PJN
ISSN 1680-5194
ansinet.com/pjn

PAKISTAN JOURNAL OF NUTRITION

Science Alert
scialert.net

ANSInet
an open access publisher
http://ansinet.com

OPEN ACCESS Pakistan Journal of Nutrition

ISSN 1680-5194
DOI: 10.3923/pjn.2020.44.50

Research Article
The Effectiveness of Cholecalciferol Addition at Improving Psychosis Symptoms in Amphetamine-Type Stimulant (ATS) Users

[1]Adhayani Lubis, [2]Aznan Lelo, [3]Dina Keumala Sari and [4]Diah S. Utami

[1]Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia
[2]Department of Pharmacology, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia
[3]Department of Nutrition, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia
[4]Indonesia National Narcotics Board, Republic of Indonesia

Abstract

Background and Objectives: Cholecalciferol plays an important role in the development of brain function and neuropsychiatric disorders, especially psychological disorders. The objective of this study was to observe the differencesin25(OH)D serum levels and Brief Psychiatric Rating Scale (BPRS) scores in individuals who use amphetamine-type stimulants (ATSs) after receiving supplementation with cholecalciferol 1000 IU per day. **Materials and Methods:** This study had a pre and post-test design with consecutive sampling. Cholecalciferol 1000 IU per day was given to 25 ATS users (intervention/I group), while the other 25 individuals, who composed the control group (C group), did not receive any cholecalciferol supplementation for 42 days. On laboratory tests, the serum level of 25(OH)D is categorized as normal if it is within 54-90 ng mL^{-1}. Psychosis was evaluated with the BPRS questionnaire. **Results:** There was a significant difference in the serum level of 25(OH)D after the intervention between the groups (I group: 23.37±4.20; C group: 20.33±4.04; p = 0.012) and the increase in the serum level of 25(OH)D was greater in the I group than that of the C group. The result also showed a significant difference in BPRS score after the intervention between the groups [I group: 25(24-27); C group: 27(26-29); p<0.001]. The decrease in the BPRS score in the I group was larger than that in the C group. **Conclusion:** The administration of cholecalciferol 1000 IU per day increased the 25(OH)D serum level and cholecalciferol supplementation in subjects using ATSs led to a significant reduction in the BPRS score.

Key words: Addict, anxiety, cognitive function, drugs, vitamin D deficiency

Received: October 03, 2019 Accepted: December 17, 2019 Published: January 15, 2020

Citation: Adhayani Lubis, Aznan Lelo, Dina Keumala Sari and Diah S. Utami, 2020. The effectiveness of cholecalciferol addition at improving psychosis symptoms in amphetamine-type stimulant (ATS) users. Pak. J. Nutr., 19: 44-50.

Corresponding Author: Dina Keumala Sari, Department of Nutrition, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia

Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Amphetamines have become the second most misused type of narcotics in East and Southeast Asia as well as Oceania[1,2]. The worldwide ATS circulation doubled, increasing from 93 tons in 2010 to 191 tons in 2015[2]. A number of studies showed a prevalence of psychosis ranging from 10-60% among those who misuse amphetamines. Ten percent of individuals in psychiatry wards who use amphetamines have diagnoses related to that use. A study conducted in Australia showed that 51 (18%) out of 277 amphetamine users suffered from symptoms of psychosis. A study in the US showed that among 43 amphetamine users, at least 60% had symptoms of psychosis[3]. In Indonesia, it was predicted that there were 1.2 million narcotics users, of whom 90% used ATS[4].

Amphetamines are able to increase the release of dopamine, serotonin and noradrenaline, which produce short moments of euphoria and alertness and a sense of energy[1,5]. The inhibition of the dopamine transporter by methamphetamine increases the amount of dopamine in thesynaptic cleft, which may induce psychosis[6].

