

Original Article

Does vitamin D affect sarcopenia with insulin resistance in aging?

Yang Du PhD, Chorong Oh PhD, Jaekyung No PhD

Department of Food and Nutrition, Kyungsoong Universtiy, Busan, Korea

There are many studies investigating nutritional factors that affect both sarcopenia and muscle formation. According to extensive research, protein has an essential role in muscle formation. More recently, vitamin D has emerged as an important factor that regulates muscle metabolism. However, studies and research of association between 25-Hydroxyvitamin D (25(OH)D) status and components of homeostasis model assessment of insulin resistance (HOMA-IR) in older are limited. Nineteen studies were found through a search of electronic databases and were subjected to a meta-analysis to investigate the differences in serum levels of 25(OH)D and HOMA-IR between patients with controls and sarcopenia. The random-effects standardized mean difference (SD) and 95% confidence interval (CI) were calculated as the effect size. Nineteen studies with 19,528 participants (5,081 with sarcopenia and 14,447 without) were analyzed. Sarcopenic participants had significantly lower serum levels of 25(OH)D (SD =1.163; 95% CI 0.514, 1.812; $p < 0.001$; $I^2 = 99.652\%$) and HOMA-IR (SD = -2.040; 95% CI -3.376, -0.705; $p < 0.005$; $I^2 = 99.837\%$) than controls. It has been reiterated that sarcopenia may be related serum levels of 25(OH)D and HOMA-IR. This relationship needs to be clarified by future longitudinal studies.

Key Words: vitamin D, insulin resistance, sarcopenia, meta-analysis, muscle

INTRODUCTION

The age-related changes in body composition, including the development of sarcopenia, carry a risk factor for frailty and disability.¹ A recent study by Lexell and other researchers show a 13-4% incidence of sarcopenia in the 65 to 70-year-old population, whereas in the 80-year-old population, the sarcopenia incidence is more than 50%.² Skeletal muscle strength, mass, and quality are key factors in the maintenance of functional independence in older adults. It is possible that decreased muscle mass consequently lead to secondary muscular disuse atrophy and the cause of the age-related neurological changes, the hormonal and metabolic milieu, pro-inflammatory cytokines, and perhaps fat infiltration-ipotoxicity loss of strength with aging.³ Treatments of age-related sarcopenia includes resistance training, protein, amino acid supplementation and energy intake, and these are key components of the prevention and management of sarcopenia.

So far, there are various studies focusing on protein as a nutritional supplement strategy for the prevention and treatment of sarcopenia.⁴ Recently, numerous studies have reported extremely low vitamin D levels in older persons due to loss its ability to generate vitamin D₃ from ultraviolet(UV) radiation⁵ and low dietary intake of vitamin D in the elderly can result in low muscle strength and occur metabolic disease.⁶ In 2014, Lee et al found that the proportion of vitamin D deficiency among people over 65 years in the United States, Germany, and South Korea was 48.4%, 64.4%, and 75.3%, respectively, even though these countries have different vitamin D deficiency standards (US <25.0 ng/mL Germany <20.0 ng/mL and Korea <20.0 ng/mL and there were no significant gender differ-

ences.⁷ The United States had the highest standards and the lowest deficiency rate. The effects of serum 25-Hydroxyvitamin D (25(OH)D) levels on muscle have been explored in numerous studies and different populations.⁸

In this case, the reduction in muscle mass is accompanied by an increase in the amount of fat, which is called muscle-reducing obesity.⁹ This indicates that muscle reduction has simultaneous insulin resistance,¹⁰ and in return, it leads to more chronic diseases.¹¹ Vitamin D supplementation may be a simple, safe, and cost-effective solution that can alleviate the adverse effects of aging on the human body.^{12,13} Supplementation of vitamin D is common in the elderly¹⁴ and is associated with sarcopenia¹⁵ and obesity^{16,17} and as well as metabolic disturbances such as insulin resistance.¹⁸

The aging problem is getting fiercer around the whole world, especially in the developed countries, for instance, Japan, South Korea, Germany, etc. There is a paucity of data that measure the effects of vitamin D and homeostasis model assessment of insulin resistance (HOMA-IR) status on risk factors of sarcopenia, and those data that do exist were often with conflicting results.^{19,20} In this background, the objectives of this study was to investigate the

Corresponding Author: Dr Jaekyung No, Department of Food and Nutrition, Kyungsoong University, Busan, 309 Suyeong-ro, Nam-gu, Busan 48434608-736, Korea.

