Assessment of Vitamin D Level in Newly Diagnosed Multiple Myeloma Patients and Patients in Remission

Thesis

Submitted for Partial Fulfillment
of Master Degree in ***Internal Medicine***

By

Mostafa Mahmoud Fouad Mahmoud
M.B.B.CH

Under Supervision of

Prof. Dr. / Shaza Abd El Wahab El Kourshy
Professor of Internal Medicine and Clinical Hematology
Faculty of Medicine - Ain Shams University

Assist. Prof. / Hanaa Fathey Abd El Samee
Assistant Professor of Internal Medicine and Clinical Hematology
Faculty of Medicine - Ain Shams University

Dr. / Nahed Moawad Ibrahim
Lecturer of Internal Medicine and Clinical Hematology
Faculty of Medicine - Ain Shams University

Faculty of Medicine – Ain Shams University
2019

سورة البقرة الآية: ٣٢

Acknowledgments

First and foremost, I feel always indebted to ***Allah*** *the Most Beneficent and Merciful.*

I wish to express my deepest thanks, gratitude and appreciation to ***Prof. Dr. / Shaza Abd El Wahab El Kourshy****, Professor of Internal Medicine and Clinical Hematology, Faculty of Medicine, Ain Shams University, for her meticulous supervision, kind guidance, valuable instructions and generous help.*

Special thanks are due to ***Assist. Prof. / Hanaa Fathey Abd El Samee****, Assistant Professor of Internal Medicine and Clinical Hematology, Faculty of Medicine, Ain Shams University, for her sincere efforts, fruitful encouragement.*

I am deeply thankful to ***Dr. / Nahed Moawad Ibrahim****, Lecturer of Internal Medicine and Clinical Hematology, Faculty of Medicine, Ain Shams University, for her great help, outstanding support, active participation and guidance.*

I would like to express my hearty thanks to all my family for their support till this work was completed.

Mostafa Mahmoud Fouad Mahmoud

List of Contents

List of Tables

List of Tables cont...

List of Figures

Fig. No.	Title	Page No.

List of Abbreviations

Abb.	Full term
AL	*Light chain amyloidosis*
ASCT	*Autologous stem cell transplantation*
BMI	*Body mass index*
CA	*Chromosomal abnormalities*
CCyD	*Carfilzomib-Cyclophosphamide-Dexamethasone*
CR	*Complete response*
CTCL	*Cutaneous T-cell leukemia*
CVD	*Cardiovascular disease*
DLBCL	*Diffuse large B-cell lymphoma*
D-S	*Durie-Salmon staging system*
ENKTL	*Extranodal natural killer/T - cell lymphoma*
FCM	*Flowcytometry*
GN	*Glomerulonephritis*
iFISH	*Interphase fluorescent in situ hybridization*
IOM	*Institute of Medicine*
ISS	*International Staging System*
KPD	*Carfilzomib, pomalidomide, dexamethasone*
KRD	*Carfilzomib-Lenalidomide-Dexamethasone*
LHCs	*Lymphohematopoietic cancers*
MF	*Mycosis fungoides*
MGUS	*Monoclonal gammopathy of unknown significance*
MIDD	*Monoclonal Ig deposition disease*
MM	*Multiple myeloma*
MP	*Melphalan-Prednisone*
MPT	*Melphalan-Prednisone-Thalidomide*

List of Abbreviations cont...

Abb.	Full term
MR	*Minor response*
MRD	*Minimal residual disease*
mSMART	*Mayo Stratification of Myeloma and Risk-Adapted Therapy*
NGF	*Next-generation flow cytometry*
NGS	*Next-generation sequencing*
NHL	*Non-Hodgkin's lymphoma*
NK	*Natural killer*
NNR	*Nordic Nutrition Recommendations*
OS	*Overall survival*
PCP	*Pomalidomide, cyclophosphamide, prednisone*
PD	*Progressive disease*
PET-CT	*Positron emission tomography-computed tomography*
Pom/Dex	*Pomalidomide-Dexamethasone*
PR	*Partial response*
PTG	*Parathyroid gland*
PVD	*Pomalidomide, bortezomib, dexamethasone*
Rd	*Lenalidomide-Dexamethasone*
RFS	*Relapse free survival*
R-ISS	*Revised-International Staging System*
sCR	*Stringent complete response*
SD	*Stable disease*
SLAMF7	*Signaling lymphocytic activation molecule F7*
SMM	*Smoldering MM*
SREs	*Skeleton-related events*

List of Abbreviations cont...

