Evaluation of serum Vitamin D (25-OH)D in Egyptian Thyroid Dysfunction patients

Thesis

Submitted for Partial Fulfillment of Master Degree in Endocrinology and Metabolism

By

Yasmin Yehia Rashwan

M.B., B.CH Supervised by

Prof. Dr. Mohamed Fahmy Abd El Aziz

Professor of Internal Medicine & Endocrinology Faculty of Medicine Ain Shams University

Dr. Salwa Seddik Hosny

Professor of Internal Medicine & Endocrinology Faculty of Medicine Ain Shams University

Dr. Mona Mohamed Abd El Salam

Assistant Professor of Internal Medicine & Endocrinology Faculty of Medicine Ain Shams University

> Faculty of Medicine Ain Shams University

Contents

CONTENTS	Page
Thesis 1st page	1
ACKNOWLEDGMENT	3
LIST OF ABBREVIATIONS	<u>5</u>
LIST OF FIGURES	7
LIST OF TABLES	9
INTRODUCTION	12
AIM OF WORK	14
REVIEW OF LITERATURE	
Chapter 1 : Vitamin D	15
Chapter 2: VITAMIN D &THYROID	<u>47</u>
SUBJECTS & METHODS	76
RESULTS	87
DISCUSSION	_ 142
SUMMARY & CONCLUSION	_ 161
RECOMMENDATIONS	_ 167
REFERENCES	_ 168
ARABIC SUMMARY	_ 1-6
Main sheet (excel)	attached

Contents

CONTENTS

Page	•
- 45	•

ACKNOWLEDGMENT	3
LIST OF ABBREVIATIONS	5
LIST OF FIGURES	7
LIST OF TABLES	9
INTRODUCTION	12
AIM OF WORK	14
REVIEW OF LITERATURE	
Chapter 1 : Vitamin D	15
Chapter 2: VITAMIN D & THYROID	47
SUBJECTS & METHODS	76
RESULTS	87
DISCUSSION	142
SUMMARY & CONCLUSION	161
RECOMMENDATIONS	167
REFERENCES	168
ARARIC SUMMARY	1.6

Acknowledgement

First of all, I wish to express my sincere gratitude to **ALLAH** for His care and generosity throughout my life.

I am greatly honored to express my deep thanks and gratitude to **Prof. Dr. Mohamed Fahmy Abdel Aziz**, Professor of Internal Medicine and Endocrinology. Faculty of Medicine, Ain Shams University, for his continuous support and valuable suggestions which have greatly helped me to complete this work.

I would like to thank **Dr. Salwa Seddik Hosny**, Professor of Internal Medicine and Endocrinology, Faculty of Medicine, Ain Shams University, for her kind supervision, and encouragement.

I would like to extend thank too **Dr. Mona Abd El Salam,** Assistant Professor of Internal Medicine and
Endocrinology. Faculty of Medicine, Ain Shams University, for
her continuous guidance throughout the work.

I would like to thank **Dr. Eman Mohamed Fahmy,** Endocrinology and Metabolism Consultant, Ain Shams University for her help in reviewing the thesis.

My sincere and deep thanks to My Great Family especially My Mother whom without her & their help this work would not have been completed.

My deep thanks to the people who accepted to participate in the study.

List of Abbreviations

1,25OH D	1, 25 di hydroxy vitamin D
24(R),25-	24,25-Dihydroxycholecalciferol
$(OH)_2D_3$	
25 OH D	25 hydroxy vitamin D
AAP	American Association Of Pediatrics
AAD	American association of dermatology
ACEE	American Association of Clinical Endocrinologists
AI	Adequte Intake
AITDs	Autoimmune thyroid disease
ALK.	Alkaline phosphatase
Phos./Alp	
ALRI	Acute lower respiratory tract infection
ATDs	Anti thyroid drugs
BMD	Bone mass density
BUN	Blood urea nitrogen
BMT	bone metabolic turnover
BMI	Body mass index
bAlp	Bone alkaline phosphatase
CBC	Complete blood count
CMAJ	Canadian Medical Association Journal
c.albicans	Candida albicans
CTX	c-terminal cross-linking telopeptide type 1
DEXA	dual energy absorptiometry
\mathbf{D}_2	Ergochalciferol
\mathbf{D}_3	Cholecalciferol
Dpd	deoxypyridinoline
EIA	enzyme <u>immunoassay</u>
ELISA	Enzyme-linked immunosorbent assay
EMBASE	Elsevier bio medical database
FNB	Food and Nutrition Board(US)
FSG	Fasting serum glucose
FT3	Free triiodothyronine
FT4	Free thyroxine
GD	Grave's disease
g/sq cm	Gram /square centimeter(unit of BMD)

