An investigation into the link between vitamin D status, erectile dysfunction and cardiovascular risk factors in ageing men in New Zealand

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ABSTRACT

Background

Cardiovascular disease (CVD) is the leading cause of death worldwide, particularly amongst ageing males. Prevention and/or early identification and effective intervention are essential in the fight against CVD. Erectile dysfunction (ED) is a prevalent and multi-factorial condition that is now accepted to be an early marker of subclinical CVD: the common denominator is endothelial dysfunction. Both the enzymatic capability for bioactivation of vitamin D and the vitamin D receptor (VDR) are expressed in endothelial cells and vitamin D may play a role in endothelial function. Vitamin D deficiency (serum 25-hydroxyvitamin D (25(OH)D) concentrations <50 nmol/L) is a worldwide pandemic and serum 25(OH)D levels <75 nmol/L may result in metabolic and vascular deterioration leading to endothelial dysfunction, ED and CVD. Assessment of erectile function can be used to identify otherwise asymptomatic men at high risk of developing clinical CVD, at a time when effective intervention may prevent, delay or reverse its progression. Vitamin D status may be associated with ED and CVD risk and could help improve erectile function and vascular health.

Objectives

The aim of this research was to investigate the postulated link between vitamin D status, ED, and CVD risk factors. The objectives were (1) to assess the prevalence of ED (using the 5-item International Index of Erectile Function (IIEF-5)) and its associated sociodemographic, lifestyle, and medical correlates in New Zealand (NZ) men aged 40-70 years; (2) to investigate the relationship between vitamin D status (serum 25(OH)D concentration), ED and other CVD risk factors in men aged 40-70 years living in the Manawatu region of NZ; and (3) to examine the impact of common VDR gene (*VDR*) polymorphisms on this relationship.

Method

Two thousand men aged 40-70 years were randomly selected from the NZ Electoral Roll and sent an anonymous postal survey designed to assess the prevalence of ED and its sociodemographic, lifestyle, and medical risk factors. Six hundred men aged 40-70 years living in the Manawatu region were randomly selected from the NZ Electoral Roll and invited to participate in an observational study designed to provide a comprehensive health profile of self-reported healthy men and investigate the relationship between vitamin D status, ED, and a range of CVD risk factors. Eligible participants (n=100) completed a comprehensive health assessment including a medical history, anthropometric and cardiovascular assessment, fasting blood sample, computer-based questionnaire, a submaximal fitness test and a handgrip

strength test. Blood samples were assessed for four common *VDR* polymorphisms (rs11568820 (*Cdx*2), rs10735810 (*Fok*I), rs1544410 (*Bsm*I) and rs731236 (*Taq*I)) using polymerase chain reaction-high resolution amplicon melt (PCR-HRM) analysis.

Results

The survey showed 38.4% of respondents presented with ED (IIEF-5 ≤21). Older age, non-European ethnicity and current smoking were significant independent predictors of an increased risk of ED, while a high household income and regular vigorous physical activity (PA) were deemed protective. The observational study showed 30 men presented with ED and a further 37 men had <75 nmol/L 25(OH)D. There was a weak positive correlation between IIEF-5 scores and 25(OH)D levels (r_s=0.238, p=0.017). Men with <75 nmol/L had lower IIEF-5 scores compared to men with ≥75 nmol/L 25(OH)D (22(7) vs. 24(3), p=0.001). Men with ED had lower 25(OH)D levels compared to men without ED (74.5(34) vs. 84.5(24), p=0.062). Every 1 nmol/L of 25(OH)D predicted a 2% decrease in the age-adjusted risk of ED (age-adjusted OR=0.98 [0.96-1.00], p=0.046). The PCR-HRM analysis showed that the *Cdx*2, *Fok*I and *Bsm*I polymorphisms were all significantly associated with an adverse cardiovascular risk profile. The *Cdx*2 G allele was associated with lower IIEF-5 scores compared to the A allele (23(4) vs. 24(2), p=0.008) and the GA and GG genotypes were predictors of an increased age-adjusted risk of ED (age-adjusted OR=18.78 [1.98-178.60], p=0.011 and 8.53 [1.00-72.73], p=0.050 respectively). However, *Cdx*2 was not found to modify the age-adjusted association between 25(OH)D levels and ED (multi-adjusted OR=0.97 [0.95-1.00], p=0.032).

Conclusions

These results suggest that over a third of NZ men aged 40-70 years suffer from ED and it is associated with sociodemographic, lifestyle and medical factors simliar to CVD. Low serum 25(OH)D is associated with the presence and severity of ED in a self-reported healthy population. Common *VDR* polymorphisms are also associated with ED; however, they do not modify the association between serum 25(OH)D and ED. A randomised placebo-controlled human intervention trial is warranted to investigate whether improving vitamin D status in men with vitamin D deficiency and ED ameliorates symptoms and reduces the risk of CVD.

