79
Figure 18	Sex distribution among patients and controls in group 1A and 2A	82
Figure 19	Mean age among patients and controls among group 1A and 2A	82
Figure 20	Associated other atopic manifestations among cases of group 1A	83
Figure 21	Family history and history of food allergy in cases of group 1A	84
Figure 22	Distribution of cases according to severity in cases of group 1A	85
Figure 23	Relationship between mean SCORAD index and atopic triad in group 1 A	86
Figure 24	Mean 25-hydroxy vitamin D levels among group 1 A and group 2 A	88
Figure 25	Relation between severity of AD and mean SCORAD index among group 1 A	90
Figure 26	Relation between severity of AD and 25 OH Vit D Level among group 1 A	90
Figure 27	Relationship between 25 OH Vit D Level and atopic triad in group 1 A	91
Figure 28	Scatter chart of correlation between severity of AD and 25 OH Vit. D level in group 1A	92
Figure 29	Scatter chart of correlation between SCORAD and 25 OH Vitamin D level in group 1A	92
Figure 30	Sex distribution of patients and controls among group 1B and 2B	94
Figure 31	Mean age of the patients and controls among group 1B and 2B	94

LIST OF FIGURES CONT.

No	Title	Page
Figure 32	Associated other atopic manifestations among cases of group 1B	95
Figure 33	Family history and history of food allergy in cases of group 1B	96
Figure 34	Distribution of cases according to severity in cases of group 1B	97
Figure 35	Relationship between mean SCORAD index and atopic triad in group 1 B	98
Figure 36	Mean 25-hydroxy vitamin D levels among group 1B and 2B	100
Figure 37	Relation between severity of AD and mean SCORAD index among group 1B	102
Figure 38	Relation between severity of AD and vitamin D levels among group 1 B	102
Figure 39	Relationship between 25 OH Vit D Level and atopic triad in group 1 B	103
Figure 40	Scatter chart of correlation between severity of AD and 25 OH Vit. D level in group 1B	104
Figure 41	Scatter chart of correlation between SCORAD and 25 OH Vit. D level in group 1B	104
Figure 42	Sex distribution among the patients of group 1A and 1B	106
Figure 43	Mean age among the patients of group 1A and 1B	106
Figure 44	Associated atopic manifestations among the patients of group 1A and group 1B	107
Figure 45	Severity of AD among the patients of group 1A and group 1B	109
Figure 46	SCORAD index among the patients of group 1A and group 1B	109
Figure 47	Relationship between SCORAD index and atopic triad in patients of group 1A and 1B	110
Figure 48	Comparison between the patients of group 1A and 1B according to (vitamin D level)	111
Figure 49	Relation between severity of AD and SCORAD index in the patients of group 1A and 1B	113
Figure 50	Relation between severity of AD and OH vitamin D in the patients of group 1A and 1B	113
Figure 51	Relationship between mean vit D level and atopic triad in the patients of group 1A and 1B	114
Figure 52	Mild case of AD in the anticubital fossa in afemale patient aged 9 yrs old.	115
Figure 53	Moderate case of AD in the back of the thigh in a female patient aged 8 yrs.	115
Figure 54	Moderate case of AD in the anticubital fossa in a male patient aged 7 yrs old	116
Figure 55	Severe lichenified AD in the back of the thigh in a female patient aged 8 years old.	116
Figure 56	Superinfected severe AD in the back of the thigh in a male patient aged 13 years old	117
Figure 57	Severe AD with lichenification in the arms of female patient aged 15 years	117

ABBREVIATIONS

7 DHC: 7 dehydrocholesterol

[1,25(OH)2 D_3]: 1,25-dihydroxyvitamin D_3

AD: atopic dermatitis

ADASI score: Atopic Dermatitis Area and Severity Index score

ALP: alkaline phosphatase

AMP: anti-microbial peptides.

