Dual Energy X-ray Absorptiometry (DEXA) and Vitamin D status in children and adolescents patients with severe hemophilia A and type 1 diabetes mellitus

Thesis
Submitted for Fulfillment of Master Degree in Pediatrics

By
Raguia Atef Mostafa
M.B.B.CH.of medicine
2012

Under Supervision of
Dr. Nevine Gamal Andrawes
Professor of Pediatrics
Pediatrics department
Ain Shams University

Dr. Manal Hashem Ahmed Fayek
Professor of Clinical Pathology
Clinical Pathology department
Ain Shams University

Dr. Nouran Yousef Salah El-Din
Lecturer of Pediatrics
Pediatrics department
Ain Shams University

Faculty of Medicine
Ain Shams University
2019

سورة البقرة الآية: ٣٢

Acknowledgment

First and foremost, I feel always indebted to **ALLAH**, *the Most Kind and Most Merciful.*

I was honored to work under the supervision of **Dr. Nevine Gamal Andrawes,** *Professor of Pediatric Faculty of Medicine Ain Shams University, for her vital assistance and unlimited co-operation. She had generously offered me much of her time, precious advice and variable guidance throughout this work.*

I wish to express my deepest thanks and gratitude to **Dr. Manal Hashem Ahmed Fayek,** *Professor of Clinical Pathology Faculty of Medicine Ain Shams University, for her close supervision, generous efforts and constant encouragement. She had scarified a lot of her busy time to teach me and revise over step of this thesis.*

I would like to express my sincere thanks to **Dr. Nouran Yousef Salah El-Din,** *Lecturer of Pediatrics Faculty of Medicine Ain Shams University, who kindly offered me much of her time, experience, valuable help and effort.*

To my family, all my colleagues and all those who helped me in this work, I am so thankful for their support and co-operation.

Last but not least my sincere thanks and appreciation to all patients participated in this study.

Raguia Atef Mostafa

List of Contents

List of Tables

List of Tables (Cont...)

List of Tables (Cont...)

List of Figures

List of Tables (Cont...)

List of Abbreviations

Abb.	Full term
%CV	Coefficients of variation
2-h PG	The 2-h plasma glucose
ADA	American Diabetes Association
ALP	Alkaline phosphatase
Alt	Alanine aminotransaminase
ANOVA	A one way analysis of variance
aPPT	Activated partial thromboplastin time
ASCVD	Atherosclerotic Cardiovascular Disease
Ast	Aspartate aminotransaminase
BMC	Bone mineral content
BMD	Bone mineral density
BMI	Body mass index
Ca	Calcium
CaBp	Calcium binding protein
Creat	Creatinine
CRS	Congenital rubella syndrome
CSII	Continuous subcutaneous insulin infusion
DCCT	Diabetes Control and Complications Trial
DCs	Dentritic cells
DEXA	Dual Energy X-Ray Absorptiometry
DKA	Diabetic Ketoacidosis
DM	Diabetes mellitus
DSMES	Diabetes self management education and support
FFM	Fat-free mass
FFP	Fresh frozen plasma
FGF23	Fibroblast growth factor 23
FH	Family history

List of Abbreviations (Cont.)

Abb.	Full term
FPG	Fasting plasma glucose
GAD	Glutamic acid decarboxylase
GIT	Gastrointestinal tract
GWA	Genome-wide association
Hb	Hemoglobin
HbA1C	Glycosylated hemoglobin
Hct	Hematocrit
HJHS	Hemophilia Joint Health score
HLA	Human leukocyte antigen
Ht	Height
ICA512	Tyrosine phosphatase-like protein
ICOS	Inducible costimulatory molecule
IL	Interleukin
INF	Interferon
ISCD	International Society of Clinical Densitometry
ISPAD	International Society for Pediatric and Adolescent Diabetes
ITI	Immune tolerance induction
ITT	Immune tolerance therapy
J-score	Joint score
LBM	Lean Body Mass
MHC	Major histocompatibility complex
MNT	Medical nutrition therapy
MODY	Maturity onset diabetes of young
NGSP	National Glycohemoglobin Standardization Program
NS	Normal saline
OGTT	Oral glucose tolerance test
P	Phosphorus

List of Abbreviations (Cont.)