Tel: +82-51-663-4651; Fax: +82-51-663-4651

Email: jkno3@ks.ac.kr

Manuscript received 24 October 2019. Initial review completed 30 December 2019. Revision accepted 19 May 2020.

doi: 10.6133/apjcn.202009_29(3).0025

relationship between serum 25(OH)D and HOMA-IR status and muscle in the elderly population. The findings of this study will provide medical workers with a deeper and better understanding of the prevention and treatment of sarcopenia.

METHODS

Search strategy

This study conducted an electronic literature search for articles published between 1989 and January, 2019. A thorough search was conducted using three electronic databases: PubMed, Science Direct, and Cochrane Library. In PubMed, the following keywords were utilized: ((((((Sarcopenia[Title/Abstract]) AND Vitamin D[Title/Abstract]) OR Receptors, Calcitriol[Title/Abstract]) AND Insulin Resistance[Title/Abstract]) OR Resistance, Insulin[Title/Abstract]) OR Insulin Sensitivity[Title/Abstract]) OR Sensitivity, Insulin[Title/Abstract] and the other two electronics (Science Direct and Cochrane Library) utilized a similar search methodology.

Study selection

Selected studies: 1) human studies, 2) the mean and standard deviation of the study data, 3) separated the data by gender and age group. Studies were excluded if 1) repeated, 2) lack of data information and the inability to obtain the full text of the data, 3) subjects were under 60 years, 4) animal models were applied.

Data extraction

The data extracted in this study include the first author information, publication year, country, sample size, gender, age, basic values of 25(OH)D in each sample (ng/mL, unit uniform) and HOMA-IR. Finally, researchers summarized the selected data into a Microsoft excel spreadsheet.

Statistical analysis

The meta-analysis was applied in this study by using comprehensive meta-analysis V2.0 (CMA) for Windows (<https://www.meta-analysis.com/>). When synthesizing these studies, the random-effects model was used to account for study heterogeneity (Q statistic · Z statistic and I² statistic) with standard mean difference (SD) and 95% confidence interval (CI). The Q statistic ($p < 0.05$ indicating significant heterogeneity) and the I² statistic (I² >75.0%, 50.0-75.0%, and <50.0% indicating substantial, moderate, and low heterogeneity, respectively) were utilized to evaluate statistical heterogeneity.²¹ Publication bias was assessed using a visual inspection of funnel plots and the Egger bias test.²²

RESULTS

The original literature search identified 30,418 papers that might be eligible, among these, there are 1,129 papers were identified to be repeated. Later, 29,289 papers were screened with titles and abstracts, and a total of 59 papers were obtained. In addition, papers which are unable to view the original article or some other reasons were