The use of amphetamines results in an excessive amount of dopamine in the striatum, which leads to the release of excess glutamate into the cortex. Over time, the excess glutamate in the cortex damages the cortical inter neurons and disturb signaling in the thalamocortical system, resulting in symptoms of psychosis, as observed in patients with schizophrenia. Therefore, amphetamines are able to increase glutamatergic signaling in the cortex from the nigrostriatal and mesolimbic reward circuits and to increase the dopaminergic signals from the mesocortical pathways. Excessive amounts of glutamate and dopamine in the cortex lead to the dysfunction ofgabaergic interneurons. As a result, signal regulation becomes damaged, which isthen related to the psychotic symptoms that can occur during amphetamine intoxication in some people and previous research has shown that this processcould be related to vitamin D deficiency[3].

Vitamin D deficiency occurs worldwide, including in tropical countries. Not only bone diseases but also metabolic diseases are caused by vitamin D deficiency. A lack of exposure to sunlight, a low level of physical activity and polymorphism of the vitamin D receptor gene are a few causes of vitamin D deficiency[7-9].

One of the main physiological functions of vitamin D or vitamin D3 (cholecalciferol) is to maintain healthy serum levels ofcalcium and phosphorus, supporting bone metabolic function and the regulation of transcription. On average, the human body needs 3000-5000 IU of cholecalciferol per day. According to Koutkia *et al.*[10], without exposure to sunlight, the level of cholecalciferol in the body is maintained at 1000 IU and the level of 25(OH)D is maintained at 30 ng mL^{-1}.

A number of studies have shown that cholecalciferol is involved in various processes in the brain, including the regulation of neurotropic factors, neuroprotection, neuroplasticity and brain development. It also plays an important role in the treatment of psychological disorders[11-13]. Based on the studies conducted in the last 10 years, there is evidence that cholecalciferol plays an important role in the development of brain function and neuropsychiatry disorders[14].

Cholecalciferol is expected to be an effective treatment for drug abuse and addiction because cholecalciferol provides protection from the effects of methamphetamine usage on the dopaminergic system[15]. The most active form of cholecalciferol playroles in the metabolism of the neurotransmitters dopamine, noradrenaline and acetylcholine, which are pathogenic substances in psychiatric illness[16].

Based on observations and studiesperformed in the field, people who are institutionalizeddue to ATS usage are not given therapy, including those with signs ofpsychiatric disorders such as delusions, hallucinations and agitation. Rehabilitations programmes are limited by the highly addictive nature of amphetamines and there is a wide range of side effects associated with the use of narcotics. In addition, mental disorders may be a factor contributing to the transmission of HIV/AIDS, hepatitis, tuberculosis and other conditions[17].

Based on previous research, the aim of this study wasto observe the impact of supplementation with cholecalciferol 1000 IU per day for 42 days on 25(OH)D serum level and the BPRS score in ATS users. This result is expected to provide new informationthat can be used in the treatment of drug abuse and addiction, includingthe misuse of amphetamine, which may lead to mental disorders.

MATERIALS AND METHODS

This study was a randomized controlled trial with a pre- and post-test design that was conductedto observe the differencesinthe serum levels of 25(OH)D and BPRS scores before and after intervention. This research received approval from the Research Ethics Committee, Faculty of Medicine, Universitas Sumatera Utara, No. 43/TGL/KEPK FK USU-RSUP HAM/2019.

Sample: Samples were taken from 50 consecutive ATS users with mental disordersdiagnosed based on the guidelines in the International Statistical Classification of Disease 10th

Revision (ICD-10). There were two groups formed in this study: the intervention (I) group was composed subjects who used ATS and received daily supplementation with cholecalciferol 1000 IU and the control (C group was composed of subjects who used ATS who did not receive supplementation with cholecalciferol for 42 days. This study was conducted in the Rehabilitation Centre of the National Narcotic Agency (Badan Narkotika Nasional/BNN), North Sumatera Province, Indonesia, from February to June 2019.

