

Research Article

The Relationship between 25-Hydroxyvitamin D and Menopausal Symptoms in Postmenopausal Women

Satiyem^{1*}, Retno Hartanti², I Wayan Arsana Wiyasa³, Umi Kalsum⁴ and Bagus Putu Putra Suryana⁵¹Master of midwifery students, Faculty of Medicine, Brawijaya University, Malang, East Java, Indonesia²Polytechnic of Ministry of Health Surakarta, Central Java, Indonesia³Master of midwifery students, Faculty of Medicine, Brawijaya University, Malang, East Java, Indonesia⁴Department of Obstetrics and Gynecology, Saiful Anwar Hospital, Malang, East Java, Indonesia⁵Department of Pharmacology Faculty of Medicine, Brawijaya University, Malang, East Java, Indonesia⁵Department of Internal Medicine Rematology, Saiful Anwar Hospital, Malang, East Java, Indonesia**Article History**

Received: 20.07.2020

Accepted: 05.08.2020

Published: 20.08.2020

Journal homepage:<https://www.easpublisher.com/easjnm>**Quick Response Code**

Abstract: Post-menopause is caused by the decreasing estrogen resulting in menopausal symptoms. Menopause Rating Scale (MRS) is a standardized questionnaire used to evaluate the menopausal symptoms. Vitamin D is believed relieving the menopausal symptoms. The purpose of this research is to figure out the relationship between 25(OH)D and menopausal symptoms based on MRS. This research employed an observational research method with a cross sectional study. The research population was all post-menopausal patients at Dr. Saiful Anwar Hospital, Malang in March 2020. The inclusion criteria are post-menopausal patients aged >45 years old. The inclusion criteria were the patients having the steroid medication, experiencing autoimmune and thyroid abnormality. The total research subjects were 39 respondents. The 25(OH)D level was examined using ELISA. The results showed that 8(20.5%) deficiency, 22(56.4%) insufficiency, and 9(23.1%) sufficiency. Based on MRS, 8 (20.5%) mild, 12(30.8%) moderate, 17(43.6%) severe, 2(5.1%) very severe menopausal symptoms. Those symptoms were divided into 3 scales: somatic scale moderately experienced by 16 (41%), psychological scale moderately experienced by 21(53.8%), and urogenital scale severely experienced by 17(43.6%) respondents. The results obtained from the spearman correlational analysis showed that there are significant and non-linear relationship of 25(OH)D with somatic symptoms ($r -0.652$; $p 0.000$), with psychological symptoms ($r -0.452$; $p 0.004$), urogenital symptoms ($r -0.368$; $p 0.021$), and with the total MRS scale ($r -0.712$; $p 0.000$). The concludes, there is a significant and negative relationship between 25(OH)D and menopausal symptoms based on MRS and close relationship respectively from the strongest to the weakest symptoms (somatic-psychological-urogenital).

Keywords: 25-hydroxyvitamin D, menopausal symptoms, Menopause Rating Scale (MRS), post-menopausal women.

Copyright @ 2020: This is an open-access article distributed under the terms of the Creative Commons Attribution license which permits unrestricted use, distribution, and reproduction in any medium for non-commercial use (Noncommercial, or CC-BY-NC) provided the original author and source are credited.

INTRODUCTION

Menopause is one development phase in reproductive system. Menopause is the last period of reproductive system started by the fluctuating estrogen level which eventually decreases that menstruation is no longer experienced for 12 months after the last occurring menstrual since the ovarian follicle activity has stopped. Menopause is generally experienced by women aged 45-50 years old (Skaznik-Wikiel *et al.*, 2015; Grady and Connor, 2017; Askin *et al.*, 2019).

Menopause is caused by the decreasing estrogen leading to the physical, hormonal, and psychological changes influenced by the neurobiochemical changes in the central nervous system. About 80% of menopausal women have experienced menopausal symptoms, such as hot flush

and sweating, sleeping disorder, depression, migraine, and decreasing cognitive function. The long-term manifestation of the decreasing estrogen may result in skin aging and urogenital atrophy which lead to the symptoms related to sexual function, urinary system, osteoporosis, and sarcopenia causing the joint and muscle pain symptoms. The decreasing estrogen also influences its receptors including in heart and blood vessel leading to the symptoms related to the cardiovascular disease. Thus, the increasing women's life expectancy may provide opportunities for women to pass their life longer during their menopausal period with various menopausal symptoms (Blumenfeld *et al.*, 2014; Monteleone *et al.*, 2018; Askin *et al.*, 2019).

