Prevalence of hypovitaminosis D and its relation to cardiovascular risk among elderly diabetic female patients

Thesis

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1,25(OH)2D	**1,25 dihydroxy vitamin D**
25(OH)D	**25 hydoxy vitamin D**
7-DHC	**7-dehydrocholesterol**
BMD	**Bone mineral density**
BMI	**Body mass index**
BP	**Blood pressure**
CP	**C peptide**
CPI	**C-peptide index**
CRP	**C reactive protein**
CVD	**Cardiovascular disease**
CYP	**Cytochrome p**
DBP	**Diastolic blood pressure**
DCs	**Dendritic cells**
DM2	**Type 2 diabetes**
FBS	**Fasting blood sugar**
FGF23	**Fibroblast growth factor 23**
GLUT-4	**Glucose 4 transporter**
HOMA	**Homeostatis model assessment**
HTN	**Hypertension**
IFN-γ	**Interferon γ**
IL-2	**Interleukine**
IOF	**International Osteoporosis Foundation**
IR	**Insulin resistance**

LDL	**Low-density lipoprotein**
MetS	**The metabolic syndrome**
NHANES	**National health and nutrition examination survey**
OGTT	**Oral glucose tolerance test**
OHG	**Oral hypoglycemic**
PTH	**Parathormone hormone**
RCTs	**Randomized controlled trials**
SBP	**Systolic blood pressure**
Th1	**T helper cell**
TLR2	**Toll like receptors 2**
TNF-α	**Tumor necrosis factor α**
UVB	**Ultraviolet B**
VDR	**Vitamin D receptor**
VDREs	**Vitamin D response elements**
VERE	**Vitamin D's element of response**
WHO	**World Health Organization**

INTRODUCTION

Vitamin D is either produced in the skin *via* the effects of ultraviolet light or ingested with food and/or supplements. It undergoes hydroxylation in the liver to produce 25(OH)D then it undergoes activation by the renal enzyme 25(OH)D-1α-hydroxylase for producing the circulating levels of the activated form of vitamin D **(Artaza *et al*., 2009).**

There is a growing evidence suggests that hypovitaminosis D is a risk factor for numerous chronic medical conditions **(Rostand, 1997, Holick, 2005, 2006).** In this study, we present data that support the link between hypovitaminosis D, diabetes and cardiovascular risk factors including hypertension, obesity and other cardiovascular diseases.

Several epidemiologic studies have suggested that there is a strong association between hypovitaminosis D, *diabetes mellitus* and cardiovascular disease (CVD). Analysis of data of the Third National Health and Nutrition Examination Survey (NHANES III) showed that hypovitaminosis D is associated with an increased prevalence of CVD risk factors **(Artaza *et al*., 2009).**

Vitamin D is not only essential for maintaining good bone health, but it also plays a role throughout the human body systems that is supported by presence of vitamin D receptors (VDRs) in

most tissues including pancreatic tissue and cardiovascular system **(Griz *et al*., 2014).**

The Endocrine Society Task Force reports the current recommended levels of serum 25(OH)D are 30 ng/ml that is required to maintain bone health, prevent disease and to provide increase benefits **(Holick *et al*., 2011),** as these levels are associated with maximal suppression of parathyroid hormone.

Most authors suggest that sufficient 25(OH)D levels above 30 ng/mL to protect against development of DM and to decrease a specific consequences **(Souza *et al*., 2016).**

There is a great controversy about the definition of hypovitaminosis D, current International Osteoporosis Foundation guidelines **(Dawson-Hughes *et al*., 2010)** define vitamin D insufficiency as 25-(OH)D levels less than 20 ng/ml and deficiency as levels less than 10 ng/ml.

Vitamin D deficiency is highly prevalent worldwide and certain groups as elderly persons, women and institutionalized persons are particularly prone to severe deficiency (**Mithal *et al*., 2009),** as many as 40% to 90% of the elderly have 25(OH) vitamin D levels below 30 ng/ml (**Chapuy *et al*., 1997, Lips, 2001, Heaney *et al*., 2003b, Snijder *et al*., 2005, Hypponen and Power, 2007, Institute of Medicine, 2010)**.