Research subjects who met the inclusion criteria were given information sheets and received explanations of the procedures and the objectives of the study. This study used sealed envelopes to assign subjects to the I or C group based on a randomized table. The data were collected in the morning between approximately 10.00 AM-12.00 PM, 2 h after breakfast and before lunch. The inclusion criteria in this research were male sex, the use of ATS, age between 18 and 45 years, with no history of antipsychotic medicine consumption, comprehension of 'Bahasa' (Indonesian language) and willingness to be interviewed and 25(OH)D insufficiency or deficiency, defined as a serum level of 25(OH)D <32 ng mL^{-1} before the intervention. The exclusion criteria in this study were comorbidities such as hepatitis, chronic kidney disease, diabetes mellitus and other diseases and psychiatric disorders.

Laboratory test: Urine tests were performed to determine the history of ATS usage in the subjects. The researcher also tested the serum levels of 25(OH)D before and after the administration of cholecalciferol 1000 IU. The Liaison 25(OH) total assay (Diasorin) was used to determine the serum level of 25(OH)D. Cholecalciferol in the body was determined based on the level of25(OH)D in the body; the normal level ranges from 54-90 ng mL^{-1}. This analysis was performed in a privately owned laboratory.

Assessment: This study used the BPRS questionnaire, which is composed of 18 items that are scored on a 7-point Likert scale (organized scale) (none, very minor, minor, moderate, moderately severe, severe and very severe). The total score ranges from 18-126. The questionnaire was used to assess psychosis. BPRS is not a diagnostic scale but it is a scale used to assess the actual clinical picture (the severity of the psychopathology) during treatment, indicating when medication is required or can best opped. As the assessment involves observing and reporting patients' symptoms, the BPRS can be used to assess patients with severe behavioural impairments. Although, the BPRS includes depressive symptoms (items 1, 2, 5, 6, 9 and 13), this scale is generally used to evaluate psychosis. Therefore, all 12 items were considered[18].

RESULTS

In terms of the demographic characteristics (Table 1), the subjects participating in the study provided their age, occupation, marital status and education status. There were no significant differences among the characteristics in the two groups ($p>0.05$).

Table 2 shows the data for the 25(OH)D serum levels in the intervention group and the normality of the distribution was determined with the Shapiro-Wilk test. The data had a normal distribution ($p>0.05$). An independent t-test showed a significant difference ($p<0.001$) in 25(OH)D serum levels before and after treatment in the intervention group. There was an increase in the average 25(OH)D serum level from18.42±4.09 before treatment to 23.37±4.20 after treatment, with a variance of 4.95. Meanwhile, the data in the control group also had a normal distribution ($p>0.05$). An independent t-test showed a significant difference ($p<0.001$)

Table 1: Demographic characteristics of research subjects

	Cholecalciferol intervention (+)		Cholecalciferol control (-)		Total		
Characteristics	No.	Percentage	No.	Percentage	No.	Percentage	p-value
Age (mean±SD), years	28.04±4.99		26.44±3.49				0.195**
Occupation							
Unemployed	17	53.1	15	46.9	32	100.0	0.384
Employed	8	44.4	10	55.6	18	100.0	
Marital status							
Unmarried	15	57.7	11	42.3	26	100.0	0.198
Married	10	41.7	14	58.3	24	100.0	
Education							
Primary school	8	61.5	5	38.5	13	100.0	0.419
Secondary school	6	37.5	10	62.5	16	100.0	
High school	11	52.4	10	47.6	21	100.0	

*Chi-square test, **Independent t-test, $p<0.05$

Table 2: The difference in 25(OH)D serum content between the two groups

	Cholecalciferol intervention group (+)		Cholecalciferol control group (-)		
Cholecalciferol	Mean	SD	Mean	SD	p-value
Before	18.42	4.09	19.73	4.13	0.264
After	23.37	4.20	20.33	4.04	0.012*

*Independent t-test, p<0.05

Table 3: The difference in BPRS scores between the two groups

	Cholecalciferol intervention group (+)			Cholecalciferol control group (-)			
BPRS	Median	Minimum	Maximum	Median	Minimum	Maximum	p-value
Before	49	45	54	48	45	54	0.969
After	25	24	27	27	26	29	<0.001

