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The role of vitamin D in metabolism and bone health

A thesis presented in partial fulfillment of the requirements for the degree of

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Abstract

Background

Hypovitaminosis D is becoming recognised as an emerging threat to health, even in countries like New Zealand which enjoy plentiful sunshine. The evidence for a role for vitamin D deficiency in the aetiology of a plethora of diseases continues to accumulate, including type 2 diabetes, and the preceding insulin resistance.

Objectives

The primary objective of the Surya Study was to investigate the effect of improved vitamin D status (through supplementation) on insulin resistance. The secondary objectives were to investigate the vitamin D status and bone mineral density of South Asian women living in New Zealand, and to investigate the effect of vitamin D supplementation on bone turnover as measured by biochemical markers of bone resorption and formation.

Method

Women of South Asian origin, ≥20 years old, living in Auckland (n = 235) were recruited for the study. All were asked to complete a 4-day food diary, invited to have a bone scan, and were screened for entry into the intervention phase which required insulin resistance (HOMA-IR >1.93) and serum 25(OH)D < 50 nmol/L.

Eighty-one completed a 6-month randomised controlled trial with 4000 IU vitamin D3 (n = 42) or placebo (n = 39). Primary endpoint measures included insulin resistance, insulin sensitivity (HOMA2%S), fasting C-peptide and markers of bone turnover, osteocalcin (OC) and collagen C-telopeptide (CTX). Ninety-one of the 239 had a bone scan and bone mineral density (BMD) was measured in the proximal femur and lumbar spine.

Results

Adequate serum 25(OH)D concentrations (>50 nmol/L) were observed in only 16% of subjects screened. Median (25^{th}, 75^{th} percentile) serum 25(OH)D increased significantly from 21 (11,40) to 75 (55,84) nmol/L with supplementation. Significant improvements were seen in insulin sensitivity and insulin resistance (P = 0·003, P = 0·02 respectively), and circulating serum insulin decreased (P = 0·02) with supplementation compared to placebo. There was no change in C-peptide with supplementation. Insulin resistance was most improved when endpoint serum

25(OH)D ≥80 nmol/L. In post-menopausal women OC and CTX levels increased in the placebo arm but CTX decreased from 0.39±0.15 to 0.36±0.17 (*P* = 0.012) with supplementation. Osteoporosis (T score <-2.5) was present in 32% of postmenopausal, and 3% of premenopausal women. Women 20 – 29 years (n=10) had very low BMD, calcium intake and serum 25(OH)D

Conclusions

Improving vitamin D status in insulin resistant women resulted in improved insulin resistance and sensitivity but no change in insulin secretion. Optimal 25(OH)D concentrations for reducing insulin resistance were shown to be ≥80 nmol/L. The prevalence of low 25(OH)D concentrations in this population was alarmingly high, especially in younger women. In post-menopausal women, vitamin D supplementation appeared to ameliorate increased bone turnover attributed to oestrogen deficiency.

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Abbreviations

1αOHase	1a-hydroxylase
1,25$(OH)_2D_3$	1α,25-dihydroxyvitamin D_3 or calcitriol
24OHase	24-hydroxylase
25$(OH)D_3$	25-hydroxyvitamin D_3
25OHase	25-hydroxylase
ALP	Alkaline phosphatase
ATP	Adult Treatment Panel
BMD	Bone mineral density
BMI	Body mass index
BTM	Bone turnover markers
CaSR	Calcium sensing receptors
CMDHB	Counties Manukau District Health Board
CRP	C-reactive protein
CTX	Cross-linked telopeptide
CVD	Cardiovascular disease
DBP	Vitamin D-binding protein
DXA	Dual energy x-ray absorptiometry
EDTA	Ethylene diamine tetraacetic acid
ER	Endoplasmic reticulum
FPG	Fasting plasma glucose
FPI	Fasting plasma insulin
HDL	High-density lipoprotein
HGO	Hepatic Glucose Output
HOMA	Homeostasis assessment model
HOMA2-IR	HOMA2-Insulin Resistance
IDF	International Diabetes Institute
IFG	Impaired fasting glucose
IGT	Impaired glucose tolerance
IL-6	Interleukin 6
IR	Insulin receptor
IRS-proteins	Insulin receptor substrate proteins
IVGTT	Intra-venous glucose tolerance test

K_{ATP}	Potassium channels
KO	Knock out
MED	Minimal erythemal dose
MoH	Ministry of Health
NCEP	National Cholesterol Education Programme
NCX-1	Na^{+}/Ca^{2+} exchanger
NEFAs	Non-esterified fatty acids
NGT	Normal glucose tolerance
NHANES	National health and Nutrition Examination Survey
NIDDM	Non-insulin dependant diabetes
OC	Osteocalcin
OGIS	Oral glucose insulin sensitivity
OGTT	Oral glucose tolerance test
OPG	Osteoprotegerin
PI3-kinase	Phosphatidylinositol 3-kinase
PICP	Procollagen type 1 C-terminal
PMCA	Plasma membrane calcium ATPase
PTH	Parathyroid hormone
PTHR	PTH receptor
PTHrP	PTH related protein
RANK	Receptor activator nuclear factor-κB
RANKL	Receptor activator nuclear factor-κB ligand
RCT	Randomised controlled trial
RDI	Recommended daily intake
RXR	Retinoid X receptor
TNF	Tumour necrosis factor
TRP	Transient receptor potential
UV	Ultraviolet
UVB	Ultraviolet beta radiation
UVR	Ultraviolet radiation
VDR	Vitamin D receptor
VDRE	Vitamin D response element
WHO	World Health Organization