
بسم الله الرحمن الرحيم
وَقُل رَّبِّ
زِدْنِي عِلْمًا
صدق الله العظيم
سورة طه: آية (١١٤)

ACKNOWLEDGEMENT

First and for most, thanks to **Allah** "The Most Merciful"

In all gratitude, I extend my most sincere thanks to **Prof. Dr. Moatassem Salah Amer,** Professor of Geriatric Medicine and Internal Medicine, Faculty of Medicine, Ain Shams University, for honoring me with his supervision of this thesis. His help, guidance, and valuable advices were a great encouragement throughout the work.

Sincere appreciation to **Prof. Dr. Randa Ali-Labib,** Professor of Biochemistry, Faculty of Medicine, Ain Shams University, for her valuable encouragement, support, and advice.

Profound thanks to **Prof. Dr. Tamer Mohammad Farid,** Professor of Geriatric Medicine, Faculty of Medicine, Ain Shams University, for his generous help, expert advice and great assistance throughout this work.

Special thanks to **Dr. Rania Mohammed Abou Hashem,** Lecturer of Geriatric Medicine, Faculty of Medicine, Ain Shams University, for her help and advice in an earlier time during this work.

I am deeply indebted and sincerely thankful to **Dr. Doha Rasheedy Aly,** Lecturer of Geriatric medicine, Faculty of Medicine, Ain Shams University, for her sincere guidance and help.

This work was supported by **Ain Shams Faculty of Medicine Grant's Office**, Grant No 2012-10.

I would also like to record my thanks and sincere gratitude to my family, my wife and my colleagues who supported and encouraged me throughout this work.

Mohammad Fahmy

List of Contents

List of Abbreviations

AGEs: .....Advanced Glycation End-products.

ADL: .....Activities of Daily Living.

AUC: .....Area Under the Curve.

BMD: .....Bone Mineral Density.

CaSR: .....Calcium Sensing Receptor.

Cbl:.....Cobalamin.

CD: .....Cluster of Differentiation.

CDC:.....Centers for Disease Control and Prevention.

CNS: .....Central Nervous System.

CoA:.....Coenzyme A.

CT:.....Computed Tomography.

CVD: .....Cardiovascular Disease.

Dkk-1: .....Dickkopf-1.

DM:.....Diabetes Mellitus.

DNA: .....Deoxyribonucleic Acid.

DXA: .....Dual-energy X-ray Absorptiometry.

EGF: .....Epidermal Growth Factor.

GIP: .....Glucose-dependent Insulinotropic Peptide.

GDS: .....Geriatric Depression Scale.

GLP:.....Glucagon-Like Peptide.

GLUT: .....Glucose Transporter.

HbA1C:.....Glycated Hemoglobin.

Hcy:.....Homocysteine.

holo-TC (holoTC):.holo-Transcobalamin.

IADL: .....Instrumental Activities of Daily Living.

List of Abbreviations (Cont.)

IGF-1: .....Insulin-like Growth Factor-1.

IgG: .....Immunoglobulin G.

IGT: .....Impaired Glucose Tolerance.

K_m: .....Michaelis constant (the substrate concentration at which the reaction rate is at half-maximum).

mcg: .....microgram(s).

MCV:.....Mean Corpuscular Volume.

MMA:.....Methylmalonic Acid.

MMSE: .....Mini-Mental State Examination.

MRI: ..... Magnetic Resonance Imaging.

NPV: .....Negative Predictive Value.

OHG: ..... Oral Hypoglycemic Agent(s)

pg/ml: .....picogram/milliliter.

PPARγ: .....Peroxisome Proliferator-Activated Receptor-Gamma.

PPIs: .....Proton Pump Inhibitors.

PPV:.....Positive Predictive Value.

PTH: .....Parathyroid Hormone.

QCT: .....Quantitative Computed Tomography.

RANKL:.....Receptor Activator of NF-κB Ligand.

rhPTH:.....recombinant human Parathyroid Hormone.

ROC: .....Receiver Operating Characteristic.

ROS: .....Reactive Oxygen Species.

SAM:.....S-Adenosylmethionine.

tHcy: .....total Homocysteine.

TNF-alpha: .....Tumor Necrosis Factor-alpha.

List of Abbreviations (Cont.)

TRAP: .....Tartrate-Resistant Acid Phosphatase.

TZDs:.....Thiazolidinediones.

US:.....United States.

WHI: .....Women's Health Initiative trial.

WHO: .....World Health Organization.

Wnt:.....Wingless-int.

yrs: .....Years.