ANOVA: Analysis of Variance

AR: allergic rhinitis

AT: atopic triad

BA: bronchial asthma

BCSS score: Basic Clinical Scoring System

CCL: chemokines ligands

CCR: chemokine receptor

CD: cluster of differentiation

CLA: cutaneous lymphocyte-associated antigen

CPDs: cyclobutane pyrimidine dimers

CYP27B1 gene: cytochrome P450, family 27, subfamily B, polypeptide 1

DCs: dendritic cells

DNA: Deoxyribonucleic acid

DRIs: Dietary Reference Intakes

FLG: filaggrin gene

FNB: Food and Nutrition Board

GM-CSF: granulocyte-macrophage colony stimulating factor

HBD2: human β-defensin-2

HPLC: high performance liquid chromatography

HSV: herpes simplex virus

ICAM: intercellular adhesion molecule

IDEC: inflammatory dendritic epidermal cells.

IFN- γ: interferon- γ

IgE: immunoglobulin E

IUs: International Units

LC-MS: liquid chromatography-mass spectroscopy

LCs: Langerhans cells

Mcg: micrograms

MCs: mast cells

MDC: macrophage-derived chemokine

NESS score: Nottingham eczema severity score

NF-κB: necrosis factor κappa beta.

Ng/mL: Nano gram per milliliter

NKc: natural killer cell

NO: nitric oxide

PBMCs: peripheral blood mononuclear cells

PDGF: platelet derived growth factor

PTH parathyroid hormone

QOL: Quality of Life

RANTES: regulated and normal T cell expressed and secreted.

RASTs: radio-allergo-immunosorbent tests

RDA: Recommended Dietary Allowance

S. aureus: Staph aureus

Sag: superantigen

SC: stratum corneum

SCORAD: SCORing Atopic Dermatitis

s-ECP: surface eosinophilic cationic proteins

sIL-2R: soluble IL-2 receptor

SPSS: Statistical Package for social science

TARC: thymus and activation-regulated chemokine

TCIs: topical calcineurin inhibitors

TGF-β: tumour growth factor-β

Th: T helper

TIS score: Three Item Severity Score

TLRs: toll like receptors

TMB: tetramethylbenzidine

TNF-α: tumor necrosis factor-α

Tr1: T-regulatory type 1

Treg: Regulatory T cells

TSLP: thymic stromal lymphopoietin

UVA: ultraviolet A radiation

UVB: ultraviolet B radiation

VCAM: vascular cell adhesion molecule

VDBP: vitamin D binding protein

VDRs: vitamin D receptors

VV: vaccinia virus

1. Introduction

Atopic dermatitis (AD) is a highly pruritic disease that usually starts in early infancy, though an adult-onset variant is recognized. Usually it is the first disease to present in a series of atopic triad allergic diseases which include bronchial asthma, and allergic rhinitis (hay fever) as well as AD in order has given rise to the "atopic march" theory, which suggests that AD is part of a progression that may lead to subsequent allergic disease at other epithelial barrier surfaces **(*Carlsten et al., 2013*).**

The immune dysregulation of AD involves a complex of immunological cascade, including disruption of the epidermal barrier, immunoglobulin E (IgE) dysregulation and a defect in the cutaneous cell mediated immune response **(*Hoare et al., 2000*).**

The role of vitamin D in calcium homeostasis has been well recognized. Recently, studies have identified additional influences of vitamin D on the immune system and several lines of evidence suggest a possible influence of vitamin D on prevalence of allergic diseases even though results are still conflicting **(*Miller and Gallo, 2010*).**

Vitamin D metabolism begins both through absorption in the skin as vitamin D_3 (cholecalciferol) and absorption through the gut as either vitamin D_2 (ergocalciferol) or vitamin D_3. Cholecalciferol and ergocalciferol are then metabolized in the liver to 25-hydroxyvitamin-D [25(OH) D], which the vitamin D pro-hormone is usually used to measure vitamin D levels clinically **(*Thacher and Clarke, 2011*).**

Vitamin D plays key roles in innate and adaptive immunity through the stimulation of Toll-like receptors, increasing pro-inflammatory cytokine production, and possibly enhancing T helper type 2 responses **(*Benson et al., 2012*).**

