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CASE REPORT

Vitamin D deficiency and risk of myasthenia gravis: An evidence-based case report

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Abstract

Background: An autoimmune condition known as myasthenia gravis (MG) targets the receptors for neurotransmitter acetylcholine at the neuromuscular junction, resulting in inhibition of muscle contraction. This results in muscle weakness resulting in a decrease in quality of life. Immunoregulation and muscle contractility are known to play a role in vitamin D. Literature on how vitamin D affects myasthenia gravis risk has not been widely carried out and the results are still controversial.
Objective: To evaluate the association between vitamin D and MG risk.
Methods: The search of the literature was conducted from PubMed, Cochrane Library, Embase, and EBSCOhost with the eligibility criteria determined by the authors. The literature search was using MeSH Term, text word, and title/abstract.
Results: Two articles were selected and critically appraised. The first article shows an odds ratio of 3.96 (CI95 1.26 to 12.52), which means that myasthenia gravis has vitamin D levels almost 4 times lower than healthy population. A case-control study that followed described a comparison of mean levels of vitamin D (25(OH)D) in myasthenia gravis (mean, 18.8±8.4 ng/mL) compared to healthy controls (26.3±6.1). ng/mL) ($p < 0.05$). Both studies revealed a strong interaction between MG and vitamin D inadequacy.
Conclusion: Both studies above support the theory that vitamin D deficiency is associated with the risk of developing MG.

Keywords: myasthenia gravis, vitamin D, adults, risk

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Introduction

Known as a rare disease, Myasthenia gravis (MG), research has shown that respiratory muscle exhaustion is increasing prevalence and mortality rates. Myasthenia gravis's prevalence worldwide varied from 2.17 to 32.0 per 100,000 population.[1] Department of Health United States estimates MG patients accounted for 5 to 14 for every 100,000 population from every ethnicity or gender.[2] In Indonesia, accurate data on MG prevalence was not available. However, based on 2016 research, 65 MG patients were living on Java Island.[3] Female to male ratio was estimated at around 3:1 at the age of less than 40-year-old. A similar ratio was estimated for the age of 40 – 50-year-old and puberty. But in people aged more than 50-year-old MG often occurred in males.[4]

Myasthenia gravis developed due to autoantibody bonded with acetylcholinesterase receptors on neuromuscular junction causing local and systemic muscle weakness.[5,6] Although the prevalence is not high, MG may cause severe mobility disability. If not properly managed, MG may lead to paralysis or mortality. Its chronic disease course required long-term therapy with adequate therapy management. Survivors often complained of difficulties in maintaining a good quality of life.[7] Therefore, it is important to discover the risk factor causing this disease.

Vitamin D deficiency was reported in almost every population in the world, both in terms of age and ethnicity. There are several factors associated with it, including environmental impact, habit, and lifestyle.[8] Low vitamin D is linked to a higher risk of developing a variety of illnesses. The significant health issue of vitamin D insufficiency is its great incidence. Lack of vitamin D levels causes a non-optimal immunity system, therefore, more vulnerable to several diseases.[9]

Through mechanisms in the muscle's vitamin D receptors, vitamin D controls the autoimmune response in MG and maintains muscular function.[10] The active form of vitamin D, 25(OH)D, was thought to regulate the immune system by raising the number of regulatory T-cells.[11] According to Asmark et al.,[12] the mean 25(OH)D in MG patients without supplementation was 5119 nM (range 27-96 nM), which is considerably lower than the mean of 6921 nM (range 29-133 nM) in healthy controls ($p = 0.017$). Guan et al.,[13] found that 69.8% and 23.2 %, respectively, of MG patients, had vitamin D deficiency and insufficiency. Furthermore, MG patients' vitamin D levels were found to be lower than those of healthy controls (17.366.64 vs. 22.117.28 ng/mL, p 0.001).

The author is searching for research to support the association between vitamin D deficiency and the risk of MG based on these descriptions.

Case

A 24-year-old female came to the hospital with dyspnea, worsening for 1 day before admission. For the last 3 weeks before presenting to our hospital, she complained of fever for 1 day, followed by coughing and an itchy throat. At the beginning of the disease course, there was no nausea, vomiting, diarrhea, sore throat, or dyspnea. Two weeks before coming to our hospital, her voice disappeared gradually. She also started to complain of difficulty in swallowing and dyspnea. Food intake started to decrease. She was diagnosed with dysphagia and dysphonia.

Five days before hospitalization, her complaint of difficulty in swallowing was increasing and she often spits. Dyspnea was becoming more severe and her body weakened. Her eyelids tend to drop, and difficult to open her eyes. Food intake was decreased further. At the time, she was still able to spontaneously open her eyes and followed orders. Weakness on all four extremities and cannot speak were also reported. The neurology division examined her and decided that she got impending myasthenia gravis.

