Medical and Research Publications
International Open Access

Research Article **Journal of MAR Diabetes and Endocrinology (Volume 1 Issue 5)**

Potential Beneficial Effects of Vitamin D and Calcium Supplementation on Physical Function in the Severely Obese: A Pilot Prospective Cohort Study

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Received Date: February 13, 2023

Published Date: March 01, 2023

Abstract

Background & Aim: *Poor physical function is common in severely obese people (BMI>40kg/m^2) and may contribute to their elevated mortality. In people without severe obesity, vitamin D supplementation can improve physical function, inflammation and glycaemia.*

Method: *We conducted a twelve-week, clinic-based, prospective cohort study, with a parallel comparator. We recruited severely obese people with a serum 25-hydroxyvitamin D (25OHD) concentration of 50nmol/L or less. Participants chose to receive, or not, 800 international units of vitamin D3 per day with 1200mg of calcium, as carbonate. We determined changes in 500 metre walk time, serum c-reactive protein concentration (CRP) and plasma glycated haemoglobin level (HbA1c).*

Result: *We recruited 54 participants (age 44.9±9.5 years, BMI 52.7±8.7kg/m^2, 48.1% male, 38.9% type 2 diabetes). Those who received supplements (n=29), compared to those who did not (n=25), experienced a decrease in 500 metre walk time (-11.7±24.4 seconds versus +15.3±45.2 seconds, p=0.036) and CRP (-3.0±7.1 mg/L versus +1.1±4.4 mg/L, p=0.013). HbA1c fell by 3.4±6.5 mmol/mol in those who received supplements (p=0.007).*

Conclusion: *Vitamin D and calcium supplementation improved markers of physical function, inflammation and glycaemia in this small cohort of severely obese people. Double-blind, placebo-controlled and randomised clinical trials are required to confirm these findings.*

Keywords: *Vitamin D, Calcium, Physical Function, Severe Obesity, Inflammation, Quality of Life.*

Abbreviations

25OHD:	25-hydroxyvitamin D
ALP:	Alkaline Phosphatase
BMI:	Body mass index
CTX:	C-terminal telopeptide of type 1 collagen
FPG:	Fasting Plasma Glucose
HbA1c:	Glycated Haemoglobin
HDL:	High Density Lipoprotein
IFCC:	International Federation of Clinical Chemistry
IOM:	North American Institute of Medicine
PINP:	Total procollagen type-1 amino-terminal propeptide
PTH:	Parathyroid hormone
T2DM:	Type 2 Diabetes Mellitus

Introduction

Severe obesity (BMI > 40kg/m2) affects 1.9% of Irish adults **[**1**]** and 6.5% of American adults **[**2**]** and confers an 85% increase in mortality **[**3**]**. In the United States of America between 2000 and 2010, the prevalence of severe obesity (BMI ≥40 kg/m2) increased by 74% **[**2**]**. Severely obese people are over eight times more likely to have poor physical function than people with a BMI in the healthy range **[**4**]**. Like people with severe obesity, people with poor physical function have elevated mortality **[**5**]**.

More than 60% of severely obese people have a 25OHD concentration below 50 nmol/L **[**6,7**]**. We have found that severely obese people with serum 25-hydroxyvitamin D (25OHD) concentrations less than 30 nmol/L take longer to complete a self-paced 500 metre walk test than their counterparts with 25OHD concentrations greater than 50 nmol/L **[**6**]**. In people without severe obesity, vitamin D supplementation can improve physical function **[**8,9**]**, inflammation **[**10**]** and glycaemia **[**11**]**. Vitamin D is thought to have direct effects on muscle physiology **[**12**]**. We hypothesized that Vitamin D supplementation would improve physical function in people with severe obesity.