Vitamin D is believed relieving the menopausal symptoms as explained by various research

results, such as relieving hot flush, depression, vaginal atrophy, osteopenia, migraine, and cardiovascular disorder (LeBlanc *et al.*, 2014; Aydogmus and Demirdal, 2018; Ghorbani *et al.*, 2019; Mann *et al.*, 2015). The vitamin D sufficiency status can be measured in blood circulation in the form of 25-Hydroxy vitamin D [25(OH)D] which has a long half-life of between 2-3 weeks (Schuster, 2011; Wrzosek *et al.*, 2013), to help absorb calcium contained in the intestines, and improve the skeletal remodeling process (Holick, 2016). Vitamin D deficiency may cause secondary hyperparathyroidism, porous bones, inadequate bone mineralization, osteoporosis, osteomalacia, weakening muscles, susceptible to falling and bone breaking, as well as worsening the symptoms during the menopausal period (Lerchbaum, 2014).

Menopause Rating Scale (MRS) is a standardized questionnaire to evaluate the menopausal symptoms. The MRS questionnaire has been validated for each question's constructs in Indonesia in 2018 resulted in the MRS questionnaire which has the construct validity possibly accepted to evaluate the menopausal symptoms experienced by women in Indonesia. The MRS questionnaire consists of 3 groups: psychological symptoms covering depression, easily offended, anxious, and fatigue; somatic-vegetative symptoms covering sweating/hot flush, heart symptoms, sleeping disorder, joint and muscle symptoms; urogenital symptoms: sexual problem, urinary symptoms, and vagina dryness (Dwi Susanti *et al.*, 2019; Heinemann, 2019)

The research conducted by Siregar M.F.G in 2014 and 2016 on menopausal symptoms, explained that the most frequently symptoms included inconvenience joints and muscles (84%), depression and mood swing (68%), physical and mental fatigue (68%), as well as vasomotoric symptoms (52%) frequently experienced by women aged 45-50 years old (96.1%). Meanwhile, the research on menopausal symptoms based on the *Menopause Rating Scale* (MRS) conducted by Zolekhah and Sholihah (2018)

mentioning that most menopausal women (24 or 80% respondents) in Sleman Yogyakarta complained related to their vaginal dryness.

Due to the above data and research, not many studies discussed the relationship between vitamin D and menopausal symptoms based on MRS. Thus, the author is highly interested in revealing the relationship between 25(OH)D and menopausal symptoms based on *Menopause Rating Scale* (MRS) in post-menopausal women.

METHOD

This research employed an observational research method with a cross sectional study design. The research population was all post-menopausal female patients at Dr. Saiful Anwar Hospital, Malang. The research was conducted in March, 2020 with a total of 39 research samples. The samples were collected using a non-probability purposive sampling technique. The inclusion criteria were post-menopausal patients aged more than 45 years old and willing to become the research subjects. The exclusion criteria were patients refusing their blood samples taken, having steroid medication, as well as suffering from autoimmune, bone infection, hypoparathyroid, hyperparathyroid, hypothyroid, and hyperthyroid.

The level of 25(OH)D was examined using *ELISA* method. The menopausal symptoms were evaluated using the MRS questionnaire. Univariate analysis was conducted to analyze the data and describe the subjects' characteristics, while the bivariate analysis was conducted to see the relationship between 25(OH)D and menopausal symptoms.

Results

Univariate analysis on the descriptions of research subjects' characteristics based on age, menopausal duration, parity, IMT was explained in table 1.