On physical examination she was compos mentis, blood pressure 130/80 mmHg, pulse 88 beats/min, respiratory 32 beats/min, and temperature 37^0C. Anthropometry examination showed a body weight of 50 kg, and a height of 155 cm. Laboratory examination revealed Hb: 12.7 g/dL, leucocyte 18,000/µL, platelets 171,000 /µL, and total vitamin D 25-OH was 18.5 ng/mL. She was interested in learning how vitamin D and the prevalence of MG are related.

Methods

The literature search was done independently by 2 authors from 4 databases PubMed, Cochrane Library, Embase, and EBSCOhost. The search was performed using advanced searching on 22 March 2022 combining MesH Terms and abstracts/titles from each PICO component. Authors also used the Boolean operator "OR" to increase sensitivity and "AND" to raise specificity. Keywords used were "myasthenia gravis", "generalized myasthenia gravis", "myasthenia gravis paralytic", "myasthenic crisis", "vitamin D", "cholecalciferol", "1 alpha, 25 dihydroxy 20 epi vitamin d3". Literature obtained from those databases was screened based on inclusion and exclusion criteria. Inclusion criteria include MG patients aged >18-year-old, vitamin D deficiency as the main risk factor and MG as the main outcome in the research, articles with research design systematic review-meta-analysis, RCT, case-control, or cohort, in English, and research on the human subject.