Hb%	Serum Haemoglobin percent
HTN	Hypertension
HT	Hashimoto thyroiditis
hMEC	Human microvascular endothelial cells
I^{131}	Radioactive iodine 131
ICU	Intensive care unit
IOM	Institute Of Medicine (US)
IU/L	International unit /litre
IU	International Unit
c-Jun	c-Jun N-terminal kinase(one of JNKs)
JNK	Jun N-terminal kinases
Kg/m ²	Weight in Kilogram / length in meter squared
LBP	ligand binding pockets
LPS	(microbial)lipopolysaccharides
LRP5	lipoprotein receptor-related protein 5
L-thyroxine	Levothyroxine
LL37	Peptide of cathilicidin anti -microbial family
Mins	Minutes
MMI	Methimazole
mmol/l	milli mole /litre
mg/dl	milli gram /deciliter
mIU/L	Milli international unit / litre
NHANES	National Health and Nutrition Examination Survey(US)
NICE	National Institute for Health and Clinical Excellence(GB)
NIH	National Institute of Health(US)
NAMS	North American Menopause Society
NFkB	Nuclear factor kappa of B cells
Nmol/l	Nano mole per litre
Ng/dl	Nano gram /deciliter
Nm	Nanometer
OC	Osteocalcin
OPG	Osteoprotogenin
OSI	Calcaneo Osteo Sono assessment indices
p.aeruginosa	Pseudomonous aeruginosa
PTH	Parathormone hormone
P value	Probability value
Pg/ml	Picogram /milliliter

Pyd	resorption pyrinodoline
QUS	Quantitative Ultrasound
RANK L	Receptor activator of nuclear factor kappa-B ligand
RDA	Required daily allowance
ROS	Reactive oxygen species
SED	Sub erythemic dose
SD	Standard deviation
SGOT/AST	Serum glutamic oxaloacetic transaminase / /aspartate aminotransferase
SGPT/ALT	Serum Glutamic Pyruvate Transaminase // Alanine transaminase
Sig.	Significance
SST	serum separating tube
TBII	Thyrotropin Binding-Inhibiting Immunoglobulins
TGI	Thyroid growth immunoglobulins
TNF α	Tumor necrosis factor alpha
TR alpha	Thyroid receptor alpha
TNG	Toxic nodular goitre
TSH	Thyroid Stimulating Hormone
TSHR	Thyroid Stimulating Hormone Receptor
TSHR	Thyroid Stimulating Hormone Receptor Antibody
Ab/TrAb	
TSI	Thyroid stimulating <u>immunoglobulins</u>
UVA	ULTRA-violet rays A
UVB	ULTRA-violet rays B
$\mu \mathbf{g}$	Microgram
VDS	Vitamin D sterol
VDBP	Vitamin D binding protein
VDR	Vitamin D receptor
VEGF	Vascular endothelial growth factor
VEGF(Flk)	Fetal liver kinase 1 a receptor for VEGF
Wk	Week
Wnt	Wnt proteins family
Yrs.	Years
HS	Highly significant
S	Significant
NS	Non significant

List of Figures

Cha pter	Figure no	Figure title	Page
C H A P	1	Vitamin D metabolism	23
T E R	2	Vitamin D endocrine system	25
1	3	Contributions of vitamin D to good health	29
	4	Vitamin D in innate immunity &clinical infections	44
R` E S U	5	Relation of vitamin D level to ionized Ca+ in the hyperthyroid group	123
L T S	6	Relation of vitamin D level to the free throxine FT4 level among the HYPERTHYROID group	124
R E S U	7	Relation of vitamin D levels to treatment dosage in the HYPOTHYROID group	127
L T S	8	Distribution of the vitamin D level in the control group	131
R	9	Distribution of FT3 in the control group	132
E	10	Distribution of ionized Calcium levels within the	133

S U		control group	
L	11	Distribution of TSH and	134
T		vitamin D levels in the	
S		hyperthyroid group.	
R	12	Distribution of FT3 levels in	135
E		the hyperthyroid group	
S U	13	Distribution and FT4 in the	136
L		hyperthyroid group	
T	4.4		107
S	14	Distribution of ionized	137
		Calcium level within the	
D		hyperthyroid group	
R E	15	Distribution of TSH and	138
S		vitamin D in the	
U		hypothyroid group	
L	1.0		120
T	16	Distribution of FT3 in the	139
S	4 🗷	hypothyroid group	1.40
	17	Distribution of FT4 in the	140
	40	hypothyroid group	1.41
	18	Distribution of ionized	141
		calcium in the hypothyroid	
		group.	
Ch 1	Attachment	Osteoporotic fractures of the	46ii
		spine	

List of Tables

	Table no.	Table title	Page
Review of literature	1	Recommended Dietary Allowances For Vitamin D.	18
	2	Amount And Percent Of Vitamin D And Calcium Given By Common Vitamin D Rich Foods.	19
Chapter 1	3	Classification of vitamin D status by serum level of 25-hydroxyvitamin D (25-OH-D)	20
Chapter 1	4	Tolerable upper levels of vitamin D3.	32
R	5	Description of demographic	93
E		characteristics of the 3 groups.	
S	6	Clothes Distribution Among The 3 Groups.	94
U L	7	Hypertension among groups.	95
Т	8	Description of vitamin D and Thyroid profile	96,97
S		among the 3 groups.	
	9	Comparison between the 3 groups as regarding	98
R		relevant types of food intake.	
Е	10	Comparison of Other Labs between 3 Groups.	99
S	11	Comparison Between 3 Groups As Regards Vitamin D And Thyroid	101