Table 1. Characteristics of research subjects

Characteristics		Mean	sd
Age	>45 tahun	66,33	8,542
Menopausal duration		15,77	9,565
		Number (N)	Percentase (%)
Parity	Nulipara	3	7.7
	Primipara	2	5.1
	Multipara	30	76.9
	Grandemultipara	4	10.3
IMT	Underweight (<18,5)	3	7.7
	Normoweight (18,5–24,9)	24	61.5
	Overweight (25,0–29,9)	10	25.6
	Obese (>30)	2	5.1

The research subjects average age and menopausal duration was respectively 66 years old (up

to 8.542) and 15.77 years (up to 9.565). Based on the body mass index, 24 (61.5 %) respondents were in

normal weight, 3 (7.7%) respondents were underweight, 10 (25.6%) respondents were overweight, and 2 (5.1%)

respondents were obese.

Table 1. Menopausal symptoms based on MRS

Item	No		Yes	
	n	%	n	%
Somatic symptoms				
- Hot flashes, sweating	23	59,0	16	41,0
- Heart discomfort	14	35,9	25	64,1
- Sleep problems	11	28,2	28	71,8
- Joint and muscular discomfort	2	5,1	37	94,9
Psychological symptoms				
- Depressed mood	25	64,1	14	35,9
- Irritability	25	64,1	14	35,9
- Anxiety	15	38,5	24	61,5
- Physical and mental exhaustion	2	5,1	37	94,9
Urogenital symptoms				
- Sexual problems	13	33,3	26	66,7
- Bladder problems	23	59,0	16	41,0
- Vaginal dryness	10	25,6	29	74,4

Table 2 describes menopausal symptoms based on MRS, uncomfortable taste symptoms in muscles and joints as much as the physical and mental fatigue of 37

people (94.9%). The next most suffered a vaginal dryness symptoms of 29 people (74.4%) And had a sleep problem of 28 people (71.8%).

Table 2. Description statistics 25(OH)D and MRS

Variable	Deficiency 25(OH)D			Insufficiency 25(OH)D			Sufficiency 25(OH)D			Total n (%)
	n (%)	Mean	sd	n (%)	Mean	sd	n (%)	Mean	sd	
25(OH)D	8 (20,5)	9,69	2,152	22 (56,4)	14,81	2,118	9 (23,1)	27,10	6,323	39 (100)
Somatik scale		5,50	1,604		3,86	1,699		1,56	0,882	
Mild	0			4 (18,2)			8 (88,9)			12 (30,8)
Moderate	2 (25)			11 (50)			1 (11,1)			16 (41)
Severe	6 (75)			6 (27,3)			0			10 (25,6)
Very severe	0			1 (4,5)			0			1 (2,6)
Psychological scale		4,00	1,069		2,73	1,120		2,00	1,500	
Mild	0			3 (13,6)			5 (55,6)			8 (20,5)
Moderate	4 (50)			15 (68,2)			2 (22,2)			21 (53,8)
Severe	4 (50)			4 (18,2)			2 (22,2)			10 (25,6)
Very severe	0			0			0			0
Urogenital scale		3,50	1,309		2,36	1,787		1,56	1,424	
Mild	0			3 (13,6)			3 (33,3)			6 (15,4)
Moderate	1 (12,5)			4 (18,2)			1 (11,1)			6 (15,4)
Severe	3 (37,5)			10 (45,5)			4 (44,4)			17 (43,6)
Very severe	4 (50)			5 (22,7)			1 (11,1)			10 (25,6)
Total MRS		13,00	2,673		8,95	3,735		5,11	2,261	
Mild	0			2 (9,1)			6 (66,7)			8 (20,5)
Moderate	0			10 (45,5)			2 (22,2)			12 (30,8)
Severe	7 (87,5)			9 (40,9)			1 (11,1)			17 (43,6)
Very severe	1 (12,5)			1 (4,5)			0			2 (5,1)

Table 3 showed that 8 (20.5%) respondents suffered from 25(OH)D deficiency, 22 (56.4%) suffered from 25(OH)D insufficiency and only 9 (23.1%) had sufficient 25(OH)D. Based on the degree of menopausal symptoms, 8 (20.5%) respondents were categorized into mild, 12 (30.8%) were categorized into moderate, 17 (43.6%) respondents were categorized into severe, and

2 (5.1%) respondents were categorized into very severe. Based on the above mentioned 3 symptom scales, most somatic scale moderately experienced by 16 (41%) respondents, most psychological scale moderately experienced by 21(53.8%) respondents, and most urogenital scale severely experienced by 17(43.6%) respondents.