List of Tables

List of Tables (Cont)

List of Figures

Introduction

Diabetes mellitus is becoming increasingly recognized as a risk factor for osteoporotic fracture. Although fracture risk in patients with type 2 diabetes is increased compared with normal subjects, not only in those with low bone mineral density (BMD) but also in those with normal or high BMD, decreased BMD remains a major determinant of fragility fracture ***(Adami, 2009).***

The implementation of a low-fat, low-energy diet in patients with obesity and hyperlipidemia has been shown to result in a decrease of the intake of certain nutrients, including B-vitamins ***(Grzybek et al., 2002).***

Patients with type 2 diabetes mellitus often follow a calorie-restricted diet, but few studies have investigated the sufficiency of nutrients for the maintenance of skeletal health ***(Yamada et al., 2011).***

Vitamin B12 is of public health importance, not only because deficiency leads to megaloblastic anaemia and irreversible nerve damage, but also because emerging evidence links low vitamin B12 to an increased risk of a number of age-related diseases ***(Hughes et al., 2013).*** In diabetic patients, vitamin B12 deficiency is a potential comorbidity that is often overlooked, despite the fact that many diabetic patients are at risk for this specific disorder ***(Pongchaidecha et al., 2004).***

Vitamin B12 is an important enzymatic cofactor in the synthesis of methionine from homocysteine (Hcy), and an elevation of Hcy can be caused by insufficiency of vitamin B12. Numerous studies have linked high circulating Hcy levels and low concentrations of vitamin B12 with increased risk of low BMD in non-diabetic subjects ***(Gjesdal et al., 2006 and Baines et al., 2007).*** However, until recently, there have been only few reports on the association of vitamin B12 with osteoporosis in patients with type 2 diabetes mellitus.

In the present study, to evaluate one of the nutritional risk factors for osteoporosis in patients with type 2 diabetes mellitus, bone mineral density and serum level of vitamin B12 were analyzed.

Aim of the Work

The aim of this work is to study the relationship between serum level of vitamin B12 and bone mineral density in elderly diabetic patients.

Osteoporosis in Elderly

Osteoporosis is a systemic skeletal disease characterized by a low bone mass and a micro-architectural deterioration of bone tissue with a consequent increase in bone fragility and susceptibility to fracture ***(WHO, 2003).***

Osteoporosis is a common disease of older adults and is a major public health problem worldwide. According to the International Osteoporosis Foundation, estimated 75 million men and women in Europe, the United States, and Japan are affected by osteoporosis. One in 3 women and 1 in 5 men more than 50 years of age experience osteoporotic fractures ***(Johnell and Kanis, 2006).***

The morbidity of osteoporosis arises from the associated fractures. The common osteoporotic fractures are those of the hip, vertebrae and forearm ***(Kanis et al., 2008).***

The lifetime risk of a hip, wrist, or clinically diagnosed vertebral fracture is about 40% for white women and 13% for white men ***(Kanis et al., 2000).***

The most serious osteoporotic fracture is that of the hip. Among elders, hip fractures are responsible for significant morbidity and are associated with excess mortality of up to 20%, with costly long-term nursing home care for most survivors. It is therefore of great importance

to identify risk factors for osteoporosis to inform interventions that may reduce the likelihood of fracture ***(Albagha, 2005).***

Risk factors consistently associated with osteoporosis include female sex, Caucasian race, low body weight and maternal or personal history of fractures ***(Albrand et al., 2003).***

Other well-known risk factors include age, the use of glucocorticoids and active cigarette smoking ***(Kanis, 2002).***

Diagnosis of osteoporosis:

Since osteoporosis is clinically silent until a fracture occurs and since it affects a large percentage of the population, prevention and early intervention are essential before a fracture occurs. In addition to assessment of a patient's potential for osteoporosis from the known risk factors there are both imaging and biochemical markers that can enhance clinical decision making ***(Levine and Belmaker, 2006).***

Prior to the introduction of bone mineral density (BMD) measurements, the diagnosis of osteoporosis was only made when fragility fractures occurred in an appropriate clinical setting, largely in postmenopausal women and older men. Today we use BMD to diagnose osteoporosis and osteopenia before fractures occur, as well as to confirm the diagnosis in patients with fragility fracture ***(Raisz, 2005).***

Dual-energy X-ray absorptiometry (DXA) measures BMD at the lumbar spine and the non-dominant hip. BMD is reported in T and Z scores, which represent standard deviations around a population mean. The T score is the postmenopausal patient's BMD compared with that of an average healthy young woman. The T score assigns a diagnostic category of bone loss and guides therapy, but the T score alone is insufficient for predicting fracture risk ***(American College of Obstetricians and Gynecologists, 2004).***

The following four general diagnostic categories for women have been proposed by a WHO Study Group based on measurements by DXA ***(WHO, 1994):***

- Normal: A value of BMD within 1 standard deviation of the young adult reference mean (T-score ≥-1).
- Low bone mass (osteopenia): A value of BMD more than 1 standard deviation below the young adult mean, but less than 2.5 standard deviations below this value (T-score < -1 and > -2.5).
- Osteoporosis: A value of BMD 2.5 standard deviations or more below the young adult mean (T-score ≤ -2.5).
- Severe osteoporosis (established osteoporosis): A value of BMD 2.5 standard deviations or more below the young adult mean in the presence of one or more fragility fractures ***(Kanis et al., 1994).***