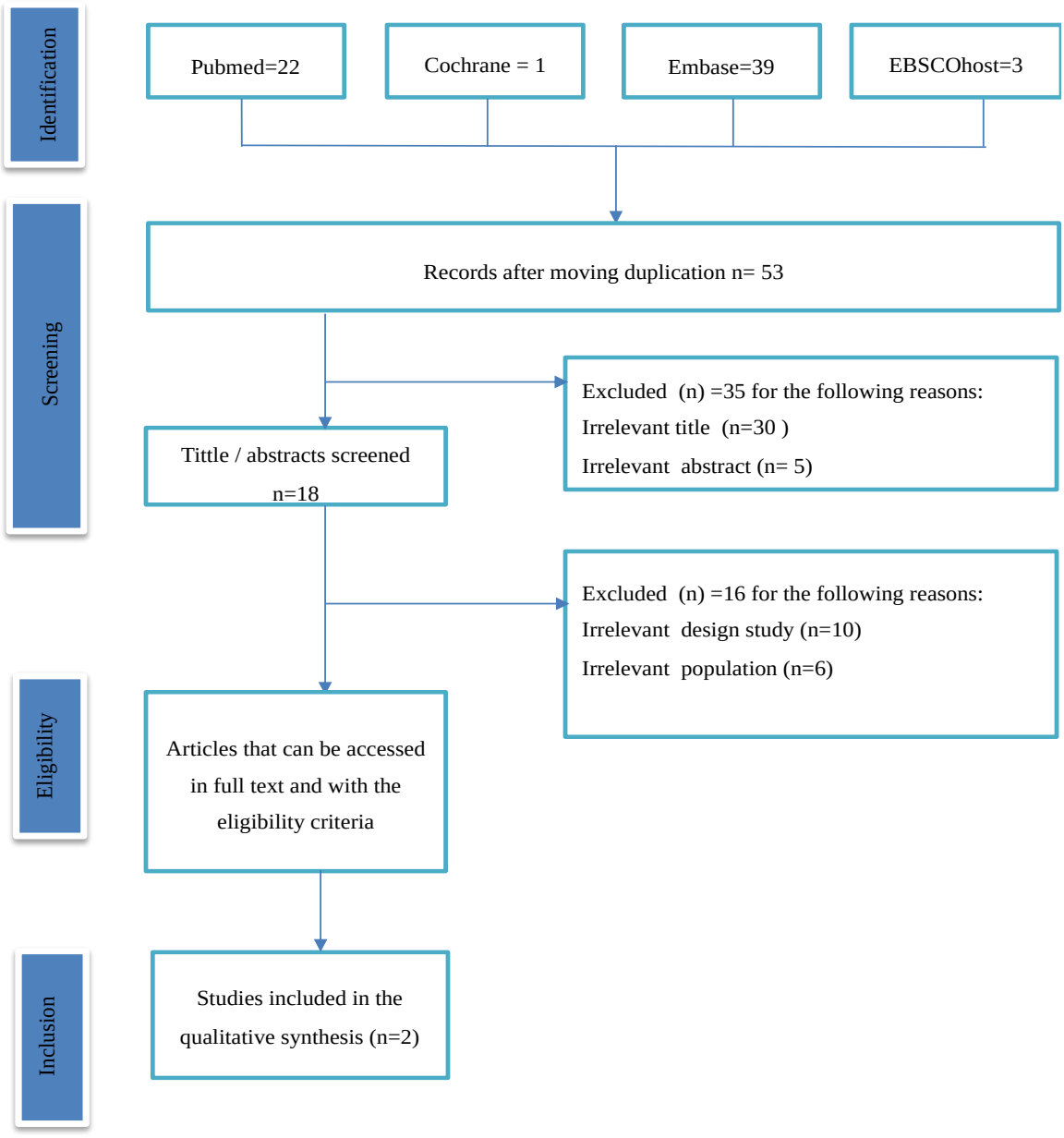

Figure 1. Prisma Flow Diagram on Literature Searching

Exclusion criteria are articles that were not available in full text, screened duplication, and availability of complete text in that literature. The literature search pathway is depicted in **Figure 1**. The critical review used in this study is based on a case-control literature guideline using the Critical Assessment Skills Programme (CASP) worksheet.

Critical appraisal was done with vitamin D deficiency as the main risk factor and myasthenia gravis as the main outcome of the research. Selection based on eligibility criteria was done to all articles available. The process was continued with critical appraisal and agreement between the 2 authors.

Result

In this study, we were able to obtain several articles: 22 from PubMed, 1 from Cochrane Library, 39 from Embase, and 3 from EBSCOhost (**Table 1**). Filtering for duplication was done with Mendeley. After that, each article was filtered based on methods, title abstract, PICO criteria, and full-text availability. The result was presented in **Figure 1**.

The research design selected in the Evidence-Based Case Report is 2 case-control studies. Literature's characteristics were displayed in **Table 2**. Moreover, both articles had a great relevance with PICO from predefined research questions (**Table 3**).

Table 1. Literature searching strategy

Database	Search Strategy		Hits
Pubmed	Search: ((((((myasthenia gravis[MeSH Terms]) OR (myasthenia gravis[Title/Abstract])) OR (Myasthenia gravis paralytica[MeSH Terms])) OR (Myasthenia gravis paralytica[Title/Abstract])) OR (generalized myasthenia gravis[MeSH Terms])) OR (generalized myasthenia gravis[Title/Abstract])) AND (((((vitamin D[Title/Abstract])) OR vitamin D[MeSH Terms]) OR (1 alpha, 25 dihydroxy 20 epi vitamin d3[MeSH Terms])) OR (1 alpha, 25 dihydroxy 20 epi vitamin d3[Title/Abstract])) Filters: Full text		22
Cochrane Library	ID		1
	#1	(Myasthenia gravis):ti,ab,kw	699
	#2	("myasthenia gravis paralytica"):ti,ab,kw	0
	#3	#1 OR #2	699
	#4	Vitamin D):ti,ab,kw	15694
	#5	#3 And #4	1
EBSCOhost	ID		3
	S1	AB myasthenia gravis OR AB myasthenia gravis paralytica OR AB myasthenic crisis	575
	S2	AB vitamin d OR AB cholecalciferol	4.104
	S3	S1 AND S2	3
Embase			39
	#1	'vitamin d'/exp	164.703
	#2	'myasthenia gravis'/exp	26.800
	#3	#1 AND #2	139
	#4	#3 AND ('cholecalciferol'/dd OR 'vitamin d'/dd) AND 'human'/de AND [adult]/lim	39

Table 2. Study characteristics

Characteristics	Justo, et al. 2021	Kang, et al. 2018
Study des	*Case-control*	*Case-Control*
Population	Patients of MG (n = 66) and healthy individuals (n = 25)	Patients of MG (n=25) and healthy individuals (n=40).
Determinant	Anti-acetylcholine receptor antibodies, complement factor C5a, and serum levels of 25(OH)D. Consumption of vitamin D and sunlight exposure.	1,25-dihydroxy vitamin D concentration [1,25(OH)2D] and 25(OH)D, a form of vitamin D.
Outcome	• Compared to 68.0 percent of the group of healthy adults, 89.4 percent of MG participants had insufficient levels of vitamin D (OR = 3.96; P = 0.024). • There was no statistically significant difference in the median serum 25(OH)D levels between the healthy group and the MG patients.	• Plasma 25(OH)D levels were lower in MG patients (18.8 8.4 ng/mL on average) than in healthy controls (26.3 6.1 ng/mL) (p 0.05). • MG patients had somewhat higher 1,25(OH)2D levels than did healthy controls. However, there was no identifiable difference between the groups.

Table 3. Relevance criteria

Authors	Similarity population	Similarity determinant	Similarity outcome	Level of evidence
Justo et al.	+	+	+	4
Kang et al.	+	+	+	4

Discussion

The literature search turned up 2 case-control studies that met the eligibility requirements. In case-control research, Justo et al.,[14] investigated the association between low vitamin D levels and a higher incidence of MG in the population of Argentina. A case-control research was also carried out by Kang et al.,[15] to examine the relationship between MG patients and vitamin D insufficiency.

