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The role of vitamin d deficiency towards cognitive deficit of schizophrenia

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Abstract

Background: Vitamin D receptor (VDR) discovery in the brain tissue demonstrates clearly that vitamin D has a significant role in the development of the brain. This study aimed to analyze the correlation between serum vitamin D levels and cognitive deficits in schizophrenic patients.

Methods: This was an observational analytic study with cross-sectional design. Serum vitamin D levels were measured using VIDAS® 25 OH Vitamin D Total (VITD). Cognitive deficits were measured using Indonesian version of the Schizophrenia Cognition Rating Scale (ScoRSvl).

Results: This study recruited 54 patients from outpatient and inpatient unit of psychiatric. Most of subjects were male as many as 25 (65.8%). Mean age of subjects was 34.84 years. Mean duration of illness was 10.58±7.4 years. There were 17 (45%) subjects experienced serum vitamin D deficiency, and 22 (58%) study subjects had cognitive deficits on the global impression of ScoRSvl assessment by rater. There was a significant negative correlation ($p < 0.001$) between serum vitamin D levels and SCoRSvl values from the impression of global observations, ScoRSvl patients, and ScoRSvl informants.

Conclusion: The lower serum vitamin D levels, the higher score of cognitive deficits from SCoRSvl. The higher SCoRSvl score shows the more severe cognitive deficit for patients with schizophrenia.

Keywords: schizophrenia, serum vitamin D levels, cognitive deficits

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INTRODUCTION

The most prevalent disorder in a group of psychotic disorders is schizophrenia (Catherine et al. 2018). Schizophrenia is a heterogeneous condition between the genetic and environmental factors that combines and leads to the severity of the disease (Hidayati et al. 2014, Samoos et al. 2017). Since it has been discovered, microorganisms like *Helicobacter pylori* have been involved in a variety of extra-digestive diseases that may have a potential role in psychiatric disorder pathogenesis which triggers dopaminergic dysfunction (Miftahussurur et al. 2017). In addition, Indonesian people have brown skin. Indonesia, geographically located at the line 06°08' north latitude - 11° 5' south latitude with a tropical climate allows sunlight to be radiated intensively throughout the territory of Indonesia (Ministry of Environment of the Republic of Indonesia 2011). Vitamin D deficiency risk factors are dark skin color and insufficient exposure to the sun (McGrath et al. 2010, Mutsatsa et al. 2013). Vitamin D is analyzed through 25-OH levels of vitamin D

(calcidiol), a form that circulates in the circulation making it possible to do assessments of Vitamin D levels in the body (Amaral et al. 2014).

Schizophrenia can be treated by minocycline which may be a potential therapeutic drug for to improve recognition memory (Liary et al. 2014). Whereas, another report revealed that occupational therapy was effective when combined with antipsychotic therapy and the group psychotherapy to improve cognitive function and the quality of life of the schizophrenia patients, especially in long term therapy (Coymak, 2019, Idrus et al. 2019). Cognitive deficits are a major source of functional and social disorder in schizophrenia and have a more positive and negative effect on everyday life (Homayoun et al. 2011), which appears to be a problem in daily activities and is related to internal goals and motivation (Falkenberg et al. 2014). Considering various

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Table 1. Characteristics of subjects

Characteristics	Results
Sex	
Male	25 (65.8 %)
Female	13 (34.2 %)
Education	
Elementary school	1 (2.6%)
Junior high school	6 (15.8%)
Senior high school	26 (68.4%)
Bachelor	2 (5.3%)
Category of schizophrenia	
Paranoid	24 (63.2 %)
Hebephrenic	7 (18.4 %)
Catatonic	1 (2.6 %)
Undifferentiated	5 (13.6 %)
Residual	1 (2.6 %)
Age of symptom onset	
≤ 18 years	11 (28.9 %)
> 18 years	27 (71.1 %)
Duration of illness	10.58±7.431

previous studies show the controversy of the relationship of vitamin D deficiency (VDD) with cognitive deficits, as well as considering the importance of vitamin D for mental health (Sotodeh-Asl et al. 2014), we hypothesized that serum VDD influence cognitive deficits on schizophrenic patients undergoing treatment at Dr. Soetomo General Academic Hospital, Surabaya. This study aimed to analyze the correlation between serum vitamin D levels and cognitive deficits in schizophrenic patients (Rajuddin Rajuddin*, Rudy Harahap 2019).