Materials and Methods

Participants

We performed a pilot, single-centre, open-label prospective cohort study with a parallel comparator group. We recruited adults aged 18 to 65 years with severe obesity (BMI ≥40 kg/m2) and low serum 25OHD (<50 nmol/L). Participants were recruited from the weight management clinic in St Columcille's Hospital in Dublin, Ireland (latitude 53.3° N) between September 2011 and November 2011. This clinic receives referrals from all over Ireland and the only criterion for referral acceptance is a BMI of 40 kg/m2 or greater. Exclusion criteria included use of vitamin D and/or calcium supplements, stage 4 or 5 chronic kidney disease (eGFR ≤30ml/min/1.73m2), nephrolithiasis, hypercalcaemia (serum calcium >2.65 mmol/L), pregnancy and breast-feeding. Written informed consent was obtained from all patients prior to study participation. The study was approved by the St Vincent's Healthcare Group Ethics and Medical Research Committee and was registered on the current controlled trials platform (www.controlled-trials.com, ISRCTN 38158659).

Intervention

Participants who chose to take a vitamin D and calcium supplement received, and were advised to ingest twice daily, Caltrate® tablets equating to 800 international units of vitamin D3 per day and 1200mg of elemental calcium per day. We chose to use a combined vitamin D and calcium supplement as vitamin D supplementation, if not combined with calcium, may lack efficacy **[**13,14**]**. Vitamin D supplementation with 800 international units per day was sufficient to increase 25OHD levels to above 50nmol/L in 97.5% of postmenopausal women with a baseline 25OHD less than 50nmol/L **[**15**]**. A study investigator advised these research participants to take the tablets by mouth, before food, with a large glass of water. Participants who chose not to take a supplement did not receive Caltrate® tablets and agreed to not take alternative forms of vitamin D and/or calcium supplementation. All participants received continuing assessment and evidence-based lifestyle advice on weight management and prevention of obesity-related complications.

Assessments

The primary outcome measure, which was decided before study commencement, was the change in the time taken to walk around a 500 metre, mapped-out path over 12 weeks. Participants were instructed to exert themselves to a level they found "slightly challenging" or to point six or less on a

ten point Borg Rating of Perceived Exertion [16]. Self-paced walking tests compare well with other markers of physical function [5], predict mortality [5] and have been used previously to assess physical function in people with severe obesity [17] and in people with vitamin D deficiency [18].

Physical function was assessed also by measuring physical performance score and dominant hand grip strength. The physical performance score was calculated from the time taken to complete a 3 metre walk test, time taken to stand five times from a seated position and ability to complete tests of standing balance (Short Physical Performance Battery) [19]. Hand grip strength was assessed by adjustable Jamar hydraulic dynamometer using the maximum value of three consecutive squeezes separated by one minute [20].

Health-related quality of life was assessed using the EuroQol 5 Dimension questionnaire [21]. Height and weight were measured to the nearest 0.5 cm and 0.1 kg respectively, while the participant was standing erect, wearing shoes, using an electronic stadiometer and an electronic scales (both from Seca, Hamburg, Germany).

Blood was taken, prior to physical function testing, between the hours of 0800 and 1100 after an overnight fast of at least 12 hours. Serum or plasma was separated within 2 hours of blood collection and was stored at 4°C for immediate analysis or -80°C for subsequent analysis. Frozen serum aliquots were stored for a maximum of two years and underwent only one freeze-thaw cycle. Serum 25OHD, parathyroid hormone (PTH), C-terminal telopeptide of type I collagen (CTX), total procollagen type I amino-terminal propeptide (PINP) and insulin concentrations were measured using Roche immunoassays on the Cobas Roche E170a automated analyzer. Serum c-reactive protein (CRP) concentrations were measured using the highly sensitive Beckman Coulter immuno-turbidimetric automated assay. HbA1c was determined by IFCC standardised high-performance liquid chromatography on a Tosoh G7 analyser. Serum calcium, alkaline phosphatase (ALP), creatinine, triglyceride, HDL cholesterol and plasma glucose concentrations were measured using standardised Roche Modular methodology. All analysis was performed in hospital clinical laboratories. The inter-assay coefficients of variation for the CRP, 25OHD and HbA1c assays, at concentrations of 1.80 mg/L, 43.7nmol/L and 5.9% respectively, were 2.39%, 7.69% and 0.98%.