*Mann-Whitney U test, p<0.05

Table 4: Variance (Δ BPRS score compared between the two groups)

	Cholecalciferol intervention group (+)			Cholecalciferol control group (-)			
Parameters	Median	Minimum	Maximum	Median	Minimum	Maximum	p-value
BPRS	23.00	19.00	29.00	21.00	17.00	27.00	0.01*

*Mann-Whitney U test, p<0.05

in the serum level of 25(OH)D after 42 days in the control group. The average serum level of 25(OH)D increased from 19.73±4.13 to 20.33±4.04, with a variance of 0.60.

Table 3 shows that the BPRS scores are not distributed normally before or after the intervention (p<0.05). To determine the differences in BPRS scores between the two groups, a Mann-Whitney U test was performed. There was no difference in the BPRS scores between the two groups before the intervention (p = 0.969); however, there was a difference in the scores after the intervention (p<0.001). The BPRS scores in the intervention group were lower than those in the control group after the intervention.

Supplementation with cholecalciferol increased the serum level of 25(OH)D and increased the effectiveness of therapy in ATS users, which was indicated by the reduction in the BPRS scores in the intervention group, as shown in Table 4. After the intervention, the serum level of 25(OH)D was higher in the intervention group than that of the control group: (intervention: 23.37±4.20 vs. control: 20.33±4.04; p = 0.012).There was also a significant difference in BPRS scores after the intervention between the two groups [intervention: 25.00(24.00-27.00); control: 27.00(26.00-29.00); p<0.001].

The BPRS scores were not normally distributed (p<0.05). To determine the difference in BPRS scores between the two groups, a Mann-Whitney U test was performed. There was a difference in BPRS scores between the two groups (p = 0.01), with a lower BPRS score in the intervention group than that of the control group after the intervention.

DISCUSSIONS

This study was a randomized controlled trial with a pre- and post-test design that was performed to determine the differences in serum vitamin D levels and BPRS scores before and after intervention with supplemental cholecalciferol 1000 IU per day for 6 weeks. In this study, any patients who dropped out were replaced by additional subjects who met the inclusion criteria and did not meet the exclusion criteria.

The results of this study showed that there were no initial differences between the I and C groups. A previous study showed that the majority of ATS users were not married, with a total of 31 unmarried people (77.5%) and 9 married people (22.75%)[19]. Another study showed a different result; the study reported that most ATS users were married and had a high school education instead of being unmarried with less than a high school education[20]. In this study, the numbers of married and unmarried individuals were almost equal and most of them had a high school education. Attention needs to be paid to the increase in the number of ATS users; methods of preventing ATS use include counseling. In addition, marriage may play a role in the prevention of ATS use.

This study found that serum vitamin D levels were higher in the intervention group than that of the control group after receiving 1000 IU of supplemental cholecalciferol daily for 6 weeks. The increase that occurred in the control group might have been the result of nutritional intake and sunlight exposure[21-24].

The increased serum vitamin D levels observed in the control group could have occurred because vitamin D can be derived from pre-vitamin D obtained from supplements or foods[21,22]. Serum vitamin D levels are also influenced by exposure to sunlight, skin colour, ethnicity, season, location and activity; however, in this study, we did not assess these parameters[23,24]. The level of vitamin D affects the serum level of 25(OH)D[21,22]. 25-Hydroxyvitamin D (vitamin D) has an important role in the growth, development and function of the brain. Possible roles for vitamin D in brain development are the regulation of growth factors such as neuronal growth factor (NGF), synaptogenesis and nerve overgrowth[20]. 25(OH)D is activated with the assistance of enzyme Iα hydroxylase and can increase the levels of GDNF and NGF, resulting in decreased levels of dopamine and cortisol. Decreased levels of dopamine and cortisol improve the symptoms of psychosis and anxiety. Therefore, it is not surprising that vitamin D status is associated with diseases that involve abnormal DA signal delivery, such as schizophrenia, the symptoms of which are similar to the psychotic symptoms and anxiety resulting from substance use[24-26]. The symptoms of psychosis that are triggered by amphetamines are very similar to the symptoms of schizophrenic psychosis[26].