METHODS

This was an observational analytic study of schizophrenia patients who received treatment at Dr. Soetomo General Academic Hospital Surabaya, Indonesia, with cross sectional design. The inclusion criteria of the study were: a) patient who received diagnosis schizophrenia according to ICD X criteria, b) aged 18-45 years, c) patients did not consume medication which affecting to serum vitamin D level (e.g bronchodilators, hormonal drugs, anti-hypertension, antibiotics, antiepileptics, antineoplastic, anti-inflammatory, antiretroviral, endocrine drugs, theophylline, isoniazid, rifampizin, cimetidine, cholestramin) in the last 7 days, d) both patients and caregivers gave consent to participate in this study, and e) speaking Indonesian fluently. We excluded patients who had mental retardation (screened by clinical psychologist), known having physical comorbidity affecting serum vitamin D level (screened using liver function and renal function test). Serum vitamin D levels were measured using VIDAS® 25 OH Vitamin D Total (VITD). Cognitive deficits were measured using Indonesian version of the Schizophrenia Cognition Rating Scale (SCoRSvl). Statistic was analyzed by SPSS using the Spearman correlation test.

Table 2. Serum Vitamin D levels and SCoRSvl of subjects

Variables	Results
Serum Vitamin D levels (ng/ml)	23.15±8.197
Deficiency (<20 ng/ml)	17 (45%)
Insufficiency (20-29 ng/ml)	12 (31%)
Sufficient (30-100 ng/ml)	9 (24%)
SCoRSvl interviewer	2.32±1.454
Cognitive deficit	22 (52%)
No cognitive deficit	16 (48%)
SCoRSvl patients	24.16±5.607
SCoRSvl informants	24.21±5.7

Table 3. Correlation between Serum Vitamin D levels and SCoRSvl

Variables	r	p value
Serum Vitamin D levels with SCoRSvl interviewer	-0.736	<0.001
Serum Vitamin D levels with SCoRSvl patients	-0.719	<0.001
Serum Vitamin D levels with SCoRSvl informants	-0.696	<0.001

RESULTS

This study involved 38 subjects, most of them were 25 males, with a mean age of 34.84 years old, had symptom onset when they were over 18 years old, with the lowest age range of 13 years old and the highest age of 36 years old. In this study, mean of duration of illness was 10.58±7.4 years, with a range of duration of illness between 1-28 years (**Table 1**). The results of the analysis in this study are shown in **Table 2**. The mean of serum vitamin D levels was 23.15±8.197 ng/mL, with range of 8.1-37.6 ng/mL. The serum vitamin D level in 17 (45%) subjects was deficiency (<20 ng/mL), 12 (31%) were insufficiency (20-29 ng/mL), and 9 (24%) were sufficient (30-100 ng/mL). There was a mean SCoRSvl score of global observational impressions from the interviewer ratings of 2.32±1.454, with the lowest score range of 1 and the highest score of 6. There was a cognitive deficit of 22 (52%) global observational impressions.

Table 3 presents correlation results. There was significant negative correlation between serum vitamin D levels and SCoRSvl interviewer of global observations impression ($p < 0.001$, $r = -0.736$), SCoRSvl patients ($p < 0.001$, $r = -0.719$) and SCoRSvl informants ($p < 0.001$, $r = -0.696$). The lower of serum vitamin D levels, the higher score of cognitive deficits obtained in SCoRSvl (**Fig. 1**). There was significant difference on SCoRSvl score of subjects who had more outdoor activities compare to more indoor activities, for patient rating ($p = 0.027$, $r = 0.028$) and informant rating ($p = 0.044$, $r = 0.45$). Subjects with a duration of sun exposure ≤ 60 minutes had a score of SCoRSvl higher than the subjects with a duration of sun exposure > 60 minutes. We found significant differences of SCoRSvl score between subjects who had less and more sun exposure rated by interviewer ($p = 0.011$, $r = 0.016$), from patient rating ($p = 0.003$, $r = 0.003$), and from informant rating ($p = 0.005$, $r = 0.004$). Significantly, subjects with less sun exposure (≤ 60 minutes/day) gained higher SCoRSvl score compared to subjects with more sun