These mechanisms may explain the growing body of evidence connecting vitamin D to allergic diseases, including asthma, food allergies, and allergic rhinitis. The data relating vitamins D to allergic skin diseases are equivocal with studies linking both high and low vitamin D levels to an increased risk of developing AD **(*Benson et al., 2012*).**

Keratinocytes possess the enzymatic apparatus to produce calcitriol, the active compound of vitamin D, from the precursor 7-dehydrocholesterol under the influence of ultraviolet (UVB) radiation. In in vitro studies, vitamin D3 (calcitriol) has been shown to induce cathelicidin expression in keratinocytes that enhances antimicrobial activity against S. aureus and selectively reduces cutaneous lymphocyte-associated antigen expression **(*Schauber et al., 2006*).**

It has been shown that cathelicidin does not influence lymphocyte migration patterns to other tissues, thus specifically decreasing T-lymphocyte homing into the skin. Oral administration of vitamin D3 induces production of cathelicidin in atopic individuals, while UVB radiation induces the expression of antimicrobial peptides in human keratinocytes in vivo, and a recent experiment confirmed improved AD among Norwegian children who were randomly selected to stay on a subtropical island for 1 month as compared with staying in Norway **(*Yamanaka et al., 2010*).**

Back et al. (2010) have demonstrated that a higher vitamin D3 intake during the first year of life was significantly correlated to atopic manifestations at 6 years of age.

However, it has also been shown that infants born from mothers with low vitamin D intake or low fish consumption during pregnancy present an increased prevalence of atopic dermatitis (AD) **(*Myalil and Thomas, 2010*).**

Moreover, cross-sectional studies have shown a greater risk of AD in infants born in autumn and winter compared with those born in spring and summer; in addition, there is a latitude effect on the prevalence of AD in children **(*Weiland et al., 2004*).**

Also five-fold increase in the likelihood of AD was found in patients with vitamin D deficiency compared with their counterparts **(*Oren et al., 2008*).**

Furthermore, ***Sidbury et al. (2008)*** reported beneficial effects on AD from oral supplementation with vitamin D in a small sample size of children with winter-related worsening of AD.

2.Aim of the work

The aim of the study was to estimate the serum level of 25-hydroxyvitamin D_3 in patients with atopic dermatitis and its relationship with the severity of the disease which was assessed by SCORAD index.

3.1.Vitamin D

3.1.1. Physiology of vitamin D

Vitamin D includes D_3 (Cholecalciferol) and D_2 (Ergocalciferol) collectively known as Calciferol. Vitamin D_3 is formed in the skin by the action of UVB on 7 dehydrocholesterol (7DHC) or is ingested. Vitamin D_2 mainly comes from plant sources. Vitamin D3 and D2 are hydroxylated in the liver by 25-hydroxylase to 25-hydroxyvitamin D (25-OHD) or calcidiol. This is the major circulating form of vitamin D and is the target for assays measuring vitamin D status. Calcidiol is further hydroxylated in the kidneys and other tissues to the active hormone 1α, 25-dihydroxyvitamin D [1α, $25(OH)_2$ D] or calcitriol. Renal production of calcitriol is regulated by parathyroid hormone (PTH), hypophosphataemia, hypocalcaemia and growth hormone **(*Benson et al., 2012*).**

Vitamin D from the diet or dermal synthesis is biologically inactive and requires enzymatic conversion to active metabolites. Vitamin D is converted to 25-hydroxyvitamin D, the major circulating form of vitamin D, and then to 1,25-dihydroxyvitamin D, the active form of vitamin D, by enzymes in the liver and kidney. 1,25-dihydroxyvitamin D binds to the intracellular vitamin D receptor to activate vitamin D response elements within target genes. The half-life of 1,25-dihydroxyvitamin D is four to six hours, compared with two to three weeks for 25-hydroxyvitamin D and 24 hours for parent vitamin D **(*Pearce and Cheeetham, 2010*).**

3.1.2. Sources of vitamin D

The major natural source of vitamin D is sun exposure, with a small amount coming from the diet (Table 1). For white populations 20-30 minutes of