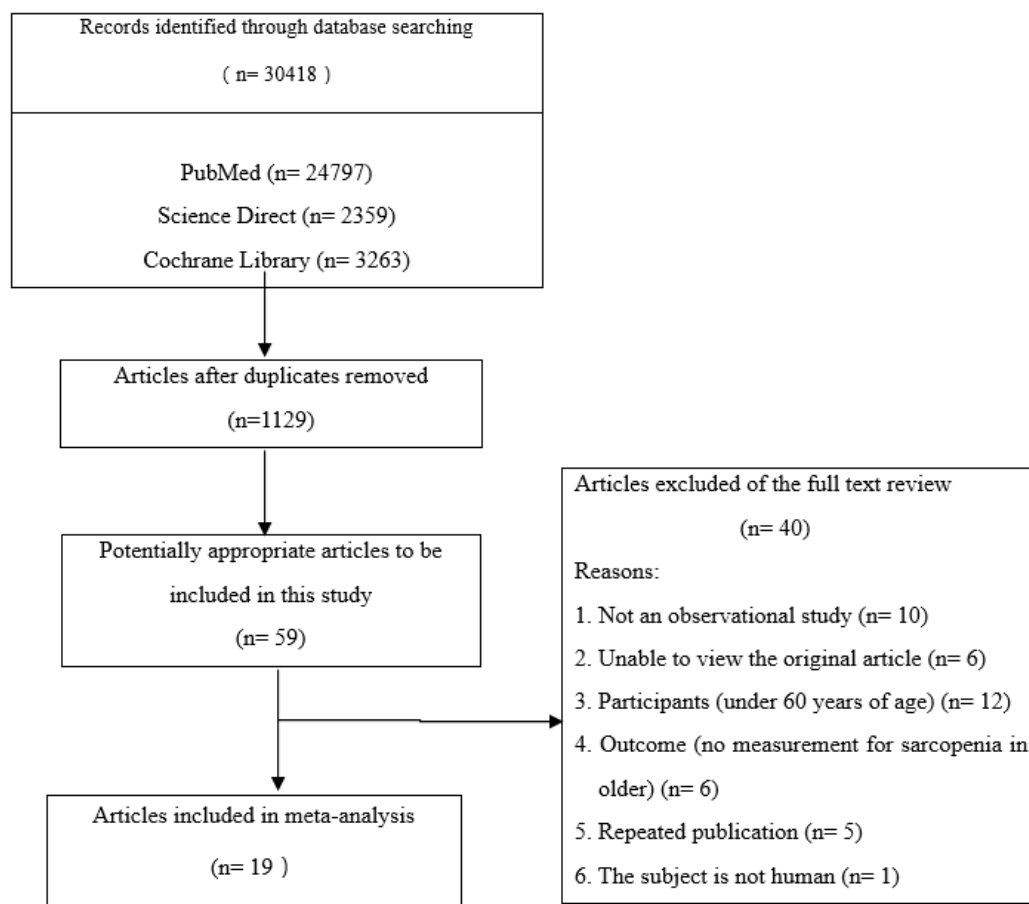


Figure 1. Flow of study analysis through different phases of the meta-analysis (from January 1, 1989 to Jan 8, 2019).

Table 1. The characteristics of included studies

First author, Year	Country	Sample size sarcopenia/without	Mean age (years)	25(OH)D Means (ng/mL)	HOMA-IR means
Chung et al. (2013) ²⁷	South Korea	2943 1248/1695	60	M: 22.8 F: 19.8	M: 2.4 F: 2.8
Huo et al. (2016) ²⁸	Australia	268 152/116	79	NO	NO
Kim et al. (2014) ²⁹	South Korea	2264 540/1724	65	NO	NO
Lee et al. (2013) ³⁰	South Korea	1535 510/1025	60	NO	NO
Bo et al. (2018) ³¹	China	496 30/30	60	NO	NO
Oh et al. (2015) ³²	South Korea	923 325/598	60	NO	NO
Oh et al. (2017) ³³	South Korea	2923 746/2177	60	NO	NO
Verlaan et al. (2017) ³⁴	UK	132 66/66	71	NO	NO
Tay et al. (2015) ³⁵	Singapore	200 50/150	65	NO	NO
Hwang et al. (2012) ³⁶	South Korea	1463 137/1326	60	NO	NO
Tajar et al. (2013) ³⁷	UK	952 76/876	60	M/F: 62.9 (nmol/L) [†]	NO
Seo et al. (2013) ³⁸	South Korea	1339 59/1280	60	NO	NO
Genaro et al. (2015) ²³	Brazil	105 35/70	70	F: 19.7	NO
Lyu et al. (2018) ⁴⁰	South Korea	1373 295/1078	60	NO	NO
Jung et al. (2017) ⁴¹	South Korea	435 138/297	70	M/F: 19.46	NO
Borg MSc et al. (2016) ³⁹	US	227 53/174	74	M/F:66.8 (nmol/L) [†]	NO
Son et al. (2019) ²⁶	South Korea	2120 508/1612	65	NO	NO
Suriyaarachchi et al. (2018) ²⁵	Australia	189 75/114	79	NO	NO
Lai et al. (2019) ²⁴	Italy	77 38/39	69.6	M/F: 19.25	M/F: 4.15

M: male; F: female; 25(OH)D: 25-Hydroxyvitamin D; HOMA-IR: homeostasis model assessment of insulin resistance.

