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EFFECT OF VITAMIN D SUPPLEMENTATION ON MUSCLE FUNCTION IN ELDERLY INDIVIDUALS: A META-ANALYSIS

Tomader Taha Abdel Rahman [1], *Mohamed Shawky Khater* [1], *Mohamad Farouk Allam* [2]
1 Geriatric Medicine & Gerontology department, Faculty of Medicine, Ain Shams University, Cairo, Egypt.
2 Department of Community, Environmental and Occupational Medicine, Faculty of Medicine, Ain Shams University.

Abstract

Background: Sarcopenia (the loss of muscle mass and strength) has estimated prevalence rates of 5-13% and 11-50% in the young-old and old-old, respectively. Recent studies have shown that vitamin D plays important roles in various systems, including the musculoskeletal system. Objective:

The aim of this meta-analysis was to determine the effects of vitamin D supplementation on muscle function in community-dwelling elderly individuals.

Methods: We conducted systematic searches of PubMed, Medline, Egyptian Knowledge Bank, and the reference sections of previous reviews, and we discussed the topic with several experts in the field. Only randomized controlled trials that evaluated the effect of vitamin D supplementation on muscle function [muscle strength was evaluated by the hand grip strength (HGS) test, and physical performance was evaluated by the timed up-and-go (TUG) test] were included. Only studies published in English between January 2000 and June 2018 were considered.

Results: In total, 14 randomized controlled clinical trials (RCTs) met our inclusion criteria. The participants in these studies were all community-dwelling elderly individuals, who were generally in good health for their age. The pooled mean difference in HGS was higher in the vitamin D supplementation group than in the control group. The pooled mean difference in the TUG test was slightly lower in the vitamin D supplementation group than in the control group.

Conclusions: Our meta-analysis shows that vitamin D supplementation could improve muscle function in elderly individuals. Future studies should use standardized durations and doses of vitamin D supplementation.

Keywords: Vitamin D supplementation, Sarcopenia, Muscle function, Meta-analysis, Randomized controlled clinical trials, Systematic review.

Background

The changes in body composition and functions that occur in the ageing population include decreases in skeletal muscle mass, strength, and mobility. These decreases in muscle mass and strength are collectively called sarcopenia, which is associated with frailty and falls [1].

The prevalence rates of sarcopenia are 5–13% and 11–50% in young-old and old-old individuals, respectively. These prevalence rates illustrate that decreases in muscle mass and strength constitute an important problem among elderly individuals. Early intervention may be helpful for limiting sarcopenia and preserving muscle mass and strength [2].

Elderly individuals are susceptible to developing vitamin D deficiency due to various risk factors, such as diminished sunlight exposure, decreased skin thickness, impaired intestinal absorption, and reduced hydroxylation in the liver and kidneys. Decreased dietary intake and limited dietary sources of vitamin D also play important roles in vitamin D deficiency among elderly individuals [3]. The decrease in vitamin D receptors that occurs with increasing age partly explains the age-related decrease in muscle function [4].

These risk factors make vitamin D deficiency more

among elderly individuals than among young adults, even without the presence of other overt nutrient deficiencies [5, 6].

Many interventions, including dietary supplementation regimens, such as supplementation with protein and *omega*-3 fatty acids [3,7], and exercise interventions [8] or combinations of the two, have been tested [9].

Supplementation with vitamin D is one possible intervention. Vitamin D supplementation has been promoted as having positive effects on older persons, particularly with regard to the risk of falls and fractures [10].

An increased risk of falls is a consequence of low muscle strength and mass [11], and sarcopenia is a risk factor for fractures in elderly individuals [12].

Although many researchers have tried to test the effects of vitamin D supplementation on muscle function, the results remain controversial, and it is still hard to conclude whether vitamin D supplementation has an effect on muscle strength in elderly individuals [6].

The aim of our meta-analysis was to investigate the effects of vitamin D supplementation (with or without calcium) on muscle function among community-dwelling elderly individuals based on the results from randomized controlled clinical trials (RCTs).