Table 3. The spearman correlational 25(OH)D with Menopausal symptoms (Base on MRS)

	Somatic symptoms	Psychological symptoms	Urogenital symptoms	Total MRS
25(OH)D r	-0.652**	-0.452**	-0.368*	-0.712**
p	0.000	0.004	0.021	0.000
n	39	39	39	39

Table 4 showed the result of bivariate analysis in which there was a non-linear significance and strong relationship between the variables of 25(OH) D and somatic symptoms with the spearman correlational value of 0.652 (p 0.000). There was also a non-linear significance and strong relationship between the variables of 25(OH) D and psychological symptoms with the spearman correlational value of 0.452 (p

0.004). There was non-linear and weak relationship between the variables of 25(OH) D and urogenital symptoms with the spearman correlational value of 0.368 (p 0.021). There was a non-linear significance and strong relationship between the variables of 25(OH) D and MRS total symptoms with the spearman correlational value of 0.712 (p 0.000).

DISCUSSION

Most post-menopausal women with the average of 66 years old averagely had the menopausal period of 16 years old. 37 (94.9%) respondents had the menopausal symptoms in the form of inconvenience joints and muscles. Another 37 (94.4%) respondents experienced physical and mental fatigue. 29 (74.4%) respondents had vaginal dryness symptoms while 28 (71.8%) respondents experienced sleeping disorder. The results of this research are similar with those obtained from the research conducted by Siregar M.F.G in 2014 and 2016 on menopausal symptoms explaining that 84% respondents experienced inconvenience joint and muscle, 68% respondents experienced depression and mood swing, another 68% respondents experienced physical and mental fatigue, 52% respondents had the vasomotoric symptoms. Zolekhah and Sholihah (2018) stated that most 24 (80%) menopausal women in Sleman, Yogyakarta had vaginal dryness symptoms.

The examination results on the level status of 25(OH)D after the spearman correlational analysis was conducted to the menopausal symptoms showed a significant (p 0.000), negative, and strong (r -0.712) relationship between 25(OH)D and menopausal symptoms based on the total MRS. The results of this research are in accordance with those of research conducted by Lerchbaum (2014) on 530 women aged 51-80 years old resulting in a significant relationship between 25(OH)D and the total menopausal symptoms, such as sleeping disorder, emotional welfare, and fatigue.

The analysis results showed that there was a significant (p 0.000), negative, and strong (r -0.652) relationship between 25(OH)D and somatic symptom

based on MRS in post-menopausal women, showing that vitamin D might decrease the somatic symptoms experienced by the post-menopausal women, including hot flushes, heart problems, sleeping disorder, as well as joint and muscle disturbance. As explained in the theory, vitamin D may reduce the hot flush symptoms by maintaining the serotonin level. Based on the research conducted on rats, vitamin D might prevent from the serotonin depletion. Thus, it was suggested to consume vitamin D to prevent from the decreasing serotonin during the menopausal period (Lerchbaum, 2014).

Vitamin D has multiple effects on the musculoskeletal system related to the bone mass/density/quality and muscle mass /strength/function. Besides, the status of vitamin D may reduce the risk of falling for elderly people, by increasing the neuromuscular function and body muscle strength (Lerchbaum, 2014).

This research proved that 25(OH)D had a significant (p 0.004) and moderately negative (r -0.451) influence on the psychological symptoms in post-menopausal women, including depression, easily offended, anxious, and fatigue that the increasing level of 25(OH)D might reduce the psychological symptoms in post-menopausal women since 25(OH)D might weaken the glucocorticoid effects, by inhibiting the glucocorticoid syntheses in the cellular differentiation. Glucocorticoid was then secreted by the adrenal gland in response to stress, while the continuously increasing level of glucocorticoid might induce the neural atrophy and eventually resulted in cell death (Harms *et al.*, 2011).