U		Profil .	
L T S	12	Comparison of demographic characteristics between the Control group and the Hyperthyroid group.	103
R E	13	Comparison between Control & Hyperthyroid group as regards food intake.	104
S U	14	Comparison between control group & hyperthyroid about the other lab findings.	105
L T	15	Comparison between Control & Hyperthyroid group as regards vitamin D and thyroid profile.	107
S R	16	Comparison of demographic data bet. the Control & the Hypothyroid group.	108
E S	17	Comparison between Control (1)& Hypothyroid group (3) as regards food intake.	109
U L	18	Comparison between Control & Hypothyroid group as regards food intake.	110
T S R	19	Comparison between Control & Hypothyroid group as regards vitamin D and thyroid profile.	111
E S	20	Comparison of	112

U L		demographic data bet. Hyperthyroid & the	
T		Hypothyroid group.	
S R E	21	Comparison bet. Hyperthyroid &Hypothyroid Group as regards food intake.	113
S		regards 1000 make.	
U L T S	22	Comparison between hyperthyroid & hypothyroid group about the other lab findings.	114
	23	Comparison bet. Hyperthyroid & Hypothyroid group as regards vitamin D and thyroid profile.	115
	24	Significance of vitamin D to demographic data between control & hyperthyroid group	116
	25	Significance of vitamin D to demographic data between Group 1 and Group 3.	117
	26	Significance of vitamin D to demographic data between Group 2 and Group 3.	118
	27	Correlations Of Vitamin D To Different Factors In The Control Group.	119,120
	28	Correlations Of Vitamin D To Different Factors In The Hyperthyroid Group.	121,122
	29	Correlations Of Vitamin D To Different Factors In The Hypothyroid	125,126

		Group.	
	30	Regression Analysis for factors affecting Vit D in the control group.	128
	31	Regression Analysis for factors affecting Vit D in the hyperthyroid group.	129
	32	Regression Analysis for factors affecting Vit D in the hypothyroid group.	130
Chapter 1	Attachment	levels of evidence and grading system	46

Introduction

Vitamin D_3 is a prohormone produced in skin through ultraviolet irradiation of 7-dehydrocholesterol. It is biologically inert and must be metabolized to 25-hydroxyvitamin D_3 in the liver and then to 1,25-dihydroxy vitamin D_3 in the kidney before function. The hormonal form of vitamin D_3 , i.e., 1,25-dihydroxy vitamin D_3 , acts through a nuclear receptor to carry out its many functions, including calcium absorption, phosphate absorption in the intestine, calcium mobilization in bone, and calcium reabsorption in the kidney (**Deluca**, **2004**). It also has several non-calcemic functions in the body as liver regeneration , myocardial contractility, vascular muscle tone and also hormone production; like insulin, prolactin (**Shoback**, **2007**_a). Serum 25-hydroxyvitamin D_3 [25(OH) D_3] concentrations are currently recognized as the functional indicator for vitamin D status (**Heaney**, **2004**).

Vitamin D deficiency is common for many reasons mostly due to decreased time and/ or wrong method of exposure to sunlight which is the major factor of providing our recommended dose of vitamin D (Holick , 2005). Other causes of vitamin D deficiency that may be common too, are low dietary intake, malabsorption diseases , chronic renal failure , nephrotic syndrome , severe liver disease, drugs like; anticonvulsants , glucocorticoids (Shoback , 2007 $_{\rm b}$).

In addition to its vital role in Ca & phosphate metabolism it affects many other systems so its deficiency is hazardous as there are associations between low 25(OH)D levels and peripheral vascular disease (**Melamed**, et al., 2008). Also certain cancers, multiple sclerosis, rheumatoid arthritis, juvenile diabetes, are said

Introduction

to be prevented or modified through manipulating vitamin D serum level (Holick, 2004).

Parkinson's and Alzheimer's disease are being investigated too for their relation to vitamin D insufficiency/deficiency and which one is related more to vitamin D (Evatt, et al., 2008).

However these associations were found in observational studies and vitamin D supplements have not been demonstrated to reduce the risks of these diseases (Pittas, et al., 2010).

Overall, excess or deficiency in the calciferol system appear to cause abnormal functioning and premature aging (McCann, 2007/ Keisala, et al., 2009/Tuohimaa, et al., 2009).

In thyroid dysfunction patients; the high incidence of muscle pains (esp. proximal) and myopathies and bone metabolic disorders arise questions whether it is related to Ca metabolism or not and whether pathological alteration of vitamin D serum levels may be the underlying pathology. It has been noticed that 30-80% of individuals with hypothyroidism, manifest neuromuscular symptoms, depending on the severity of hypothyroidism. Muscle weakness is observed in one third of patients with hypothyroidism. Carpal tunnel syndrome-although not part of the myopathy- is a peripheral nerve dysfunction found in 15-30% of patients with hypothyroidism (Cakir, et al., 2003). On the other hand, Thyrotoxic myopathy is a well-known problem. It can sometimes be the first presentation of the underlying hyperthyroid state (Victor and Ropper, 2005).