Hypovitaminosis D could be related to endogenous factors such as increasing age, body mass index **(Molina and Londoño, 2012)** and / or exogenous factors including altitude, pollution, season, clothing and sunscreen usage **(Veiga and Campos, 2014).**

In various population, more than 80% of diabetic patients have hypovitaminosis D, also it is related to poor glycemic control **(Bashir *et al*., 2016).**

There is an emerging evidence that supports the role of vitamin D deficiency in DM, cardiovascular disease and endothelial dysfunction through various biological associations **(McGreevy and Williams, 2011).**

Vitamin D deficiency appears to predispose individuals to diabetes, as it affects beta cells function in various ways, as it has effect of on insulin synthesis and secretion (**Sergeev and Rhoten, 1995)** and its link to insulin resistance **(Sowers, 2004).**

Endogenous insulin secretion could be assessed by measurement of C-peptide as it is produced in equal amounts to insulin especially in insulin treated persons **(Jones and Hattersley, 2013).**

Vitamin D may also affect insulin resistance through the renin-angiotensin-aldosterone system as angiotensin II increases insulin resistance **(Sowers, 2004).**

Insulin resistance is a hallmark of diabetes, obesity, cardiovascular diseases and metabolic syndrome **(Singh and Saxena, 2010).**

Measurement of insulin resistance (IR) could be done by various measurements such as fasting insulin level **(Thomas *et al*., 2000)** and Homeostatis model assessment (HOMA-IR) utilizing population specific cut-off values **(Geloneze *et al*., 2009).**

Also fasting C-peptide correlates with known IR markers including HOMA-IR **(Patel *et al*., 2012).**

Vitamin D has a protective role against cardiovascular disease, as it improves endothelial function and cardiac contractility **(Artaza *et al*., 2009).**

Vitamin D deficiency proposed to be linked to hypertension as it triggers secondary hyperparathyroidism that promotes vascular remodelling **(Das *et al*., 2013),** also vitamin D has a role in the inhibition of the renin–angiotensin–aldosterone system **(Xiang *et al*., 2005, Zhou *et al*., 2008).**

Several studies proposed major links between hypovitaminosis D and obesity and an inverse relationship between vitamin D level and body mass index (BMI) **(Pérez-Loopez, 2009).**

The high prevalence of hypovitaminosis D and its related consequences makes vitamin D supplementation necessary in most elderly due to inadequate sources of vitamin D related to current lifestyles, poor diet and limited sunlight exposure **(Hollis, 2005).**

The Food and Drug Administration recommends a daily intake of vitamin D 400 IU for those 51–70 years old and 600 IU for those over age 70, whereas the National Osteoporosis Foundation recommends 800 to 1,000 IU per day for everyone over the age of 50. To achieve levels of vitamin D of more than 30 ng/ml (75 nmol/L) **(Heaney, 2004).**

REVIEW OF LITERATURE

Vitamin D and health outcomes

Vitamin D has several important functions for good overall health and healthy bones. It's also an important factor in making well function of muscles, heart, lungs and brain and to fight infections and cancer.

Perhaps good bone health is the most prominent role of vitamin D, but researchers now are discovering that vitamin D may be important for many other reasons outside of good bone health, as hypovitaminosis D has been linked to some other conditions such as type-II diabetes, high blood pressure, asthma, cancer, depression, Alzheimer's and autoimmune diseases like type-I diabetes, multiple sclerosis and Crohn's disease **(Vitamin D Council, 2013).**

Vitamin D Production

It is essential to understand the different aspects of vitamin D metabolism and mechanisms of action that can be utilized to identify tissue-specific action and its clinical applications in various diseases **(Bikle, 2014).**

Vitamin D_3 (cholecalciferol) could be produced endogenously in the skin from 7-dehydrocholesterol (7-DHC) through a two-step process by UV light (spectrum 280–320 UVB) radiation from the sun, forming previtamin D3 that isomerizes to D_3 in a thermo-sensitive manner **(Bikle, 2014).**