The study by Justo et al.,[14] included 25 healthy controls and 66 patients with MG diagnosis. In this study, patients with chronic diseases causing severe deficiency in vitamin D were excluded. Vitamin D level was tested in all subjects using the chemiluminescence method. Research results showed an odds ratio of 3.96 (CI95 1.26–12.52) implying MG patients had vitamin D levels almost 4 times lower compared to the healthy population. A statistically significant positive link between vitamin D deficit and MG patients (p=0.024) was also established in one study, which indicated that 89.4% of MG patients and 68.0% of healthy controls had vitamin D deficiency.

The advantage of the study by Justo et al.,[14] is the author identified seasons as a confounding factor where there are 4 seasons in Argentine and vitamin D concentration also depended on sun exposure. However, statistically, no significant vitamin D fluctuation in MG patients in this research. In healthy controls, there was a change in vitamin D levels, with summer being the peak and spring being the lowest. Another advantage of this study is there was a questionnaire on vitamin D intake and sun exposure. However, one of the limitations of this study was limited patient and control, and patients were only included from 1 hospital. Based on the review, we concluded this

study has good validity and importance, however, it cannot be applied in Indonesia due to differences in season and sun exposure intensity.

Myashthenia gravis patients' mean vitamin D levels were compared to those of healthy controls in a case-control study by Kang, et al., [15] Patients with MG were shown to have lower plasma concentrations of 25(OH)D than healthy controls (18.88.4 ng/mL and 26.36.1 ng/mL, respectively, p 0.05). Myasthenia gravis patients had slightly greater 1,25(OH)2D levels than healthy controls, but there was no discernible difference between the two groups. Patients with generalized myasthenia gravis and ocular myasthenia gravis were separated. Ocular MG (50.9 28.7 ng/mL) and generalized MG (48.6 25.7 ng/mL) had similar 1,25(OH)2D levels. A similar outcome was also observed in 25(OH)D (generalized MG: 19.810.1 ng/mL; ocular MG: 17.24.9 ng/mL).[15]

Twenty-five MG patients were grouped as cases and did not consume vitamin D. Control group was gained of healthy volunteers with no medical history and no vitamin D supplementation. Vitamin D level was measured by chemiluminescence microparticle immunoassay. The blood sample was taken directly to hospital for testing. Several limitations in this study included a small number of patients, only performed in 1 hospital, and there was no odds ratio of vitamin D deficiency in case and control groups, therefore, the risk cannot be assessed.[15] Based on critical appraisal, study validity was good, however, the study result was not presented completely and cannot be applied in Indonesia due to climate differences.

According to Askmark et al.,[12] MG patients in Sweden had a vitamin D deficiency, and vitamin D therapy was linked to a reduction in muscle tiredness. This review supports their findings. In MG patients who were not receiving any supplements, the mean value of 25(OH)D was 51 19 nM (range 27 - 95 nM). With a mean value of 69 21 nM (range: 29–133 nM) and a significant difference from healthy controls (p = 0.017).

Additionally, vitamin D deficiency was found in studies of the Tiongkok community. Guan et al.,[13] found that 23.2% of MG patients had vitamin D insufficiency and that 69.8% of MG patients had a vitamin D shortage. In addition, patients with MG had lower levels of vitamin D (17.36 6.64 vs. 22.11 7.28 ng/mL, p 0.001) than healthy controls. Patients with MG may experience altered muscular function due to vitamin D's capacity to regulate adaptive immune response. The amount of vitamin D a person has varies on their race, age, sex, weight, creatinine status, color of skin, nutrition, exposure to sunlight, and use of sunscreen. As a result, vitamin D status may differ between nations.[16,17]

Vitamin D is an important nutrient needed for muscle contraction and preventing autoimmune disease. In addition to directly influencing cellular functions, vitamin D also conducts its biological effects by modulating gene expression via the vitamin D receptor. The central nervous system, Schwann cells, muscles, and peripheral neurons all express vitamin D receptors.[18] The immune system is regulated by vitamin D, which also inhibits plasma cells and B-cell activation promotes T-cell modulation and regulates T-cell reactivity, which in turn prevents an autoimmune reaction.[19]

Both studies mentioned above support the theory stating vitamin D was related to the risk of myasthenia gravis incidence. This may be the basis for testing vitamin D status in the adult population and suggesting consuming food with high vitamin D levels and adequate sun exposure.

Conclusion and recommendation

Based on this journal review, it was concluded that vitamin D deficiency was associated with MG incidence. Vitamin D deficiency may be prevented through adequate intake of high vitamin D food sources and sun exposure. Vitamin D supplementation can be given in vitamin D deficiency cases. It may be possible to do more studies using a cohort, RCT, systematic review, or meta-analysis design to examine the relationship between vitamin D insufficiency and the risk of MG.

Conflict of interest

The authors declare that there is no conflict of interest.

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