Statistical Analyses and Sample Size Calculation

All statistical analyses were performed using IBM SPSS for Windows version 20 (Armonk, NY). Continuous variables were compared between groups using the independent-samples Mann-Whitney U test and within groups using the related-samples Wilcoxon Signed Rank test. Dichotomous variables

were compared using the Chi squared test. The relationships between percentage changes in continuous outcome variables were assessed using Spearman correlation analyses. The level of statistical significance was set at less than 0.05 for all analyses. Continuous data are expressed as mean ±standard deviation in the manuscript text and as mean (95% confidence interval) in the manuscript tables. Categorical data are expressed as number (percentage).

We calculated that we would require at least 25 participants in each group to detect a greater than 15% difference in the times taken to walk 500 metres with 80% power and a two-sided significance level of 5%. This calculation was based on data from a cross-sectional study of severely obese people where the time taken to walk 500 metres was 427 ±82 seconds for those with a 25OHD <50 nmol/L and was 372 ±68 seconds for those with a 25OHD ≥50 nmol/L **[**6**]**.

Results

Characteristics of the Study Population

We approached sixty six people of whom twelve declined study participation (Figure 1). Of the remaining fifty four, 29 elected to take supplements and 25 did not. One of the participants who received supplements withdrew participation as did six of the participants who did not receive supplements. No adverse events were reported by study participants. Participants and non-participants did not differ significantly in terms of age (44.7 ±10.0 years vs 47.9 ±8.8 years, p=0.221), BMI (52.7 ±9.1 kg/m2 vs 51.8 ±6.4 kg/m2, p=0.983) or gender (44.7% male vs 47.4% male, p>0.99). Supplement users did not differ from non-users in age (45.9 ±9.5 years vs 42.8 ±10.7 years, p=0.186) or BMI (52.1 ±9.7 kg/m2 vs 53.5 ±8.5 kg/m2, p=0.386). Male gender was more common in non-users (32.1% vs 63.2%, p=0.043) and non-users had lower baseline CRP concentrations (8.7 ±6.1 mg/L vs 15.5 ±10.5 mg/L, p=0.016). There were no other significant differences between groups at baseline (Table 1 and Table 2).

Outcomes

Serum 25OHD concentrations rose by 29.3 ±59.0% in participants who received supplements and fell by 33.1 ±25.0% in participants who did not receive supplements (Table 2). Serum 25OHD concentrations rose to above 50 nmol/L in 34.6% of those who received supplements (9 participants) and in 5.6% of those who did not receive supplements (1 participant, p=0.031). The time taken to walk 500 metres fell by 2.4 ±5.4% in those who received vitamin D and rose by 3.2 ±10.5% in those who

did not (p=0.047). The change in weight, physical function score and grip strength did not differ between the two groups.

The change in quality of life did not differ significantly between the two groups although the EuroQol visual analogue scale rating increased by 23.5 ±38.3% in those who received supplements (p=0.008). Serum c-reactive protein concentrations fell by 17.9 ±31.1% in those taking supplements and rose by 29.4 ±65.6% in those not taking supplements (p=0.008). Plasma HbA1c concentrations decreased also from 48.3 ±16.9 mmol/mol to 45.0 ±14.0 mmol/mol (p=0.007) in those taking supplements although this change was not significantly different from those not taking supplements. Fasting plasma glucose and HOMA-IR did not change significantly following supplementation (Table 2).

Bone turnover marker concentrations tended to decline in those supplemented and tended to increase in those not supplemented accounting for significant differences between the two groups for ALP (p=0.049) and CTX (p=0.018), but not for PINP (p=0.101). PTH concentrations did not differ between the two groups (p=0.129). There was a significant inverse correlation between percentage change in 25OHD and CTX (r=-0.51, p=0.006, Figure 2). Serum calcium concentrations increased slightly from 2.41 ±0.1 mmol/L to 2.46 ±0.1 mmol/L in those who took supplements. Serum calcium concentrations did not rise to above the upper limit of the normal reference range (2.65mmol/L) in any of the participants.