Cholecalciferol is suspected to have a neuroprotective effect on dopaminergic pathways in adult brains. When 6-hydroxydopamine, a type of selective dopaminergic toxin, was given to animals that had previously been given $1,25(OH)_2D_3$for 1 week, no changes in dopaminergic functions were observed. Lab rats that were postnatally injected with 1 dose of cholecalciferol showed an increase in dopamine (DA) in their brain stems and changes in the caudate putamen and hypothalamus. In vitro, $1,25(OH)_2D_3$ increases tyrosine hydroxylase expression in medulla adrenal cells. Therefore, vitamin D affects dopaminergic processes and there is evidence that cholecalciferol increases the expression of tyrosine hydroxylase15. This relationship is supported by the results of this study.

The increase in the serum level of 25(OH)D in the control group could have occurred due to the cholecalciferol content in the body, which comes from pre-vitamin D obtained from supplements or food[22-23]. However, another study found differences in the factors that affect the serum levels of 25(OH)D; the intensity of sun exposure and supplements or food consumed by schizophrenia patients were not significantly related to the serum level of 25(OH)D[24].

The BPRS score was higher in the intervention group than that of the control group, which is supported by some theories regarding the control of serotonin synthesis by cholecalciferol. The consumption of cholecalciferol reduces the risk of neuropsychiatric diseases and repairs brain function. This may be mediated partially through the activation of tryptophan hydroxylase 2 (TPH2). Cholecalciferol, which controls >900 genes, is the main regulator of serotonin synthesis in the brain through TPH2, which contains a vitamin D response element (VDRE) based on its activation status. Two different VDREs were identified in the TPH2 control area and tryptophan hydroxylase 1 (TPH1). These genes are responsible for the conversion of tryptophan to serotonin in the brain; therefore, in the presence of vitamin D, serotonin synthesis increases. VDRE-controlled activation of TPH2 explains why vitamin D is needed for normal serotonin synthesis in the brain and how low cholecalciferol levels affect neuropsychiatric diseasedevelopment[25,26].

Low levels of vitamin D increase the risk of psychosis up to 6 times. Vitamin D plays an important role in forming developing brain structures, reducing psychosis and improving brain function[24]. Symptoms of substance use psychosis include a lack of concentration, delusions, increased motor activity, disordered thoughts, erratic speech, lack of knowledge, anxiety, suspicion and auditory hallucinations; these symptoms are similar to those of schizophrenia[16,26].

Vitamin D intake can reduce the risk of neuropsychiatric diseases and improve brain dysfunction. This may be mediated in part through the ability of vitamin D to activate tryptophan hydroxylase 2 (TPH2). The vitamin D hormone, which apparently controls >900 genes, is the main regulator of brain serotonin synthesis via TPH2, which contains a vitamin D response element (VDRE). Two different VDREs exist in the regulatory regions of TPH2 and tryptophan hydroxylase 1 (TPH1), the 2 genes responsible for converting tryptophan to serotonin in the brain; therefore, serotonin synthesis is increased in the presence of vitamin D. The activating role of the VDRE found in TPH2 provides new insight into why vitamin D is needed for the synthesis of normal serotonin in the brain and the mechanism by which a low level of vitamin D can affect the development of neuropsychiatric diseases. Furthermore, vitamin D intake is a safer therapeutic treatment than serotonin-enhancing drugs, which often have side effects[25,26].