[†]Unit is different.

excluded. Finally, a total of 19 studies were included in the meta-analysis, which can be seen in Figure 1.²³⁻⁴¹

Studies and patients

Study and patient characteristics are summarized and it was shown in Table 1. The 19 meta-analyzed studies included 19,528 participants (5,081 with sarcopenia and 14,447 without). The majority of the studies were conducted in Asia. All of studies were published after 2010. The average age of the subjects was 60–64 years old in 9 publications, 65 and older in 10 publications. Among the 19 studies for the meta-analysis, the number of adjusted variables of 25(OH)D levels was 26 and HOMA-IR was 12 because there were differences between male and female participants in the groups.

Effect sizes

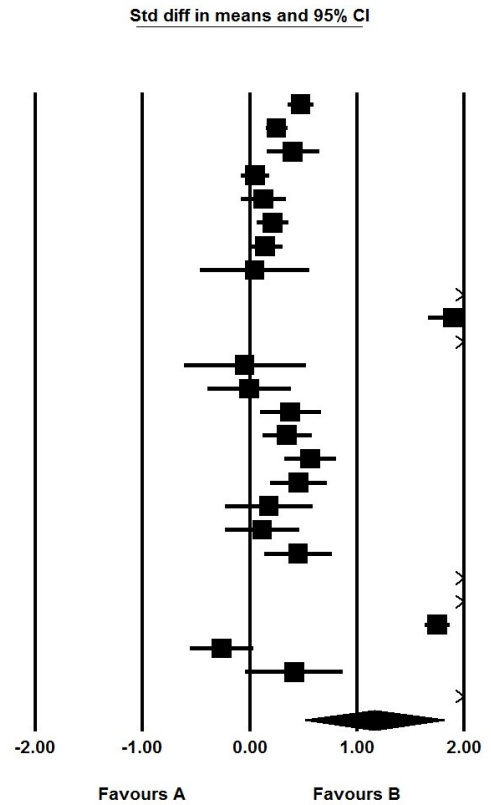
This study found that serum levels of 25(OH)D and HOMA-IR have a significant effect on sarcopenia (see Figure 2). Overall effect sizes (ESs) under random-effects assumptions indicated that 25(OH)D levels (SD=1.163; 95% CI 0.514, 1.812; $p<0.001$) had a significant overall effect on sarcopenia. Large heterogeneity existed between studies with $I^2=99.506\%$. Similarly, people with sarcopenia had immense difference in levels of HOMA-IR compared to those without sarcopenia (SD=-2.040; 95% CI -3.376, -0.705; $p<0.005$; $I^2=99.837\%$).

Publication bias

The examination of the impact of publication bias were further conducted. As shown in Figure 3, the funnel plot is asymmetrical left and right at the bottom, and there

(A)

Study name	Statistics for each study						Z-Value	p-Value
	Std diff in means	Standard error	Variance	Lower limit	Upper limit			
Chung et al., M	0.479	0.058	0.003	0.365	0.593	8.246	0.000	
Chung et al., F	0.254	0.049	0.002	0.157	0.350	5.142	0.000	
Huo et al., F	0.408	0.125	0.016	0.164	0.652	3.273	0.001	
Kim et al., M	0.053	0.065	0.004	-0.075	0.181	0.811	0.417	
Kim et al., F	0.132	0.104	0.011	-0.071	0.336	1.273	0.203	
Lee et al., M	0.218	0.074	0.006	0.073	0.364	2.942	0.003	
Lee et al., F	0.150	0.080	0.006	-0.006	0.307	1.887	0.059	
Bo et al., M	0.050	0.258	0.067	-0.456	0.556	0.193	0.847	
Oh et al., M	3.857	0.160	0.026	3.543	4.172	24.048	0.000	
Oh et al., F	1.900	0.115	0.013	1.673	2.126	16.449	0.000	
Oh et al., M/F	4.263	0.070	0.005	4.126	4.400	60.847	0.000	
Tay et al., M	-0.042	0.289	0.084	-0.609	0.525	-0.146	0.884	
Tay et al., F	0.000	0.198	0.039	-0.388	0.388	0.000	1.000	
Hwang et al., M	0.383	0.142	0.020	0.105	0.662	2.696	0.007	
Hwang et al., F	0.353	0.117	0.014	0.125	0.581	3.029	0.002	
Tajar et al., M/F	0.569	0.120	0.014	0.333	0.805	4.732	0.000	
Seo et al., M/F	0.461	0.133	0.018	0.199	0.723	3.455	0.001	
Genaro et al., F	0.182	0.207	0.043	-0.224	0.589	0.878	0.380	
Verlaan et al., F	0.121	0.174	0.030	-0.221	0.462	0.692	0.489	
Borg et al., M/F	0.455	0.158	0.025	0.145	0.766	2.873	0.004	
Jung et al., M	3.789	0.165	0.027	3.467	4.112	23.011	0.000	
Son et al., M	5.400	0.097	0.009	5.209	5.591	55.502	0.000	
Son et al., F	1.755	0.058	0.003	1.642	1.867	30.475	0.000	
Suriyaarachchi et al., M/F	-0.259	0.149	0.022	-0.552	0.034	-1.735	0.083	
Lai et al., M/F	0.418	0.230	0.053	-0.033	0.870	1.816	0.069	
Ryu et al., F	4.822	0.113	0.013	4.600	5.043	42.645	0.000	
	1.163	0.331	0.110	0.514	1.812	3.514	0.000	