Abb.	Full term
SS	*Sézary syndrome*
TD	*Thalidomide-Dexamethasone*
TMA	*Thrombotic microangiopathy*
TTT	*Time-to-treatment*
VCD or CyBorD	*Bortezomib-Cyclophosphamide-Dexamethasone*
VD	*Bortezomib-Dex*
VDR	*Vitamin D receptor*
VDT-PACE	*Bortezomib, dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, and etoposide*
VGPR	*Very good partial response*
VMP	*Bortezomib-Melphalan-Prednisone*
VRD	*Bortezomib-Lenalidomide-Dexamethasone*
VTD	*Bortezomib-Thalidomide-Dexamethasone*
WHO	*World Health Organization*

INTRODUCTION

Vitamin D (D represents D_2, D_3, or both) is a secosterol produced endogenously in the skin from sun exposure or obtained from foods that naturally contain vitamin D, including cod liver oil and fatty fish (eg, salmon, mackerel, and tuna); UV-irradiated mushrooms; foods fortified with vitamin D; and supplements ***(Hossein-nezhad et al., 2012)***. So, Vitamin D levels can be significantly affected by skin pigmentation, sun-protection habits, geographic residency and diet. No seasonal variation in vitamin D status was noted ***(Ng et al., 2009).***

1,25(OH)2D3, the hormonal derivative of vitamin D exerts its growth-regulatory effect through binding to the intranuclear receptor vitamin D receptor (VDR) ***(Baker et al., 1988).***

Vitamin D deficiency is the most common nutritional deficiency worldwide ***(Maier et al., 2013).*** As yet there is no universally accepted classification of vitamin D levels, sufficient vitamin D status is defined as a serum 25-OH-D level of above 30 ng/ml. Vitamin D inadequacy is defined as serum 25-OH-D level under 30 ng/ml and further divided into vitamin D insufficiency (10 to 30 ng/ml) and vitamin D deficiency (under 10 ng/ml) ***(Gallagher et al., 2010).***

Moderate vitamin D deficiency can cause a decrease in intestinal calcium absorption and an increase in PTH. PTH activates osteoblasts, which stimulate the transformation of

preosteoclasts into mature osteoclasts. These cells dissolve the mineralised collagen matrix in bone, causing osteoporosis and increase fracture risk ***(Souberbielle et al., 2006).***

Several studies have begun to examine the relationship between circulating vitamin D levels and hematologic malignancies; Vitamin D insufficiency is associated with inferior time-to-treatment and Overall survival in chronic lymphocytic leukemia patients ***(Shanafelt et al., 2011),*** also there is a significant decrease in non-Hodgkin lymphoma risk with increased sun exposure ***(Kelly et al., 2012),*** vitamin D insufficiency in follicular lymphoma (FL) is predictive of early clinical failure among all patients ***(Tracy et al., 2017),*** the pretreatment serum 25(OH)D level was higher in patients with the indolent type of lymphoproliferative disease, CLL, than in patients with DLBCL, FL, and HL ***(Djurasinović et al., 2018).***

Multiple myeloma (MM) accounts for 1.6% of all cancers and 5% to 10% of all hematologic malignancies ***(Anwer et al., 2018).*** It is considered a treatable but incurable disease, and thus lifelong observation and follow- up are recommended ***(Anderson et al, 2016).***

International Myeloma Working Group updated indications to start treatment in MM patients. Some laboratory and radiographic variables are added to existing CRAB features. These features include bone marrow plasma cells ≥60%, abnormal MRI with more than one focal lesion, with

each lesion >5 mm, and involved/uninvolved serum free light chain ratio ≥100 ***(Rajkumar, 2016).***

Osteolytic lesions develop in nearly 90% of patients with MM, and these are frequently complicated by skeleton-related events (SREs) such as severe bone pain, pathologic fractures, vertebral collapse, hypercalcemia, and spinal cord compression ***(O'Donnell and Raje, 2017);*** It is estimated that 20% of MM patients present with pathologic fractures, 40% develop a fracture in the first year after diagnosis, and up to 60% develop pathologic fractures over the course of their disease) ***(Melton et al., 2005).***

Vitamin D deficiency is extremely common in multiple myeloma, with 40% of patients having vitamin D levels in the deficient range of levels less than 36 nmol/L and it represents a surrogate feature for clinical multiple myeloma disease status ***(Diamond et al., 2010).***

It has a significant clinical role in MM patients because of their interrelationship with calcium homeostasis and bone metabolism ***(Holick, 2007).***

The prevalence of vitamin D deficiency increased in parallel with International Staging System (ISS) ***(Greipp et al., 2005);*** 16% of patients in Stage I, 20% in Stage II, and 37% in Stage III ***(Ng et al., 2009).***

AIM OF THE WORK

The aim of the present study is to compare between vitamin D level in newly diagnosed patients with Multiple Myeloma and patients in remission.

Chapter 1:

MULTIPLE MYELOMA

Definition:

Multiple myeloma is characterized by the uncontrolled proliferation of monoclonal plasma cells in the bone marrow, leading to production of nonfunctional intact immunoglobulins or immunoglobulin chains ***(Swerdlow et al, 2011).***

It is considered a treatable but incurable disease, and thus lifelong observation and follow- up are recommended ***(Anderson et al, 2016).***

Plasma cell dyscrasias encompass a spectrum of disease which include asymptomatic premalignant proliferation of plasma cells (monoclonal gammopathy of unknown significance [MGUS]) and asymptomatic MM (smoldering MM (SMM)) to malignant disease (MM and plasma cell leukemia) with end-organ damage and associated significant patient morbidity ***(Landgren, 2013).***

Incidence:

Multiple myeloma (MM) is the second most commonly diagnosed hematological neoplasm, with an incidence rate of 6.2 per 100 000 individuals ***(Seigel et al, 2016).***