This was a study with no drop-outs because all the procedures were well controlled, such as nutritional intake and supplement intake. This study also did not find any side effects of daily supplementation with vitamin D 1000 IU. The limitations of this study were that the research did not specify the length of amphetamine usage history and that there was

nutritional status of ATS users was not controlled for in the analysis. Based on the study performed, fibre consumption is one of the factors that may reduce the fat level in the body and influence the level of vitamin D; the opposite may also be true, with fats accumulating in the body due to a low vitamin D level[27]. Some people with higher fat mass and fat mal absorption tend to suffer from vitamin D deficiency[27-29]. In addition, we did not assess polymorphisms of the vitamin D receptor gene .

CONCLUSION

Supplementation with cholecalciferol increases the 25(OH)D serum content as well as the effectiveness of therapy in ATS users, as indicated by the reduction in the BPRS score.

ACKNOWLEDGMENTS

This study was supported by the Rehabilitation Centre of North Sumatera, National Narcotics Agency (Badan Narkotika Nasional/BNN), Sumatera, Indonesia, which facilitated the inclusion of subjects in the study. I would also like to express my gratitude to my supervisors in the doctoral programme of the Faculty of Medicine, Universitas Sumatera Utara.

REFERENCES

1. Thurn, D., E. Kuntsche, J.A. Weber and J. Wolstein, 2017. Development and validation of the amphetamine-type stimulants motive questionnaire in a clinical population. Front. Psychiatry, Vol. 8. 10.3389/fpsyt.2017.00183
2. United Nations Office on Drugs and Crime, 2017. World Drug Report: Executive Summary, Conclusions and Policy Implications. United Nations Austria.
3. Hsieh, J.H., D.J. Stein and F.M. Howells, 2014. The neurobiology of methamphetamine induced psychosis. Front. Hum. Neurosci., Vol. 8. 10.3389/fnhum.2014.00537
4. United Nations Office Drug and Crime, 2013. Patterns and Trends of Amphetamine-Type Stimulants and Other Drugs: Challenges for Asia and The Pacific. United Nations Office Drug and Crime Research.
5. Triswara, R. and N. Carolia, 2017. Gangguan fungs ikognitifakibatpenyalahgunaanamfetamin. Med. J. Lampung Univ., 7: 49-53.
6. Medscape, 2017. Amphetamine-related psychiatric disorders. http://emedicine.medscape.com/article/289973-overview.
7. Sari, D.K., Z.Z. Tala, S. Lestari, S.V. Hutagalung and R.A. Ganie, 2017. Vitamin D receptor gene polymorphism among Indonesian women in North Sumatera. Asian J. Clin. Nutr., 9: 44-50.
8. Sari, D.K., Z.Z. Tala, S. Lestari, S.V. Hutagalung and R.A. Ganie, 2017. Lifestyle differences in rural and urban areas affected the level of vitamin D in women with single nucleotide polymorphism in North Sumatera. Asian J. Clin. Nutr., 9: 57-63.
9. Sari, D.K., Z.Z. Tala, S. Lestari, S.V. Hutagalung and R.A. Ganie, 2017. Body mass index but not 25(OH)D serum is associated with bone mineral density among Indonesian women in North Sumatera: A cross sectional study. Asian J. Clin. Nutr., 9: 37-43.
10. Koutkia, P., T.C. Chen and M.F. Holick, 2001. Vitamin D intoxication associated with an over-the-counter supplement. N. Engl. J. Med., 345: 66-67.
11. McGrath, J.J., T.H. Burne, F. Féron, A. Mackay-Sim and D.W. Eyles, 2010. Developmental vitamin D deficiency and risk of schizophrenia: A 10-year update. Schizophr. Bull., 36: 1073-1078.
12. Menkes, D.B., K. Lancaster, M. Grant, R.W. Marsh, P. Dean and S.A. du Toit, 2012. Vitamin D status of psychiatric inpatients in New Zealand's Waikato region. BMC Psychiatry, Vol. 12. 10.1186/1471-244X-12-68
13. Sotodeh-Asl, N., M.R. Tamadon, F. Malek and M. Zahmatkesh, 2014. Vitamin D deficiency and psychological disorders. J. Parathyr. Dis., 2: 21-25.
14. Eyles, D.W., F. Feron, X. Cui, J.P. Kesby and L.H. Harms *et al*., 2009. Developmental vitamin D deficiency causes abnormal brain development. Psychoneuroendocrinology, 34: S247-S257.
15. Eserian, J.K., 2013. Vitamin D as an effective treatment approach for drug abuse and addiction. J. Med. Hypotheses Ideas, 7: 35-39.
16. Szigeti, V., 2016. Vitamin D levels in patients with psychosis: A marker of burden of care? Örebro University School of Medicine Degree project, 30 ETCS. http://www.diva-portal.org/smash/get/diva2:905907/FULLTEXT01.pdf.
17. BNN., 2017. Kerjabersamaperangmelawannarkoba. Badan Narkotika Nasional, Jakarta. https://docplayer.info/71355248-Press-release-akhir-tahun-2017-kerja-bersama-perang-melawan-narkoba.html.
18. Bech, P., M. Kastrup and O.J. Rafaelsen, 1986. Mini-compendium of rating scales for states of anxiety, depression, mania, schizophrenia with corresponding DSM-III syndromes. Acta Psychiatr. Scand., Vol. 73, No. 326, Suppl.
19. Yüksel, R.N., N. Altunsoy, B. Tikir, M.C. Külük and K. Unal *et al*., 2014. Correlation between total vitamin D levels and psychotic psychopathology in patients with schizophrenia: therapeutic implications for add-on vitamin D augmentation. Ther. Adv. Psychopharmacol., 4: 268-275.
20. Hendoiee, N., F. Sheikhmoonesi, M. Zarghami, S. Mamashli and J.Y. Charati*et al*., 2016. Effectiveness of vitamin D Supplement therapy in chronic stable schizophrenic male patients: A randomized controlled trial. Iran. J. Pharm. Res., 15: 941-950.