(B)

Study name	Statistics for each study						Z-Value	p-Value
	Std diff in means	Standard error	Variance	Lower limit	Upper limit			
Kim et al. M	0.194	0.066	0.004	0.065	0.322	2.959	0.003	
Kim et al. F	-0.234	0.104	0.011	-0.438	-0.030	-2.244	0.025	
Lee et al. M	-0.448	0.075	0.006	-0.595	-0.302	-5.994	0.000	
Lee et al. F	-0.233	0.080	0.006	-0.390	-0.077	-2.919	0.004	
Oh et al. M	-4.000	0.164	0.027	-4.322	-3.678	-24.367	0.000	
Oh et al. F	-1.393	0.107	0.012	-1.604	-1.183	-12.970	0.000	
Oh et al. M/F	-5.600	0.085	0.007	-5.766	-5.434	-66.161	0.000	
Hwang et al. M	-0.640	0.143	0.020	-0.920	-0.360	-4.484	0.000	
Hwang et al. F	-0.698	0.118	0.014	-0.928	-0.468	-5.937	0.000	
Seo et al. M/F	-0.774	0.134	0.018	-1.036	-0.511	-5.775	0.000	
Son et al. M	-7.305	0.123	0.015	-7.546	-7.063	-59.301	0.000	
Son et al. F	-3.360	0.072	0.005	-3.502	-3.218	-46.367	0.000	
	-2.040	0.681	0.464	-3.376	-0.705	-2.994	0.003	

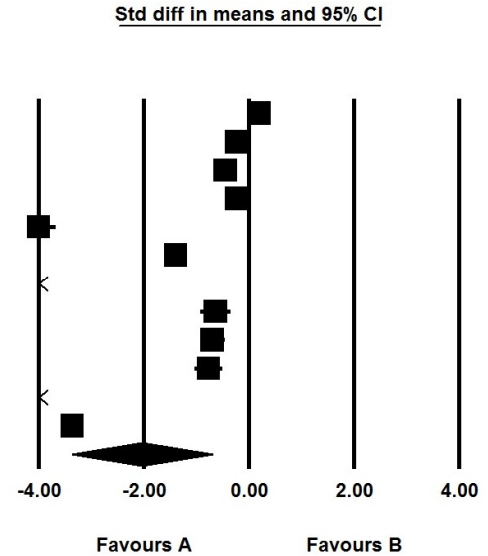


Figure 2. Forest plots of (A) 25(OH)D, (B) Homa-IR in subjects with sarcopenia vs. without sarcopenia. Std diff, standard difference; CI, confidence interval; M: male; F: female.

may be a publication bias. Egger linear regression was used to detect the degree of publication bias.⁴² However, no new research has been incorporated, from asymmetry to symmetry. Therefore, the funnel plot has not changed and this study cannot ensure that the included studies have no publication bias and no evidence of the validity of the results.