Methods

I. Literature Review

Published RCTs on sarcopenia and vitamin D supplementation were identified through a comprehensive PubMed and Medline search (from January 2000 to June 2018) using a variety of keywords and subject headings related to sarcopenia, vitamin D supplementation, muscle strength and elderly individuals. We conducted additional searches of Egyptian Knowledge Bank and the cited references of previously published reviews, and we discussed the topic with several experts in the field. Published descriptive and analytical observational studies dealing with sarcopenia and vitamin D were excluded. We did not attempt to locate any unpublished studies.

Only RCTs with elderly community-dwelling individuals >60 years of age were included. We applied no restrictions with regard to the dose, forms and duration of vitamin D supplementation or the duration of follow-up; we included studies regardless of their use of calcium supplements and dietary advice. Measures of muscle function included the determination of muscle strength by the hand grip strength (HGS) test and the measurement of physical performance by the timed up-and-go test (TUG). These measures were compared before and after intervention for both groups (vitamin D supplementation versus placebo).

II. Data Extraction

Only 14 RCTs out of 2408 studies met the inclusion criteria and were included in this meta-analysis. A copy of each RCT was obtained, and relevant data were abstracted by the first author (T.T.A.) for a quantitative overview. In case of discrepancies or when the information presented in a study was unclear, the data was extracted by a second reviewer (M.F.A.) to resolve the discrepancy.

III. Statistical Methods for Meta-Analysis

Mean differences between cases and controls groups were calculated by subtracting the mean of the outcome of each result in each paper at the end of the study from the mean at the baseline or the start of the same study; Microsoft Excel 2010 was used for these calculations.

The pooled mean differences were obtained by weighing each study by the inverse variance of the effect measure on a logarithmic scale. This approach to pooling the results assumes that the study populations being compared were similar and hence corresponds to a fixed effect analysis. The validity of pooling the mean differences was tested (test of homogeneity) using the chi-square test.

A violation of this test suggests that the studies being pooled differ from one another. In the presence of significant heterogeneity of the effect measure among studies being compared, we performed a random effect analysis that was based on the method described by Der Simonian and Laird. The random effect analysis accounts for inter-study variation. Because the test of homogeneity has low power, we reported the figures of the random effect analysis even in the absence of significant heterogeneity.

All statistical analyses pertaining to the 14 pooled RCTs were performed with STATA version 14.0 (Stata Corp. 2015, College Station, Texas, USA).

RESULTS

We included 14 RCTs, with a total of 2127 participants aged 60 years and older. The average age of the included participants was 68.8 years (ranging from 60 to 88 years). The ratio of women to men was approximately 3.25:1 (1627/500).

All selected studies reported randomization in their design. The participants were all community-dwelling elderly individuals who were generally in good age-related health. All studies excluded patients with acute illnesses.

Vitamin D was measured as the 25(OH)D concentration in all included RCTs using chromatographic methods, radioimmunoassays (DiaSorin Inc., Stillwater, MN, USA), the IDS gamma-B 25-OH immunoassay (IDS, Tyne & Wear, UK), and the Liaison method (DiaSorin Inc.). One RCT study did not report which method had been used. The mean baseline concentration of vitamin D ranged from 11 to 55 nmol/L.

One RCT used different supplementation dosages, and another RCT used different durations of follow-up, and we considered each one as two clinical trials.

Vitamin D3 supplementation was administered orally at various doses (ranged from 400 – 3333 IU) and for different treatment periods (ranged from 3– 24 months)

Season was an important covariate as a result of internal vitamin D production due to exposure to ultraviolet-B radiation. The seasons during which the clinical trials were conducted were not documented in all studies.

Seven of the fourteen included RCTs added calcium supplements to the vitamin D supplements. The dose of calcium supplementation ranged from 500 to 1000 mg. Two studies evaluated the overall nutrient intake in addition to supplementation.