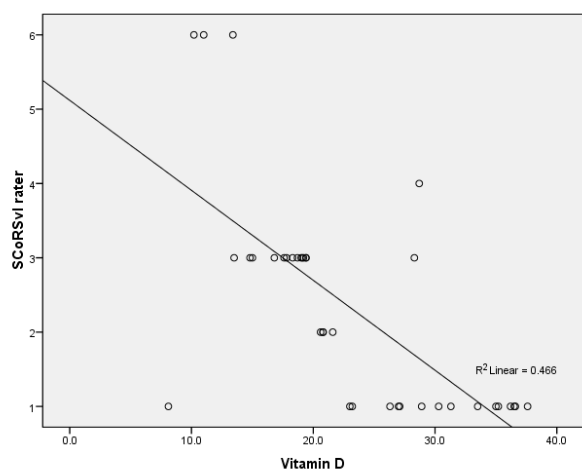


Fig. 1. Plot chart shows the correlation between serum vitamin D levels and SCoRSvl rater

exposure (> 60 minutes/day). It means that with more sun exposure, subjects had less cognitive deficit. The majority of subjects were exposed to the duration of sunlight before 12.00 a.m. ≤ 60 minutes. The majority had the type of activity indoors and obtained serum vitamin D deficiency. Researchers suspected that the research subjects were exposed to less sunlight.

DISCUSSION

Our analysis has demonstrated serum vitamin D levels in schizophrenic patients correlated with cognitive deficits. Vitamin D enhances tyrosine hydroxylase expression in the adrenal medullary cells, implying that vitamin D can modulate the dopaminergic procedure (Eserian 2013). The dopamine theory suggests that dopamine dysfunction is central to the pathogenesis of schizophrenia (Kesby et al. 2013). In Schizophrenia patients, the attention, concentration, verbal and visual memory tests and output tests show substantially cognitive shortfalls, and nearly all test results are worse as compared to normal controls (Krishnadas et al. 2007). The extent of this disorder, schizophrenia is concluded as a complex neurodevelopmental disorder with a global profile of cognitive impairment as a major part (Bowie et al. 2006, Utami et al. 2018). Some cognitive approaches in combination with other therapeutic methods could improve the physical function of chronic pain patients, such as schizophrenia (Afrina et al. 2019).

The geographical position of a Vitamin D deficiency in schizophrenia also affects the sun exposure of people who live in the region (Akbar et al. 2018). This study was conducted in Surabaya, Indonesia which is located in the Indonesian territory with the location of low latitude and intensive sun exposure in all regions of Indonesia. VD, which is also called sunshine vitamin, requires exposure time every day 1-2 hours to maintain serum vitamin D levels, which are carried out in urban Indian

men aged 40-60 years. Excessive exposure to sunlight >2 hours every day cannot linearly increase serum vitamin D levels (Patwardhan et al. 2018). Conversely, another study found that UVB reception from sun exposure for 25 minutes, 3 times a week, for 6 weeks can increase serum vitamin D levels, in elderly women ≥60 years old in Jakarta and Bekasi. The optimal time for sun exposure is 1 hour before and after noon, but the heat of the sun when midday, 11.00 - 13.00, causes discomfort and avoidance of sun exposure, thus the recommended time for sun exposure is 9 am (Setiati et al. 2007).

Vitamin D has several roles in the brain. In dopamine transmission, low levels of vitamin D cause Catechol-O-methyl-transferase (COMT) to down-regulation in the forebrain, which causes a decrease in HVA concentration, which is a marker of dopamine activity. Reduction in homovallinic acid (HVA) levels in prefrontal cortex (PFC) is associated with poor working memory in schizophrenia (Amaral et al. 2014). Vitamin D is a strong inducer of the glial cell line-derived neurotrophic factor (GDNF), capable of enhancing the survival of dopaminergic neurons. GDNF participates in the development of dopaminergic pathways and immediately regulates dopaminergic cell apoptosis in substantia nigra after birth. Vitamin D affects the dopamine pathways in the brain neuroprotectively, that is when 6-hydroxydopamine (6-OHDA) which is a dopaminergic selective poison is administered to animals pre-treated with 1,25-(OH)2D3 for 1 week, getting dopaminergic function is maintained. Evidence is obtained that DVD deficiency in neonatal rats has reduced GDNF expression in the brain (Eserian 2013).