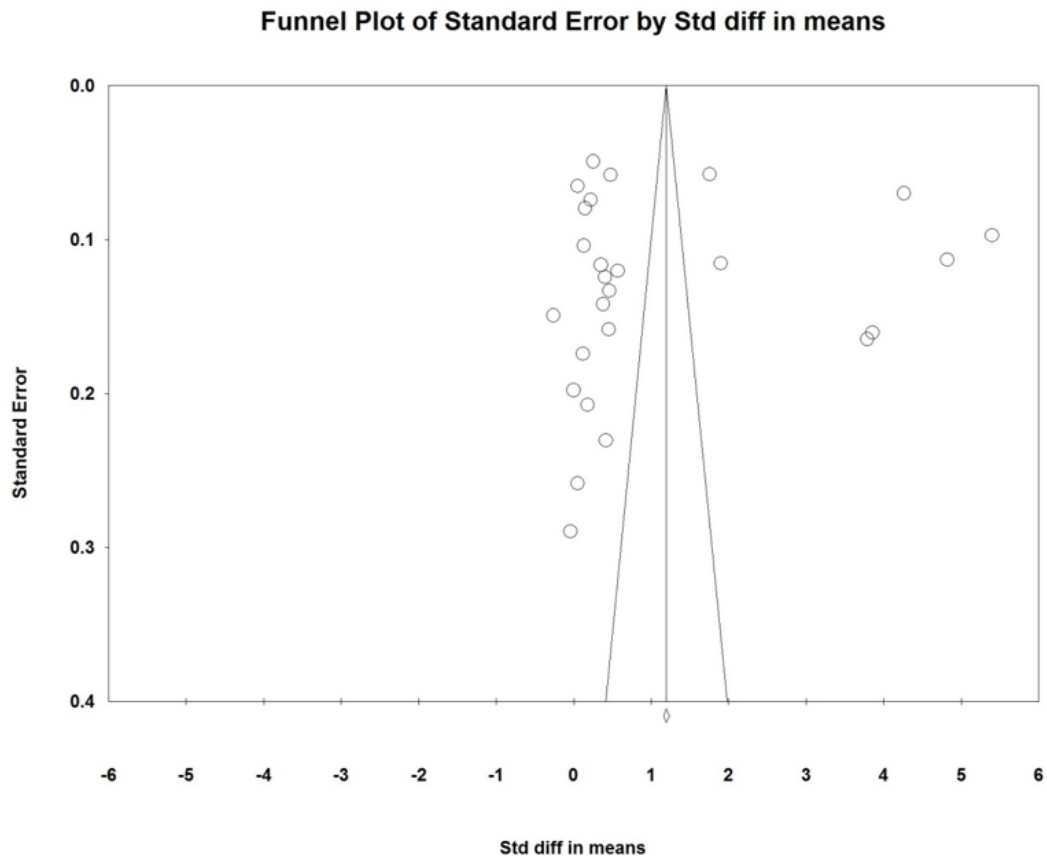
DISCUSSION

The purpose of this review was to explore the effect of vitamin D and HOMA-IR on change in body composition, sarcopenia in older adults. In this meta-analysis which included 5,081 people with sarcopenia and 14,447 with-

out, the results demonstrated that high serum 25(OH)D levels significantly improved muscle mass in older adults, while high HOMA-IR had a negative effect (Figure 2). Sarcopenia, a common age-related disease in the elderly, is characterized by low muscle mass and high fat mass, which increases the risk of fragility fractures and various chronic diseases.

Since the discovery of sarcopenia, an increasing number of reports and studies⁴³⁻⁴⁵ have mentioned the role of vitamin D in muscle reduction.⁴⁶ Moreover, the lack of vitamin D can lead to many diseases.^{47,48} For instance, the reduction in muscle mass is associated with low circulating vitamin D levels and can cause frailty, falls and meta-

(A)



(B)