Other variables, such as body mass index, ethnicity and smoking, were usually not considered.
The dropout rate was reported in 2 RCTs as 10% and 22%. In one RCT, the authors noted that the dropout rate was low without providing more details; in 11 RCTs, the dropout rate was not reported at all.

Compliance was not reported in 3 of the 14 RCTs. In 8 RCTs, the compliance was reported to be good. In 2 RCTs, the compliance rate was 100% for the participants completing the study. In one RCT, it was stated that a daily compliance calendar had been used but the results were not reported. One RCT did not mention whether it had been blinded. We found an improvement in mobility and muscle function in 10 RCTs.

Study outcomes

The pooled mean difference in HGS was higher in the vitamin D supplementation group than in the control group. The pooled mean difference in the TUG test was slightly lower in the vitamin D supplementation group than in the control group. The meta-analysis shows that vitamin D supplementation could improve muscle function in elderly people.

Table (1): The mean values of hand grip strength among the studied RCTs.

Authors	Hand grip baseline (vitaminD group)	Hand grip after supplementation (vitamin D group)	Mean difference (vitaminD group)	Hand grip baseline (control group)	Hand grip after supplementation (control group)	Mean difference (control group)
Anne et al., 2003	36.1±6.7	37.6±7.9	1.50	32.9±9.1	34.7±8.0	1.80
Behnaz et al., 2016	24.5±10.64	24.6±4.84	0.10	24.05±5.86	23.02±6.18	-1.03
Mirjam et al., 2014	32±3	31±3.1	-1.00	33±2.3	35±4.8	2.00
Verhaar et al., 2000	20.3±2.5	21.7±2.6	1.40	22.6±1.5	23.0±1.3	0.40
Bischoff et al., 2003	20.5±1.3	22.3±3.2	1.80	19.0±1.5	19.0±1.5	0.00
Pfeifer et al., 2009	21.1±8.3	23.6±7.5	1.25	21.7±9.0	22.4±8.3	0.35
Pfeifer et al., 2009	21.1±8.3	22.9±8.3	1.80	21.7±9.0	21.3±9.2	-0.40
Verschueren et al., 2011	24.48±2.5	29.6±2.5	5.12	27.98±4.6	29.0±4.7	1.02
Verschueren et al., 2011	28.4±2.8	23.34±3.5	2.47	25.2±6.3	26.19±5.5	0.5
Roseane et al., 2015	17.4±2.68	19.9±3.53	2.50	16.87±3.99	17.93±4.91	1.06
Hansen et al., 2015	18.8±2.5	19.86±2.5	0.53	19.77±3.02	20.32±2.88	0.28
Hansen et al., 2015	18.78±2.09	19.83±2.27	1.05	19.77±3.02	20.32±2.88	0.55
Kirsti et al., 2015	23.4±7.7	23.6±6.6	0.20	23.1±6.1	22.2±6.0	-0.90
Mariangela et al., 2016	16.63±4.99	19.83±2.27	3.20	19.62±6.01	20.32±2.88	0.70
Sonja et al., 2009	24.2±7.4	24.4±7.5	0.20	21.2±7.5	21.1±7.7	-0.10
Sonja et al., 2009	24.2±7.4	25.2±7.6	0.5	21.2±7.5	21.1±7.4	-0.05
Kana et al., 2018	33.3±6.35	34.0±5.92	0.70	31.3±7.6	33.1±6.04	1.80
Cangusus1 et al., 2015	23.8±12.3	24.4±13.4	0.60	24.2±10.5	23.9±10.7	-0.30