Mesocortical dopamine pathway is the pathway from the cell body in the area of the ventral tegmentum to the prefrontal cortical area. Branches from this pathway to the dorsolateral prefrontal cortex (DLPFC) regulate cognitive and executive functions. Deficit dopamine activity starting from mesocortex to DLPFC causes cognitive symptoms in schizophrenia (Stahl et al. 2013). Interaction of vitamin D with calcium channels on the development of schizophrenia is related to parvalbumin calcium-binding proteins (CBP) expression. The low prenatal vitamin D supply significantly changes CBP expression. The decrease in parvalbumin-positive neurons has increased the incidence of schizophrenia, through down regulation of Lhx6 which is an essential transcription factor for migration and maturation of parvalbumin-positive neurons. Decreased GABAergic neurotransmitters between parvalbumin-positive interneurons and pyramid cells are believed to support impaired working memory in schizophrenia (Amaral et al. 2014).

In previous research, lower serum vitamin D levels were related to serious cognitive deficits in young adult patients, assessed using the summary cognition value and lower verbal fluency scores. This can be caused by

schizophrenia patients suffering from negative symptoms and/or extreme cognitive deficits leading to lower serum vitamin D levels. Symptoms that appear include: social isolation, no motivation, which is related to the overall lower level of function which has the potential to cause poorer nutrition which causes less time spent outdoors which ultimately contributes to lower serum vitamin D levels (Graham et al. 2015).

Limitations of this study include only analyzing serum vitamin D levels and SCoRSvl scores in schizophrenic patients without taking into account other therapies given during treatment. This raises the possibility of different treatments for each research subject to the different psychopharmaceuticals given, so that further research is needed with a larger population with longer observations than this study to compare the relationship between serum vitamin D levels and cognitive deficits in schizophrenic patients by controlling other confounding factors, such as controlling therapy. In this study, the measurement of serum vitamin D levels was carried out with a tool that measured serum total vitamin D (vitamin D2 and D3) levels, so it was necessary to research with serum vitamin D levels that were more specific to differentiate vitamin D2 and D3 levels. SCoRSvl cognitive measurement instrument evaluates attention,

memory, reasoning and problem solving, working memory, language production and motor skills, without grouping each question into these cognitive domains. Thus, other cognitive measurement instruments are needed to be able to evaluate more specifically of what aspects of the cognitive domain are disturbed.

CONCLUSION

There is evidence of a correlation that the lower serum vitamin D levels the more severe the cognitive deficits of schizophrenic patients, so if possible, schizophrenic patients need to be exposed to sunlight routinely, and of course still given antipsychotics as the main therapy. Thus, improvement in cognitive symptoms is obtained and patients get more treatment well.

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REFERENCES

- Afrina R, Karimah A, (2019) Cognitive Behavioral Therapy for Chronic Pain. *Biomolecular and Health Science Journal* 2(2): 129-134.
- Akbar NL, Effendy E, Amin MM, (2018) Vitamin D and plain type: A study of male patients with schizophrenia. In: *IOP Conference Series Earth and Environmental Science* Vol. 125. Institute of Physics Publishing <https://doi.org/10.1088/1755-1315/125/1/012180>
- Amaral AD, Calhau C, Coelho R, (2014) Schizophrenia: implications of vitamin D deficit on brain development. *IJCNMH* 1(16): 1-14.
- Bowie CR, Harvey PD, (2006) Cognitive deficits and functional outcome in schizophrenia. *Neuropsychiatric disease and treatment* 2(4): 531.
- Catherine, Amin MM, Effendy E, (2018) The relationship between intelligence and cognitive function in schizophrenic. In: *IOP Conference Series Earth and Environmental Science* Vol. 125. Institute of Physics Publishing <https://doi.org/10.1088/1755-1315/125/1/012184>
- Coymak A (2019) An Experimental Study of the Effect of Computer Assisted Learning on Metacognitive Performance Development in Psychology Teaching. *Contemporary Educational Technology*, 10(1): 94-105. <https://doi.org/10.30935/cet.512539>
- Eserian JK, (2013) Vitamin D as an effective treatment approach for drug abuse and addiction. *Journal of Medical Hypotheses and Ideas* 7(2): 35-39.
- Falkenberg LE, Westerhausen R, Craven AR, Johnsen E, Kroken RA, Specht K, Hugdahl K, (2014) Impact of glutamate levels on neuronal response and cognitive abilities in schizophrenia. *NeuroImage: Clinical* 4: 576-584.
- Graham KA, Keefe RS, Lieberman JA, Calikoglu AS, Lansing KM, Perkins DO, (2015) Relationship of low vitamin D status with positive, negative and cognitive symptom domains in people with first-episode schizophrenia. *Early intervention in psychiatry* 9(5): 397-405.
- Hidayati AN, Febriyana N, (2014) Prenatal factors on schizophrenia. *Jurnal Psikiatri Surabaya* 3(1): 1-10.
- Homayoun S, Stip E, Luck D, Nadeau-Marcott F, (2011) Subjective and objective cognitive dysfunction in schizophrenia-is there a link? *Frontiers in psychology* 2: 148.
- Idrus F, Limoa E, Honest I, Ganda IJ, Tammasse J, Syamsuddin S, Lisal ST, (2019) The effectiveness of the combination therapy of risperidone, group psychotherapy and occupational therapy on cognitive functions and