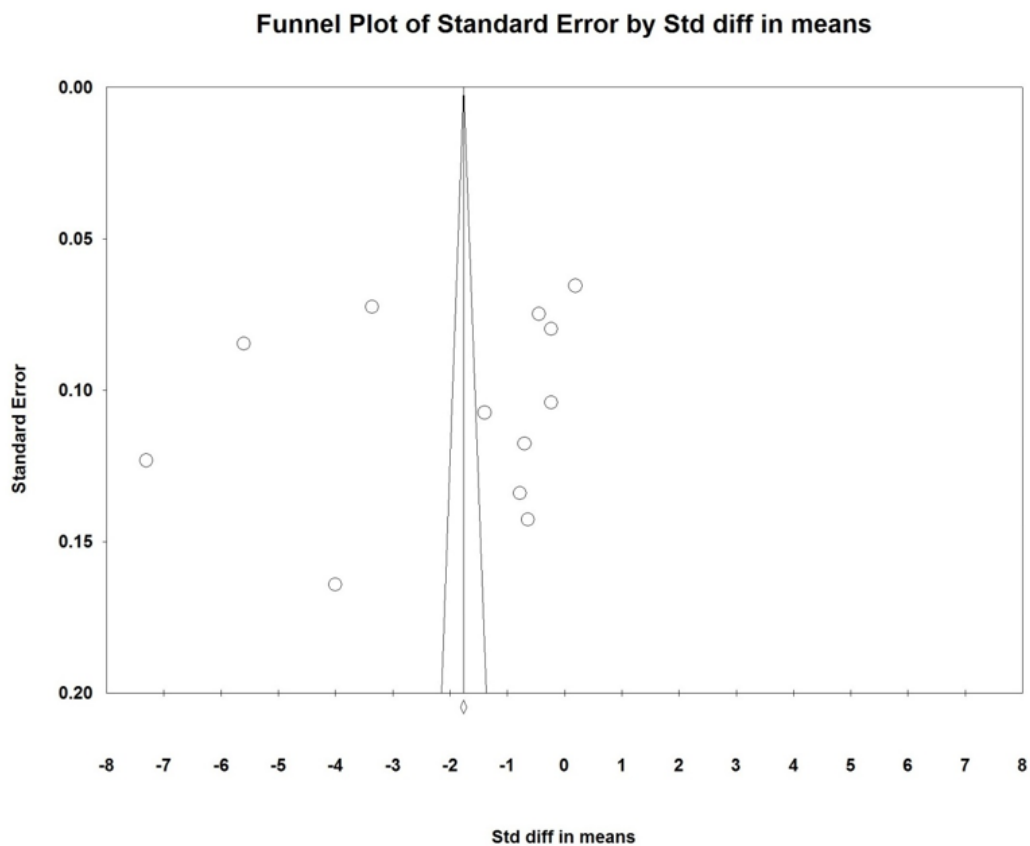


Figure 3. Funnel plots of (A) 25(OH)D, (B)HOMA-IR in subjects with without sarcopenia vs. sarcopenia.

bolic syndrome in the elderly.^{43-45,49} This is in agreement with the fact that patients with higher 25(OH)D levels have better muscle performance in the lower extremities than patients with lower levels.^{50,51} The findings of study

conducted by Girgis suggested that vitamin D was an effective nutritional intervention for preservation of muscle mass in healthy older adults.⁵² Vitamin D supplementation also positively impacted on muscle atrophy in

several pathological conditions, including HIV, hypocalcaemia, and osteoporosis.⁵³⁻⁵⁵ Older adults, especially those with pathological conditions, were the main subjects of study and performed limited physical activities, which can accelerate muscle loss.

The effects of vitamin D levels on muscle have been explored by a great number of studies and among different populations.⁵⁶ As a result of comparison between domestic and foreign studies, vitamin D and muscle mass were found to be significantly related.⁵⁷⁻⁵⁹ Despite this, very high doses of vitamin D increase the risk of falling (24,000 IU/month) and have no benefit for lower limb muscle function, which is beyond everyone's expectations.⁵⁹ Vitamin D plays a role not only in maintaining muscle tissue function, preserving muscle strength, increasing calcium absorption, but also acting as a hormone.⁶⁰ In muscle cells, vitamin D induces *de novo* synthesis of proteins that regulate cell proliferation and differentiation and also increases the calcium pool essential for muscle contraction. Therefore, vitamin D is intimately involved in maintaining muscle mass and function.^{61,62} Aging induces human skin to lose its ability to generate vitamin D₃ from UV radiation and low dietary intake of vitamin D in the elderly can result in vitamin D insufficiency.^{62,63} It could increase fracture risk due to muscle loss and muscle weakness in the aged people. Furthermore, sarcopenia is also known to cause low muscle mass, due to less mechanical stimulation and the pro-inflammatory cytokines underlying sarcopenia. Several recent epidemiological studies have examined the interaction between sarcopenia, and vitamin D insufficiency. Our study has confirmed the higher prevalence of sarcopenia in subjects with vitamin D insufficiency, which consistent with the findings of the Rancho Bernardo and other studies.³⁶⁻³⁸