Table 1. Participant Characteristics

Parameter	Vitamin D and calcium supplementation (n=28)	No Supplementation (n=19)	P
Age, years	45.9 (42.3-49.6)	42.8 (37.7-48.0)	0.186
BMI, kg/m^2	52.1 (48.3-55.8)	53.5 (49.5-57.6)	0.386
Male, n (%)	9 (32.1)	12 (63.2)	**0.036**
T2DM, n (%)	12 (42.9)	6 (31.6)	0.435
OSAS, n (%)	6 (21.4)	4 (21.1)	0.975
OA, n (%)	7 (25.0)	7 (36.8)	0.384
Hypoglycaemic medication, n (%)	11 (39.3)	6 (31.6)	0.589
Lipid lowering agent, n (%)	10 (35.7)	9 (47.4)	0.424
Antihypertensive, n (%)	17 (60.7)	10 (52.6)	0.582
Antidepressant, n (%)	6 (21.4)	5 (26.3)	0.698
Smoking, n (%)	1 (3.6)	2 (10.5)	0.338
Employed, n (%)	16 (57.1)	7 (36.8)	0.172

Abbreviations: n, number of participants; BMI, body mass index; T2DM, type 2 diabetes; OSAS, obstructive sleep apnoea syndrome; OA, osteoarthritis.
Data are expressed as mean (95% confidence interval) or as number (percentage).
For continuous variables, probability (p) values were calculated using the independent-samples Mann-Whitney U test.
For categorical variables, p values were calculated using the Chi Squared test.

Table 2. Effects of vitamin D and calcium supplementation

Outcomes	Vitamin D and calcium supplementation (n=28)			No Supplementation (n=19)			P
	Before	After	Change (%)	Before	After	Change (%)	
25OHD, nmol/L	30.9 (26.7-35.1)	**37.8[a] (31.4-44.2)**	+29.3 (+5.5- +53.2)	35.0 (27.0-43.1)	**21.8[b] (16.2-27.4)**	-33.1 (-45.5- -20.7)	**<.001**
500m walk time, s	430 (394-465)	**418[c] (385-450)**	-2.4 (-4.6- -0.3)	411 (354-468)	427 (359-494)	+3.2 (-2.2- +8.6)	**0.047**
Performance Score	8.3 (7.5-9.1)	8.8 (8.0-9.5)	+7.3 (-0.6- +15.3)	9.1 (7.9-10.3)	9.1 (7.8-10.3)	-0.3 (-5.1- +4.5)	0.217
Grip Strength	34.3 (30.3-38.3)	34.2 (30.1-38.3)	+0.3 (-4.1- +4.7)	43.7 (36.4-51.0)	42.2 (35.6-48.8)	-2.2 (-6.8- +2.4)	0.409
Weight, kg	147 (134-161)	146 (132-160)	-1.1 (-2.0- -0.1)	158 (144-172)	156 (141-171)	-1.5 (-3.4- +0.3)	0.795
EQ-5D Index	0.63 (0.56-0.70)	0.59 (0.51-0.67)	-3.5 (-13.9- +7.0)	0.60 (0.47-0.73)	0.64 (0.53-0.75)	+15.8 (-4.4- +36.1)	0.128
EQ-5D VAS	50.0 (41.8-58.2)	**57.6[d] (49.1-66.2)**	+23.5 (+8.1- 39.0)	48.0 (38.1-57.9)	55.7 (44.1-67.2)	+20.4 (-7.8- +48.6)	0.914
CRP, mg/L	15.5 (11.2-19.8)	**12.5[e] (8.7-16.4)**	-17.9 (-30.7- -5.0)	8.7[*] (5.7-11.6)	9.8 (6.4-13.1)	+29.4 (-2.2- +61.0)	**0.008**
FPG, mmol/L	6.4 (5.4-7.5)	6.3 (5.1-7.6)	+0.7 (-14.2- +15.5)	5.5 (5.1-5.9)	5.3 (5.0-5.7)	-2.7 (-9.7- +4.3)	0.434
HbA1c, mmol/mol	48.3 (41.2-55.5)	**45.0[f] (39.0-50.9)**	-5.8 (-9.5- -2.2)	39.7 (36.3-43.1)	38.5 (36.2-40.9)	-1.9 (-6.8- +2.9)	*0.085*
HOMA-IR	6.7 (4.6-8.8)	6.7 (2.9-10.5)	-0.6 (-30.7- +29.5)	6.8 (4.1-9.5)	6.2 (2.5-10.0)	-2.3 (-42.4- +37.8)	0.698
ALP, U/L	93.9 (76.6-111.2)	90.7 (74.0-107.4)	-2.8 (-7.2- +1.6)	83.2 (72.8-93.6)	87.0 (75.8-98.2)	+5.4 (-1.7- +12.5)	**0.049**
PTH, ng/L	38.6 (31.3-45.9)	37.3 (29.1-45.4)	+0.9 (-15.9- +17.8)	44.7 (33.3-56.1)	47.1 (37.0-57.1)	+9.9 (-1.2- +21.0)	0.129
CTX, ug/L	0.27 (0.20-0.34)	0.25 (0.19-0.31)	+0.5 (-18.3- +19.3)	0.27 (0.21-0.33)	0.31 (0.25-0.37)	+25.1 (+8.1- +42.1)	**0.018**
PINP, ug/L	47.9 (34.7-61.0)	42.9 (34.3-51.6)	-4.1 (-12.6- +4.4)	45.6 (37.2-54.0)	49.7 (41.7-57.6)	+24.4 (-17.2- +66.0)	0.101