- the quality of life of schizophrenia patients. *Indian Journal of Public Health Research and Development* 10(10): 649-654. <https://doi.org/10.5958/0976-5506.2019.02887.0>
- Kesby JP, Cui X, Burne THJ, Eyles DW, (2013) Altered dopamine ontogeny in the developmentally vitamin D deficient rat and its relevance to schizophrenia. *Frontiers in cellular neuroscience* 7: 111.
- Krishnadas R, Moore BP, Nayak A, Patel RR, (2007) Relationship of cognitive function in patients with schizophrenia in remission to disability: a cross-sectional study in an Indian sample. *Annals of general psychiatry* 6(1): 19.
- Liaury K, Miyaoka T, Tsumori T, Furuya M, Hashioka S, Wake R, Tsuchie K, Fukushima M, Limoa E, Tanra AJ, Horiguchi J, (2014) Minocycline improves recognition memory and attenuates microglial activation in Gunn rat: A possible hyperbilirubinemia-induced animal model of schizophrenia. *Progress in Neuro-Psychopharmacology and Biological Psychiatry* 50: 184-190. <https://doi.org/10.1016/j.pnpbp.2013.12.017>
- McGrath JJ, Burne TH, Féron F, Mackay-Sim A, Eyles DW, (2010) Developmental vitamin D deficiency and risk of schizophrenia: a 10-year update. *Schizophrenia bulletin* 36(6): 1073-1078.
- Miftahussurur M, Nusi IA, Graham DY, Yamaoka Y, (2017) Helicobacter, hygiene, atopy, and asthma. *Frontiers in microbiology* 8: 1034.
- Ministry of Environment of the Republic of Indonesia, (2011) Status Lingkungan Hidup Indonesia 2010. Jakarta: Ministry of Environment of the Republic of Indonesia
- Mutsatsa S, Mushore M, Ncube K, Currid T, (2013) Vitamin D: the role of the sunshine vitamin. *British Journal of Mental Health Nursing* 2(4): 182-187.
- Patwardhan VG, Mughal ZM, Chiplonkar SA, Webb AR, Kift R, Khadilkar V V, Padidela R, Khadilkar A V, (2018) Duration of casual sunlight exposure necessary for adequate Vitamin D status in Indian Men. *Indian journal of endocrinology and metabolism* 22(2): 249.
- Samoës B, Silveira C, (2017) The role of vitamin D in the pathophysiology of schizophrenia. *Neuropsychiatry* 7(4): 362-369.
- Setiati S, Oemardi M, Sutrisna B, (2007) The role of ultraviolet-B from sun exposure on vitamin D3 and parathyroid hormone level in elderly women in Indonesia. *Asian J Gerontol Geriatr* 2: 126-132.
- Sotodeh-Asl N, Tamadon M-R, Malek F, Zahmatkesh M, (2014) Vitamin D deficiency and psychological disorders. *J Parathyroid Dis* 2(1): 21-25.
- Stahl SM, Stahl SM, (2013) Stahl's essential psychopharmacology: neuroscientific basis and practical applications. Cambridge university press
- Utami N, Effendy E, Amin MM, (2018) BDNF (brain-derived neurotrophic factor) serum levels in schizophrenic patients with cognitive deficits. In: IOP Conference Series Earth and Environmental Science Vol. 125. Institute of Physics Publishing <https://doi.org/10.1088/1755-1315/125/1/012181>