Vitamin D might influence mood swing, brain function, vitamin D deficiency related to the vascular neuropathology (Pludowski *et al.*, 2013). There was a positive effect of 25(OH)D level on memory, cognition, all dementia causes, and Parkinson disease risk. Vitamin D was also related to the depression and 25(OH)D deficiency as one prevalence factor to the arising affective disorders, such as depression (Eyles *et al.*, 2013). The observational research findings reported that the increasing depression risk was subject to the uneasily-interpreted 25(OH)D deficiency since proven that the subjects suffering from depression frequently had the life style in which their activities were mostly done outdoor and tended to result in vitamin D deficiency (inversed causality). A research conducted on vitamin D showed that there was a relationship between the insufficient level of vitamin D and the occurring depressions (Milaneschi *et al.*, 2010; Bertone-Johnson *et al.*, 2011). Thus, the 25(OH)D deficiency and the decreasing estrogen during the menopausal transition period were the conditions related to the increasing mood disorders, such as depression.

The results of correlational analysis between 25(OH)D and urogenital symptoms also showed that there was a significant (p 0.021), negative, and very weak (r -0.638) relationship. Those were probably due to the data collection which was only based on the questionnaire results that the subjects probably had their own alternative solutions in overcoming their urogenital symptoms, such as sweating and feeling painful when having the sexual intercourse. However, some respondents even had no desire to do sexual intercourses. Thus, some considered those as symptoms while some other did not. Meanwhile, the questionnaire results showed that the urogenital symptom scale score had mild or severe degree, yet indicated that there was a significant, non-linear, and weak relationship between 25(OH)D and urogenital symptoms based on MRS in post-menopausal women.

The vaginal dryness symptoms in post-menopausal women were mainly due to the decreasing estrogen hormone supported by the research results showing that the subjects experienced 25(OH) D deficiency and insufficiency. Thus, most subjects experienced vaginal dryness problems.

Lee *et al.* (2017) explained that vitamin D positively managed the cell-to-cell deviation by increasing the VDR/p-RhoA/p-Ezrin pathway. Vitamin D mediated the RhoA and Ezrin mediation through VDR. Vitamin D managed the cellular response through the RhoA kinase phosphorylation, cytoplasm membrane and protein, as well as VDR receptor. VDR-RhoA-Ezrin pathway mainly managed the proliferation, differentiation, and life sustainability of vaginal epithelium.

Thus, vitamin D is not only functioning as the keratinocyte differentiation promoter but also as the keratinocyte proliferation modulator. Vagina which is surrounded by the layered squamosal epithelium and vitamin D may improve the epithelium proliferation and differentiation (Palacios *et al.*, 2015).

CONCLUSION

From the analysis results, it is concluded that 25(OH)D may decrease the menopausal symptoms. Based on the spearman correlational analysis, there is a significant (p 0.004), non-linear, and strong (r -0.712) relationship between 25(OH)D and menopausal symptoms based on MRS in post-menopausal women.

The correlation between 25(OH)D and somatic scale symptoms has proven that there is a significant and non-linear (r -0.652; p 0.000) relationship with the psychological symptoms (r -0.451; p 0.004), and urogenital symptoms (r -0.638; p 0.021).

It is suggested for future research to conduct a research by adding the number of respondents with the control group classified based on the menopausal duration to avoid symptom biases.

REFERENCES

1. Askin, M., Koc, E. M., Soyoz, M., Aksun, S., Aydogmus, S., & Sozmen, K. (2019). Relationship between postmenopausal vitamin D level, menopausal symptoms and sexual functions. *J Coll Physicians Surg Pak*, 29(9), 823-827.
2. Aydogmus, H., & Demirdal, U. S. (2018). Vitamin D deficiency and lower urinary tract symptoms in women. *European Journal of Obstetrics & Gynecology and Reproductive Biology*, 228, 48-52.
3. Bertone-Johnson, E. R., Powers, S. I., Spangler, L., Brunner, R. L., Michael, Y. L., Larson, J. C., ... & Wassertheil-Smoller, S. (2011). Vitamin D intake from foods and supplements and depressive symptoms in a diverse population of older women. *The American journal of clinical nutrition*, 94(4), 1104-1112.
4. Blumenfeld, O., Williams, F. M., Valdes, A., Hart, D. J., Malkin, I., Spector, T. D., & Livshits, G. (2014). Association of interleukin-6 gene polymorphisms with hand osteoarthritis and hand osteoporosis. *Cytokine*, 69(1), 94-101.
5. Dwi Susanti, H., Chang, P. C., & Chung, M. H. (2019). Construct validity of the Menopause Rating Scale in Indonesia. *Climacteric*, 22(5), 454-459.
6. Eyles, D. W., Burne, T. H., & McGrath, J. J. (2013). Vitamin D, effects on brain development, adult brain function and the links between low levels of vitamin D and neuropsychiatric disease. *Frontiers in neuroendocrinology*, 34(1), 47-64.
7. Ghorbani, Z., Togha, M., Rafiee, P., Ahmadi, Z. S., Magham, R. R., Haghighi, S., ... & Mahmoudi, M.