Abbreviations: N, number of participants for whom data were available; 25OHD, serum 25-hydroxyvitamin D concentration; EQ-5D, EuroQol 5 Dimension Questionnaire; VAS, visual analogue scale; CRP, serum concentration of C-reactive Protein; FPG, fasting plasma glucose concentration; HbA1c; plasma glycated haemoglobin concentration; HOMA-IR, Homeostatic Model of Insulin Resistance; ALP, serum alkaline phosphatase concentration; PTH, serum parathyroid hormone concentration; CTX, serum C-terminal telopeptide of type 1 collagen concentration; PINP, serum total procollagen type-1 amino-terminal propeptide concentration.
Data are expressed as mean (95% confidence interval).
Probability (p) values were calculated using the independent-samples Mann-Whitney U test comparing the change in parameters between the two groups and using the related-samples Wilcoxon Signed Rank test comparing parameters before and after intervention.
Superscript symbol indicates a significant between groups at baseline: [*], p=0.016;
Superscript letters indicate a significant difference from before intervention: [a], p = 0.026; [b], p < .001; [c], p = 0.027; [d], p = 0.008; [e], p = 0.025; [f], p = 0.007.

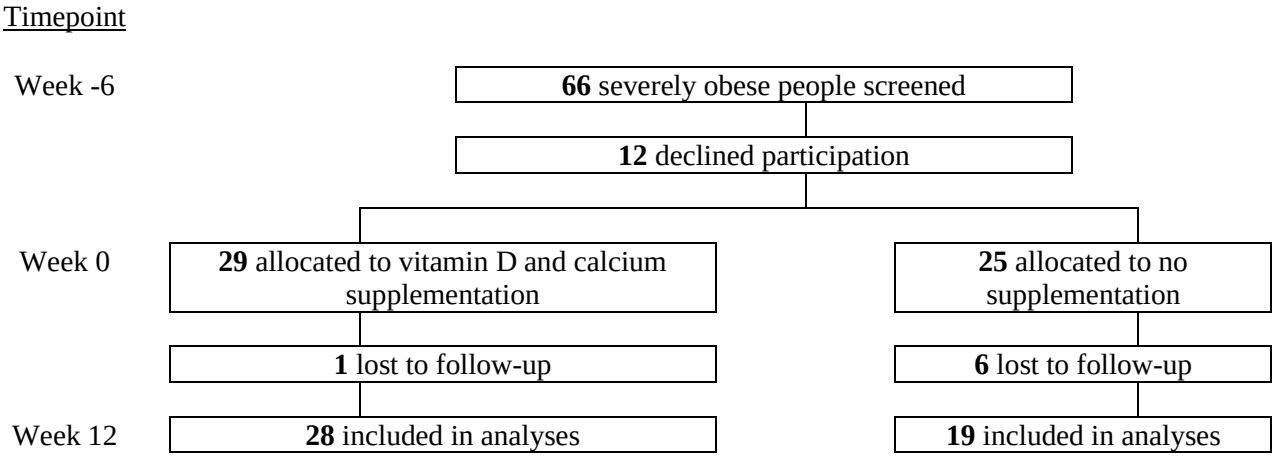

Figure 1. Flowchart of participants.