21. Pirnia, B., F. Givi, R. Roshan, K. Pirnia and A.A. Soleimani, 2016. The cortisol level and its relationship with depression, stress and anxiety indices in chronic methamphetamine-dependent patients and normal individuals undergoing inguinal hernia surgery. Med. J. Islam Repub Iran, 30: 679-687.
22. Brannon, P.M., E.A. Yetley, R.L. Bailey and M.F. Picciano, 2008. Overview of the conference vitamin D and health in the 21st century: An update. Am. J. Clin. Nutr., 88: 483S-490S.
23. Holick, M.F., N.C. Binkley, H.A. Bischoff-Ferrari, C.M. Gordon and D.A. Hanley *et al*., 2011. Evaluation, treatment and prevention of vitamin D deficiency: An Endocrine Society clinical practice guideline. J. Clin. Endocrinol. Metab., 96: 1911-1930.
24. Itzhaky, D., D. Amital, K. Gorden, A. Bogomolni, Y. Arnson and H. Amital, 2012. Low serum vitamin D concentrations in patients with schizophrenia. Isr. Med. Assoc. J., 14: 88-92.
25. Patrick, R.P. and B.N. Ames, 2015. Vitamin D and the omega-3 fatty acids control serotonin synthesis and action, part 2: relevance for ADHD, bipolar disorder, schizophrenia and impulsive behavior. FASEB J., 29: 2207-2222.
26. Bramness, J.G., Ø.H. Gundersen, J. Guterstam, E.B. Rognli and M. Konstenius *et al*., 2012. Amphetamine-induced psychosis - A separate diagnostic entity or primary psychosis triggered in the vulnerable? BMC Psychiatry, Vol. 12. 10.1186/1471-244X-12-221
27. Wemm, S.E. and R. Sinha, 2019. Drug-induced stress responses and addiction risk and relapse. Neurobiol. Stress, Vol. 10. 10.1016/j.ynstr.2019.100148
28. Holick, M.F., 2005. Vitamin D for health and in chronic kidney disease. Semin. Dial., 18: 266-275.
29. Holick, M.F., 2007. Vitamin D deficiency. N. Engl. J. Med., 357: 266-281.