- (2019). Vitamin D in migraine headache: a comprehensive review on literature. *Neurological Sciences*, 40(12), pp.2459–2477.
8. Grady, D., & Connor, E.B. (2017). MENOPAUSE. In: Goldman's Cecil Medicine. Elsevier, pp. 1623–1629.
 9. Harms, L. R., Burne, T. H., Eyles, D. W., & McGrath, J. J. (2011). Vitamin D and the brain. *Best practice & research Clinical endocrinology & metabolism*, 25(4), 657-669.
 10. Heinemann, L.A.J. (2019). MRS -The Menopause Rating Scale [Online]. Available at: <http://www.menopause-rating-scale.info/>.
 11. Holick, M.F. (2016). Vitamin D: A D-lightful solution for health. *Journal of Investigative Medicine*, 59(6), pp.872–880.
 12. LeBlanc, E. S., Desai, M., Perrin, N., Wactawski-Wende, J., Manson, J. E., Cauley, J. A., ... & Johnson, K. C. (2014). Vitamin D levels and menopause-related symptoms. *Menopause (New York, NY)*, 21(11), 1197–1203.
 13. Lerchbaum, E. (2014). Vitamin D and menopause - A narrative review. *Maturitas*, 79(1), pp.3–7. Available at: <http://dx.doi.org/10.1016/j.maturitas.2014.06.003>.
 14. Mann, M.C., Hollenberg, M.D., Hanley, D.A. and Ahmed, S.B., 2015. Vitamin D, the autonomic nervous system, and cardiovascular risk. *Physiological Reports*, 3(4), pp.1–6.
 15. Milaneschi, Y., Shardell, M., Corsi, A. M., Vazzana, R., Bandinelli, S., Guralnik, J. M., & Ferrucci, L. (2010). Serum 25-hydroxyvitamin D and depressive symptoms in older women and men. *The Journal of Clinical Endocrinology & Metabolism*, 95(7), 3225-3233.
 16. Monteleone, P., Mascagni, G., Giannini, A., Genazzani, A. R., & Simoncini, T. (2018). Symptoms of menopause—global prevalence, physiology and implications. *Nature Reviews Endocrinology*, 14(4), 199–215. Available at: <http://dx.doi.org/10.1038/nrendo.2017.180>.
 17. Pludowski, P., Holick, M. F., Pilz, S., Wagner, C. L., Hollis, B. W., Grant, W. B., ... & Soni, M. (2013). Vitamin D effects on musculoskeletal health, immunity, autoimmunity, cardiovascular disease, cancer, fertility, pregnancy, dementia and mortality—a review of recent evidence. *Autoimmunity reviews*, 12(10), 976-989.
 18. Schuster, I. (2011). Cytochromes P450 are essential players in the vitamin D signaling system. *Biochimica et Biophysica Acta - Proteins and Proteomics*, 1814(1), pp.186–199. Available at: <http://dx.doi.org/10.1016/j.bbapap.2010.06.022>.
 19. Skaznik-Wikiel, M.E., Traub, M.L., & Santoro, N. (2015). *Menopause Seventh Ed.*, Elsevier.
 20. Wrzosek, M., Łukaszewicz, J., Wrzosek, M., Jakubczyk, A., Matsumoto, H., Piątkiewicz, P., ... & Nowicka, G. (2013). Vitamin D and the central nervous system. *Pharmacological reports*, 65(2), 271-278.