Table 2: The mean values of the timed up-and-go test among the studied RCTs

Authors	Timed up-and-go test baseline (vitamin D group)	Timed up-and-go test after supplementation (vitamin D group)	Mean difference (vitamin D group)	Timed up-and-go test baseline (control group)	Timed up-and-go test after supplementation (control group)	Mean difference (control group)
Anne et al., 2003	10.5±2.5	10.9±2.6	-0.40	10.6±4.5	11.3±5.7	-0.70
Behnaz et al 2016	9.75±2.07	8.27±1.74	1.48	10.05±1.79	10.29±2.03	-0.24
Mirjam et al, 2014	10.7±2.3	10.9±2.3	-0.20	10.5±4.8	10.9±5.7	-0.40
Verhaar et al., 2000	13.2±4.7	8.4±4.7	4.80	4.6±0.22	5.0±0.25	-0.40
Bischoff et al., 2003	15.0±9.5	15.0±9.5	0.00	13.0±7.0	10.0±5.0	3.00
Pfeifer et al., 2009	9.0±5.9	7.5±3.4	0.75	8.5±3.9	8.3±5.1	0.1
Pfeifer et al., 2009	9.0±5.9	7.3±3.4	1.70	8.5±3.9	8.2±4.8	0.30
Verschueren et al 2011	10.5±2.5	10.9±2.6	-0.40	10.6±4.5	11.3±5.7	-0.70
Verschueren et al., 2011	9.75±2.07	8.27±1.74	0.74	10.05±1.79	10.29±2.03	-0.12
Roseane et al., 2015	9.75±2.07	8.27±1.74	1.48	10.05±1.79	10.29±2.03	-0.24
Hansen et al., 2015	8.04±1.56	7.6±1.59	0.22	8.28±1.69	7.92±1.59	0.18
Hansen et al., 2015	8.03±1.7	7.65±1.77	0.38	8.28±1.69	7.92±1.59	0.36
Kirsti et al., 2015	12.6±3.3	9.3±2.1	3.30	12.0±2.4	9.7±6.4	2.30
Mariangela et al., 2016	9.0±5.9	7.5±3.4	1.50	8.5±3.9	8.3±5.1	0.20
Sonja et al., 2009	9.9±2.9	13±6	-3.10	10.3±2.8	10±7	0.30
Sonja et al., 2009	9.9±2.9	13±7	-1.55	10.3±2.8	15±6	-2.35
Kana et al., 2018	10.6±11.2	9.65±13.8	0.95	9.76±11.3	8.62±9.6	1.14
Cangusus1 et al., 2015	12.6±6.6	15.8±4.6	-3.20	13.3±6.2	13.1±5.4	0.20

Table 3: Effect of vitamin D supplementation on hand grip strength

Study	N1	N2	Total	SMD	SE	95% CI
Anne et al., 2003	32	32	64	0.360	0.249	-0.137 to 0.858
Behnaz et al 2016	37	34	71	0.283	0.236	-0.188 to 0.754
Mirjam et al, 2014	65	65	130	-0.984	0.185	-1.350 to -0.619
Verhaar et al., 2000	27	13	40	-0.561	0.337	-1.243 to 0.121
Bischoff et al., 2003	62	60	122	1.305	0.198	0.912 to 1.698
Pfeifer et al., 2009	121	121	242	0.151	0.128	-0.102 to 0.404
Pfeifer et al., 2009	121	121	242	0.182	0.128	-0.0709 to 0.435

Table 3(continued):

Study	N1	N2	Total	SMD	SE	95% CI
Verschueren et al 2011	26	29	55	0.155	0.267	-0.380 to 0.690
Verschueren et al., 2011	28	28	56	-0.610	0.270	-1.150 to -0.0688
Roseane et al., 2015	19	19	38	0.451	0.322	-0.202 to 1.104
Hansen et al., 2015	75	76	151	-0.170	0.162	-0.490 to 0.151
Hansen et al., 2015	79	76	155	-0.188	0.160	-0.505 to 0.128
Kirsti et al., 2015	102	102	204	0.221	0.140	-0.0548 to 0.497
Mariangela et al., 2016	69	61	130	-0.189	0.175	-0.536 to 0.157
Sonja et al., 2009	45	44	89	0.430	0.213	0.00783 to 0.853
Sonja et al., 2009	45	44	89	0.542	0.214	0.116 to 0.967
Kana et al., 2018	43	44	87	0.149	0.213	-0.274 to 0.572
Cangusus1 et al., 2015	80	80	160	0.0410	0.157	-0.270 to 0.352
Pooling Fixed effects	1076	1049	2125	0.0884	0.0437	0.00267 to 0.174
Pooling Random effects	1076	1049	2125	0.0905	0.110	-0.126 to 0.307