Vitamin D deficiency is associated with the development of type 2 diabetes and with increased insulin resistance and impaired insulin secretion in human and animal studies.⁶⁴⁻⁶⁸ Cross-sectional and prospective studies have revealed that vitamin D deficiency is involved in the derangement of insulin resistance and insulin secretion which is commonly involved in the etiology of type 2 diabetes mellitus.⁶⁹⁻⁷² A systematic review and meta-analysis of prospective studies suggested that maintaining adequate levels of vitamin D may be a useful preventive measure for metabolic diseases including type 2 diabetes.⁶⁹ A few studies have evaluated the alteration of glucose metabolism in type 2 diabetic rats, but the mechanisms were not studied.^{73,74} Vitamin D consumption (10 IU/kg body weight) for 60 days decreased fasting plasma glucose levels, HbA_{1c} and insulin resistance index in male Wistar rats intraperitoneally injected with a single low dose of streptozotocin (35 mg/kg body weight).⁷⁴ Furthermore, it also demonstrated that HOMA-IR, an insulin resistance index, was higher, and whole-body glucose infusion rates at euglycemic and hyperglycemic states were lower in vitamin D-low than vitamin D-normal rats. In addition, Non-Government Organisations at hyperinsulinemic states were higher in vitamin D low than vitamin D-normal. This indicated that vitamin D deficiency exacerbated both whole-body and hepatic insulin resistance during euglycemia and hyperglycemia.

However, the beneficial effects of vitamin D on insulin sensitivity were attenuated in the vitamin D-high group in comparison to the sufficient state of vitamin D, as shown by the increased triglyceride storage in the liver and skeletal muscles as with vitamin D deficiency. These effects on insulin sensitivity may be related to the increase in visceral fat mass in vitamin D-high.

In conclusion, vitamin D plays an important role in muscle and insulin metabolism, and its deficiency is closely associated with sarcopenia which can also lead to metabolic disease.⁵⁴ In additions, in the research of Ceglia (2009), vitamin D receptor-deficient mice indicated more muscle damage than normal mice.⁷⁵ While the study by Sanders et al. demonstrated that no significant correlation exists between vitamin D treatment and muscle decline in elderly people (n=354) aged 70 years and older.⁷⁶ However, this trial level of vitamin D is low (400 IU/d). Supplementing with 500,000 IU of vitamin D in the fall or winter may increase serum 25(OH)D levels in older women, leading to a decreasing risk of sarcopenia.^{45,77-79} Therefore, further research is necessary to investigate the optimal amount of vitamin D supplement. Finally, it is proved that vitamin D's nutrition for sarcopenia is probably not the deficiency of vitamin D caused by body aging, but the lack of vitamin D intake.

To the best of our knowledge, this study is the first one to utilize meta-analysis to explore the linkage among sarcopenia, serum vitamin D and HOMA-IR status. Though the study is finished, the interpretation of this study is still needed to be in the light of some limitations. First, a small number of studies were covered and the sample sizes were relatively limited. Additionally, the diagnosis of sarcopenia patients was performed without certain diagnostic criteria. Finally, variation in the diagnostic criteria of sarcopenia among studies could have influenced the overall results. Uniform measurements of sarcopenia are needed for a stronger meta-analysis.

Conclusion

To sum up, as reflected in this meta-analysis, serum 25(OH)D levels are linked with sarcopenia and are associated with chronic disease risk factors (HOMA-IR). Longitudinal research are needed to further validate the findings of this study.

AUTHOR DISCLOSURES

The authors declare no conflict of interest. This research was supported by Kyungshung University in 2019, Busan, Korea.

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