Abb.	Full term
Plts	Platelets
PT	Prothrombin time
PTH	Parathormone
RAAS	Renin Angiotensin Aldosterone System
RAS	Renin-angiotensin system
Rbcs	Red blood cells
RIN	Rat insulinoma
ROI	The region of interest
SD	Standard deviations
SDS	Standard deviation score
T1DM	Type 1 diabetes mellitus
Tc	Total cholesterol
TCNS	Toronto Clinical Neuropathy Score
TG	Triglyceride
TGF	Transforming growth factor
Th	T helper cell
TNF	Tumor necrotic factor
Tregs	Regulatory T cells
USA	United State of America
VD	Vitamin D
VDD	Vitamin Ddeficiency
VDR	Vitamin D receptor
Wbcs	White blood cells
WHO	World Health Organization
Wt	Weight
ZnT8	Zinc T8 transporter

ABSTRACT

Background: Vitamin D (Vit D) deficiency (<20ng/ml) or insufficiency (20-30 ng/ml) are common in pediatric patients with severe hemophilia A and patients with type 1 diabetes mellitus (T1DM). It affects bone mineral density (BMD) which is assessed by Dual Energy X-ray Absorptiometry (DEXA) scan (osteoporosis ≤-2.5 z-score and osteopenia -1≥ z-score > -2.5).

The aim of this study was to measure 25-hydroxyvitamin D level in patients with severe hemophilia A and those with T1DM and correlate it to their DEXA scan score, glycemic control and the presence of microvascular complications in T1DM and annual bleeding rate in severe hemophilia A.

Methods: This 1-year cross-sectional study was conducted on 50 patients with T1DM and 50 patients with severe hemophilia A who were compared to 50, age and sex matched, healthy controls. They were recruited from Pediatric diabetes clinic and hematology clinic, Ain Shams University. All participants were subjected to full history, examination, laboratory investigations included hemogram, serum 25(OH)Vit D, calcium, phosphorus, alkaline phosphatase, glycosylated hemoglobin (HbA1c), lipid profile, ALT, urea, creatinine; urine analysis for microalbuminuria and DEXA scan.

Results: The mean patients' age was 13.56 years (9 – 16). Vit D deficiency and insufficiency were demonstrated in 56% and 22% respectively in T1DM, and 97% deficiency on severe hemophilia A. Mean Vit D in our diabetics and hemophilics was correlated with their DEXA scan score. An inverse correlation was found between mean Vit D and HbA1C, diabetes duration, and presence of microvascular complications in patients with T1DM and joint score in patients with severe hemophilia.

Conclusion: Vit D deficiency (<30 ng/ml) was related to longer diabetes duration, elevated HbA1C and presence of microvascular complications in patients with T1DM and annual bleeding rate and joint score in patients with severe hemophilia A. Hence, Vit D supplementation might help in control of diabetes and possible delay or prevention of its microvascular complications in diabetics and improve mobilization and quality of life in hemophilics.

Keywords: Dual Energy X-ray Absorptiometry; Vitamin D; type 1 diabetes mellitus

INTRODUCTION

Osteoporosis is a disorder characterized by decreased bone mass and microarchitectural deterioration, resulting in loss of bone strength and fragility fractures. The fundamental pathogenetic mechanisms includes: failure to achieve optimal strength during growth, excessive bone resorption resulting in loss of bone mass, and failure to replace lost bone due to defects in bone formation ***(Sözen et al., 2017).***

Hemophilia is an inherited bleeding disorder characterized by the absence of one of the coagulation factors including factor VIII in hemophilia A and factor IX in hemophilia B. The type of inheritance is X-linked and recessive. However, occasionally, there are some spontaneous mutations ***(Rodriguez, 2010).*** There are three grades of hemophilia according to the percentage of coagulation factor in the patient's blood: severe (<1%), moderate (1% to 5%), and mild (>5%) ***(Rodriguez, 2010).***

Patients with hemophilia may be at risk for developing reduced bone mineral density (BMD) for a number of reasons such as recurrent hemoarthrosis, immobilization ***(Abdelrazik et al., 2007),*** lack of adequate exercice, and low vitamin D (VD) levels ***(Albayrak and Albayrak, 2015).***

These factors may also affect the peak bone mineral density (BMD). Children achieve peak bone density at the end of sexual and skeletal development ***(Wren et al., 2014).***

Low bone mass in childhood may be reflected in low BMD in adolescence and adult life. Low peak bone density facilitates the development of osteoporosis in later life. Achieving a normal bone mass in childhood is therefore a positive factor for preventing adult osteoporosis. To avoid osteoporosis and its complications such as pathologic fractures, preventive measures need to be taken in childhood as body growth takes place ***(Wallny et al., 2007).*** Some useful measures are early assessment of bone mass, ensuring normal vitamin D (Vit D) status, and preventing and early correction of joint mobility limitations. Of these, Vit D supplementation is easy and cheap to implement, provided the vitamin D deficiency is known ***(Alioglu et al., 2012 and Barnes et al., 2004).***

Hematologists dealing with hemophilia may overlook the possibility of vitamin D deficiency (VDD) in hemophilic patients by focusing on matters such as bleeding and factor use. In many hospitals, Vit D measurement is not available for routine use in patients. If physicians cannot measure vitamin D levels during routine patient visits, they will not be aware of the extent and depth of Vit D deficiencies. For this reason, we do