Table 4: Test for heterogeneity of HGS

Q	101.8827
DF	17
Significance level	P < 0.0001
I^2 (inconsistency)	83.31%
95% CI for I^2	74.82 to 88.94

Figure 1 Standardized mean differences in hand grip strength

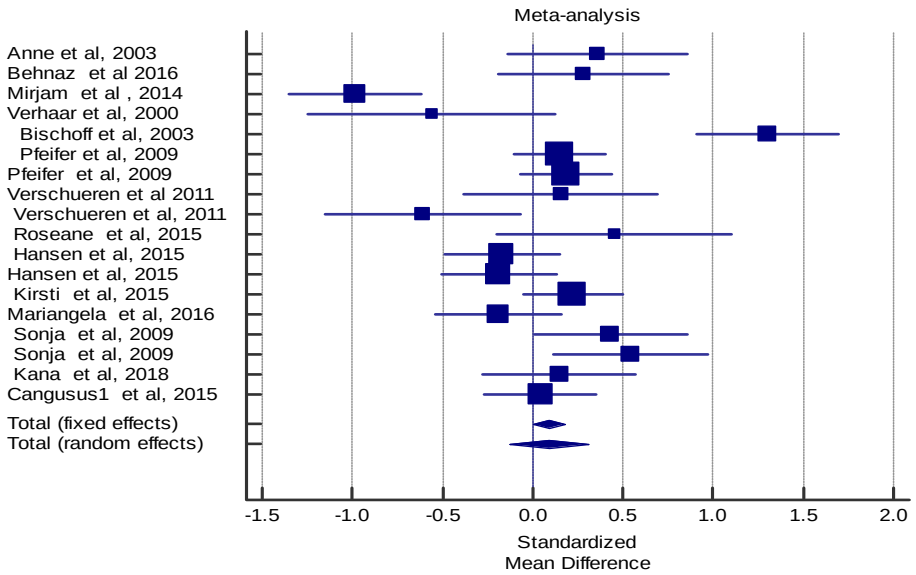


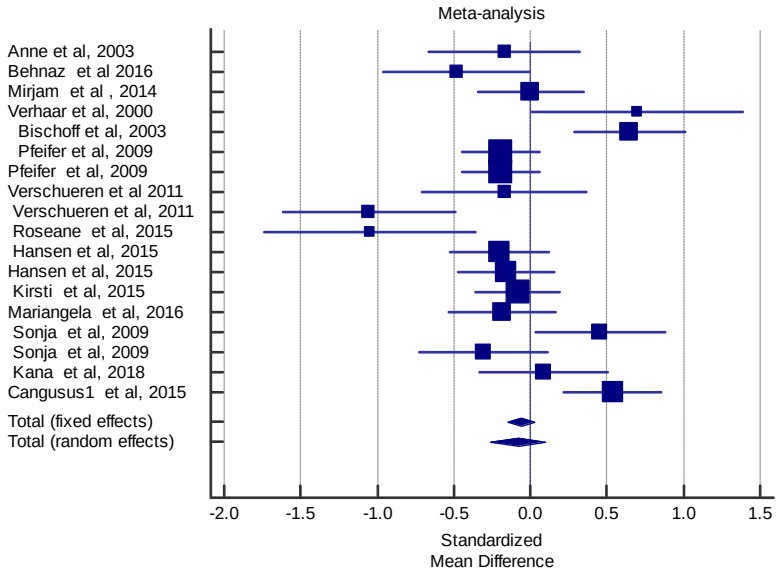
Table 5: Effect of vitamin D supplementation on the timed up-and-go test