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1α-hydroxylase	25-hydroxyvitamin D 1-alpha-hydroxylase
24-hydroxylase	1,25 dihydroxyvitamin D 24-hydroxylase
$1,25(OH)_2D_3$	1,25-hydroxyvitamin D_3 (calcitriol)
25(OH)D	25-hydroxyvitamin D
95% CI	95% confidence interval
χ^2	Chi-squared
A:G	Android-to-gynoid fat ratio
AIx@HR75	Augmentation index adjusted to a heart rate of 75 bpm
AP@HR75	Augmentation pressure adjusted to a heart rate of 75 bpm
ANOVA	One-way analysis of variance
ANZSCO	Australian and New Zealand Standard Classification of Occupations
AUC	Area under curve
BACH	Boston Area Community Health Survey
BF%	Body fat percentage
BMI	Body Mass Index
BMSFI	Brief Male Sexual Function Inventory
BP	Blood pressure
BPH	Benign prostatic hyperplasia
CATI	Computer Assisted Telephone Interview
CC	Corpus cavernosum
CHD	Coronary heart disease
CVD	Cardiovascular disease
CVOD	Corporal veno-occlusive dysfunction
DBP	Diastolic blood pressure
DE	Delayed ejaculation
DM	Diabetes mellitus
DNA	Deoxyribonucleic acid
ED	Erectile dysfunction
EDV	End-diastolic velocity
EMAS	European Male Ageing Study
EPIC-PAQ	European Prospective Investigation into Cancer and Nutrition Physical Activity Questionnaire
FAMAS	Florey Adelaide Male Ageing Study

FFQ	Food Frequency Questionnaire
FPG	Fasting plasma glucose
FPI	Fasting plasma insulin
FT	Free testosterone
GOSS	Global Online Sexuality Survey
GSSAB	Global Study of Sexual Attitudes and Behaviours
HDL-c	High-density lipoprotein cholesterol
HOMA1	Homeostatic Model Assessment Index 1
HPFS	Health Professionals Follow-Up Study
HR	Heart rate
HRM	High resolution amplicon melt
ICSM	International Consultation in Sexual Medicine
IHD	Ischemic heart disease
IIEF	International Index of Erectile Function
IIEF-5	5-item International Index of Erectile Function
IQR	Interquartile range
IR	Insulin resistance
LD	Linkage disequilibrium
LDL-c	Low-density lipoprotein cholesterol
MAF	Minor allele frequency
MALES	Multinational Men's Attitudes to Life Events and Sexuality
MATeS	Men in Australia Telephone Survey
MetS	Metabolic syndrome
MI	Myocardial infarction
MMAS	Massachusetts Male Aging Study
mRNA	Messenger ribonucleic acid
MSAM-7	Multinational Survey of the Aging Male
NHANES	National Health and Nutrition Examination Survey
NHSLS	National Health and Social Life Survey
NPT	Nocturnal penile tumescence
NZANS	New Zealand Adult Nutrition Survey
OR	Odds ratio
PA	Physical activity
PCa	Prostate cancer

PCAW	Prostate Cancer Awareness Week
PCR	Polymerase chain reaction
PDE_5	Phosphodiesterase type 5
PDS	Penile Doppler sonography
PE	Premature ejaculation
PHQ-6	9-item Patient Health Questionnaire
PP	Pulse pressure
PSA	Prostate specific antigen
PSV	Peak systolic velocity
PTH	Parathyroid hormone
PTSD	Post-traumatic stress disorder
PVD	Peripheral vascular disease
PWA	Pulse Wave Analysis
PWV	Pulse Wave Velocity
RCT	Randomised controlled trial
RFLP	Restriction fragment length polymorphisms
RR	Relative risk
r_s	Spearman's rho
RXR	Retinoid-X receptor
SBP	Systolic blood pressure
SD	Standard deviation
SHBG	Sex hormone binding globulin
SHIM	Sexual Health Inventory for Men
SMC	Smooth muscle cell
SNP	Single nucleotide polymorphism
T2DM	Type 2 diabetes mellitus
TC	Total cholesterol
TG	Triglyceride
TT	Total testosterone
Tukey's HSD	Tukey's honest significant difference
UTR	Untranslated region
VDR	Vitamin D receptor
VDR	Vitamin D receptor gene
VDRE	Vitamin D response element

VO_2peak	Maximal oxygen consumption
WAMHS	Western Australia Men's Health Study
WC	Waist circumference
Well-LaD	Wellness, Lifestyle and Diet
WHO	World Health Organization
WHR	Waist-to-hip ratio
WHtR	Waist-to-height ratio
WSP	World Standard Population