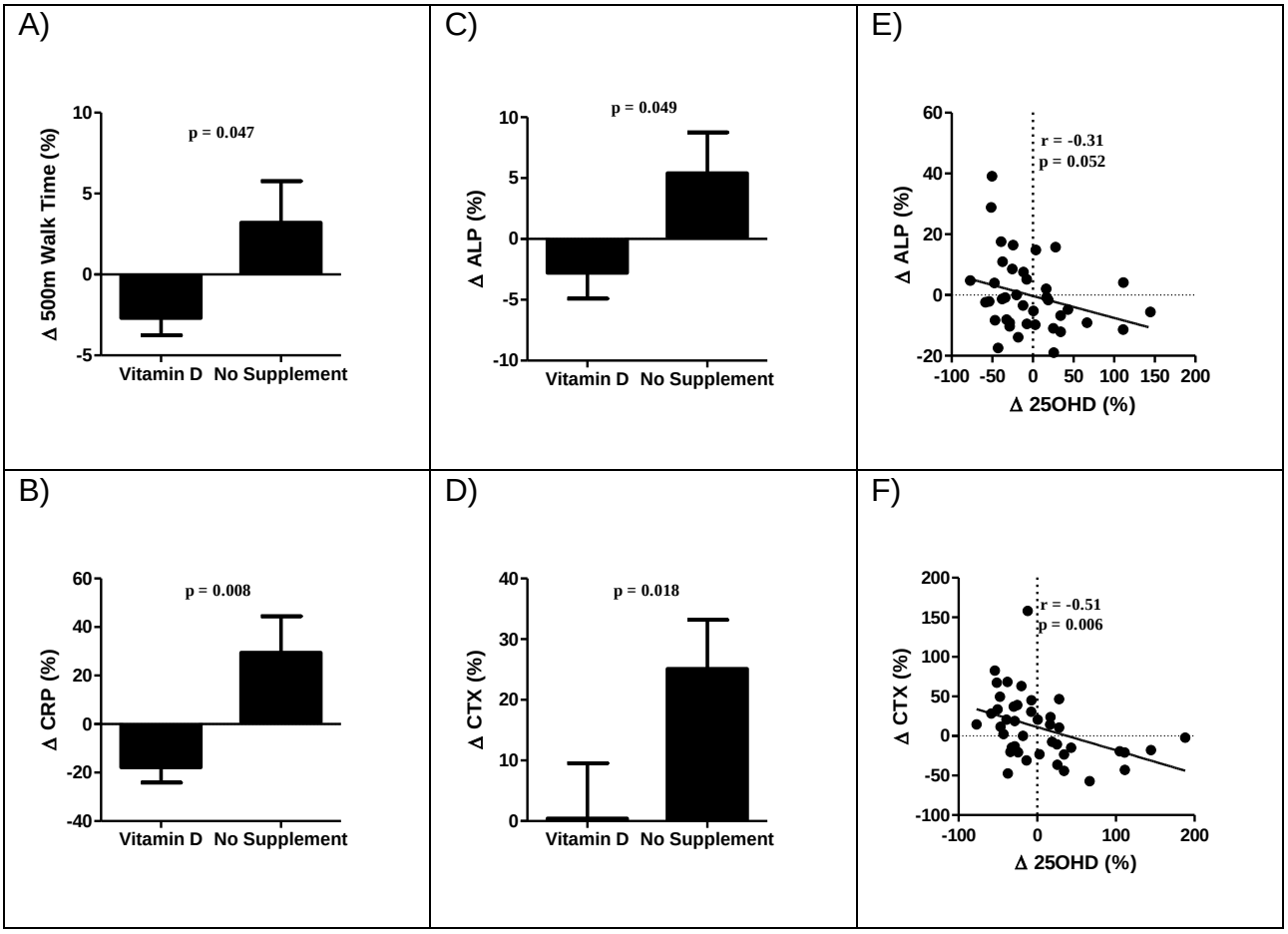

Figure 2. Relationships between vitamin D and calcium supplementation with percentage change in: A) 500 metre walk times; B) serum c-reactive protein (CRP) concentrations; C) serum alkaline phosphatase (ALP) concentrations; and D) serum C-terminal telopeptide of type 1 collagen (CTX)