Study	N1	N2	Total	SMD	SE	95% CI
Anne et al., 2003	32	32	64	-0.169	0.247	-0.664 to 0.325
Behnaz et al 2016	37	34	71	-0.483	0.238	-0.959 to -0.00721
Mirjam et al, 2014	65	65	130	0.000	0.174	-0.345 to 0.345
Verhaar et al., 2000	27	13	40	0.695	0.340	0.00670 to 1.383
Bischoff et al., 2003	62	60	122	0.649	0.185	0.283 to 1.014
Pfeifer et al., 2009	121	121	242	-0.192	0.128	-0.445 to 0.0613
Pfeifer et al., 2009	121	121	242	-0.191	0.128	-0.444 to 0.0619
Verschueren et al 2011	26	29	55	-0.170	0.267	-0.705 to 0.365
Verschueren et al., 2011	28	28	56	-1.054	0.282	-1.618 to -0.489
Roseane et al., 2015	19	19	38	-1.046	0.340	-1.735 to -0.357
Hansen et al., 2015	75	76	151	-0.200	0.162	-0.521 to 0.121
Hansen et al., 2015	79	76	155	-0.160	0.160	-0.476 to 0.157
Kirsti et al., 2015	102	102	204	-0.0837	0.140	-0.359 to 0.192
Mariangela et al., 2016	69	61	130	-0.186	0.175	-0.532 to 0.161
Sonja et al., 2009	45	44	89	0.457	0.213	0.0333 to 0.880
Sonja et al., 2009	45	44	89	-0.304	0.211	-0.724 to 0.116
Kana et al., 2018	43	44	87	0.0861	0.213	-0.337 to 0.509
Cangusus1 et al., 2015	80	80	160	0.536	0.160	0.219 to 0.852
Pooled fixed effects	1076	1049	2125	-0.0612	0.0435	-0.147 to 0.0242
Pooled random effects	1076	1049	2125	-0.0814	0.0913	-0.260 to 0.0977

Table 6: Test for heterogeneity of the timed up-and-go test

Q	**109.4471**
DF	18
Significance level	P < 0.0001
I^2 (inconsistency)	75.52%
95% CI for I^2	71.35 to 84.49

Figure 2 Standardized mean differences in the times up-and-go test



DISCUSSION

The geriatric population is a heterogeneous age group. Individuals in this group differ in terms of age, place of living, social status, existence of chronic illnesses, and quality of life. Therefore, it is predicted that studies among the geriatric population will, in general, present mixed results unless the population is defined more precisely according to the factors mentioned previously. Therefore, we limited the present meta-analysis to community-dwelling apparently healthy elderly individuals. It is known that community-dwelling elderly populations are usually healthier than those who are hospitalized or institutionalized. Community-dwelling individuals were targeted to limit the heterogeneity among the geriatric population.

The outcomes of this study were determined by the results of the HGS and the TUG tests, which are the only quantifiable outcomes that have been used as measurements of the decline in muscle strength and muscle function [1].

The aim of this meta-analysis was to investigate whether vitamin D supplementation (with or without calcium) in community-dwelling elderly individuals contributes to improved muscle function. Based on the findings of this meta-analysis, we conclude that vitamin D supplementation has a significant effect on muscle function, (HGS, p=0.043; TUG, p=0.049). This can be explained by the effect of vitamin D on type 2 muscle fibres [13]. In addition to the effects of vitamin D on neuromuscular control and neural coordination, there is growing evidence supporting a neurotrophic effect of vitamin D [14].

Strengths and limitations

The strength of this meta-analysis was the usage of data from 14 RCTs, with approximately 2127 participants. The HGS and TUG tests are the only quantifiable outcomes that have been used as measurements of the decline in muscle strength and muscle function.

The limitations of this study are the discrepancies between RCTs in terms of the doses of vitamin D, type of supplement, duration of supplementation, and participants' baseline vitamin D status, which made comparisons between studies difficult.

CONCLUSION

Our meta-analysis shows that vitamin D supplementation could improve muscle function in elderly individuals. Future studies should use standardized durations and doses of vitamin D supplementation.

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Appendix 1

Authors	Number of participants	Male cases	Male controls	Female cases	Female controls
Anne et al., 2003	65	33	32	0	0
Behnaz et al 2016	71	0	0	37	34
Mirjam et al, 2014	130	40	40	25	25
Verhaar et al., 2000	40	0	0	27	13
Bischoff et al., 2003	122	0	0	62	60
Pfeifer et al., 2009	242	26	25	95	96
Pfeifer et al., 2009	242	26	25	95	96
Verschueren et al 2011	55	0	0	26	29
Verschueren et al., 2011	56	0	0	28	28
Roseane et al., 2015	38	0	0	19	19
Hansen et al., 2015	151	0	0	75	76
Hansen et al., 2015	155	0	0	79	76
Kirsti et al., 2015	204	0	0	102	102
Mariangela et al., 2016	130	29	24	40	37
Sonja et al., 2009	89	45	44	0	0
Sonja et al., 2009	89	45	44	0	0
Kana et al., 2018	88	11	10	32	34
Cangusus1 et al., 2015	160	0	0	80	80

Appendix 2:

Authors	**Mean age of cases**	**Mean age of controls**
Anne et al, 2003	77.0±4.0	76.0±5.0
Behnaz et al 2016	45.2±2.6	45.7±3.1
Mirjam et al, 2014	48.9±10.3	51.5±10.5
Verhaar et al., 2000	75±3.2	76.5±1.4
Bischoff et al., 2003	84.9±7.7	85.4±5.9
Pfeifer et al., 2009	76.0±4.0	77.0±4.0
Pfeifer et al., 2009	76.0±4.0	77.0±4.0
Verschueren et al 2011	80.3±5.3	78.7±5.6
Verschueren et al., 2011	79.8±5.3	79.6±5.2
Roseane et al., 2015	62.2±7.6	62.3±8
Hansen et al., 2015	60.0±6	61±6
Hansen et al., 2015	60.0±5	61±6
Kirsti et al., 2015	74.1±3.0	73.8±3.1
Mariangela et al., 2016	80.77±6.29	80.21±8.54
Sonja et al., 2009	61.7±7.7	59.9±7.4
Sonja et al., 2009	61.7±7.7	59.9±7.4
Kana et al., 2018	68.8±5.3	71.2±6.8
Cangusus1 et al., 2015	58.8±6.6	59.3±6.7

Appendix 3:

Authors	Vitamin D supplementation (dose)	Duration of supplementation	Daily or weekly supplementation	Cal supplen
Anne et al., 2003	1000 IU	6 months	Daily	500
Behnaz et al 2016	1000 IU	3 months	Daily	
Mirjam et al, 2014	1200 IU	4 months	Daily	5
Verhaar et al., 2000	1000 IU	6 months	Daily	
Bischoff et al., 2003	400 IU	3 months	Daily	6
Pfeifer et al., 2009	800 IU	12 months	Daily	5
Pfeifer et al., 2009	800 IU	20 months	Daily	5
Verschueren et al 2011	1600 IU	6 months	Daily	100
Verschueren et al., 2011	880 IU	6 months	Daily	100
Roseane et al., 2015	942 IU	3 months	Daily	
Hansen et al., 2015	800 IU	12 months	Daily	
Hansen et al., 2015	3333 IU	12 months	Daily	
Kirsti et al., 2015	800 IU	24 months	Daily	
Mariangela et al., 2016	1000 IU	3 months	Daily	
Sonja et al., 2009	800 IU	12 months	Daily	
Sonja et al., 2009	800 IU	18 months	Daily	
Kana et al., 2018	1000 IU	6 months	Daily	
Cangusus1 et al., 2015	1000 IU	9 months	Daily	