concentrations. Data are expressed as means (upper boundary of columns) and standard errors of the mean (error bars). Probability values were determined using Mann-Whitney U analyses.

Relationships between percentage change in 25-hydroxyvitamin D concentrations with percentage change in: E) serum alkaline phosphatase concentrations; and F) serum C-terminal telopeptide of type 1 collagen concentrations. Probability values were determined using Spearman correlation analyses. r, co-efficient of correlation.

Discussion

In this small cohort of severely obese people with 25OHD <50 nmol/L, vitamin D and calcium supplementation was associated with improved physical function and decreased inflammation. Baseline CRP concentrations were higher in the supplemented group than in the non-supplemented group. Glycaemic control and quality of life improved also in those taking supplements, although these changes were not significantly different from those in the comparator, non-supplemented group. Bone turnover markers decreased non-significantly in those supplemented, but tended to increase in those not supplemented such that there were significant differences in the two groups for CTX and ALP. This suggests an effect of changing vitamin D status between both groups. The study was conducted during the winter months, specifically in order to avoid the effect of sunlight exposure on vitamin D status. In Ireland it is well known that vitamin D status declines during the winter months **[**22,23**]**. So, in our study, supplementation led to an improvement in vitamin D status compared to a decline in the non-supplemented group; the difference in vitamin D status coupled with calcium supplementation probably accounted for the differences in bone turnover markers.

Our findings add to, and are consistent with, the existing literature. This is the only study, to our knowledge, designed specifically to determine whether vitamin D and calcium supplementation improves markers of physical function in people with severe obesity. Zhu et al performed a double-blind, randomised clinical trial of vitamin D2 therapy (1,000 units per day) for one year in ambulant women aged 70 to 90 years **[**9**]**. They found that the time to complete an Up and Go Test decreased from 11.0 ±5.3 seconds to 8.1 ±3.9 seconds in those allocated to receive vitamin D and calcium supplementation. Mason et al conducted a double-blind, randomised clinical trial of 2,000 units per day of vitamin D3 for one year in overweight and obese women **[**10**]**. They found that CRP concentrations fell by 1.18mg/L (46%) in those taking vitamin D supplements: this was significantly less than the fall of 0.46mg/L (25%) in those taking placebo (p=0.03).

In our study supplementation led to modest improvement in physical function. Effecting a higher 25OHD concentration, with a higher dose of vitamin D [24], may have resulted in greater improvements in physical function [18]. For the majority (65%) of this cohort of people with severe obesity, 800 units of vitamin D3 daily in wintertime, which is more than the recommended daily allowance specified by the Institute of Medicine (IOM) [25], was not adequate to achieve 25OHD concentrations above 50nmol/L within twelve weeks. In people with obesity, the dose response to low dose vitamin D supplementation is slightly blunted which may be due to excess adipose tissue [15].

Our study is limited by small sample size, by lack of blinding and by lack of randomisation. Such limitations are inherent to a pilot, pragmatic, prospective cohort study. The small size prevented adjustment for potential confounders. A positive finding in such a small cohort suggests, however, a clear treatment effect. We elected to perform a pilot, single-centre, open-label prospective cohort study with a parallel comparator group because of the significant costs and delays associated with conducting a double-blind, placebo controlled, randomised clinical trial [26]. Our pilot study generates the imperative to perform such a trial and its results can serve as a useful basis for sample size calculations.

Conclusion

We conclude that vitamin D and calcium supplementation in people with severe obesity is likely to improve physical function. Larger, double-blinded and randomised clinical trials are required to ascertain this with certainty.

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