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Vitamin D deficiency and its Receptor Gene Polymorphisms as a risk factor of depression in Saudi Men

Ayman Al-hazmi[1], Anas Alomery[1], mohab samarkandi[1], Aseel Alsaadi[1], Mazen Almehmadi[1], Sarah Al-Bogami[2], Ashjan Shami[1], Saleh Alghamdi[1], Ahmad El Askary[1,3] , Saad Al-Shehri[1], Alaa Shafie[1], Bassem M. Raafat [1]and Ahmed Alhabs[4].

[1]Faculty of Applied Medical Sciences, Taif University, Taif city, **Saudi Arabia**
[2] Faculty of Sciences, Taif University, Taif city, **Saudi Arabia**
[3]Department of Medical Biochemistry, Al-Azhar University, New Damietta, **Egypt**
[4] Ministry of health, Taif city, **Saudi Arabia**.

***Correspondence:** omarianas1@hotmail.com **Accepted:** 08 Mar. 2019 **Published online:** 10 Apr. 2019

Depression is a global problem that causes disability all over the world. It characterized by persistent low mood and despair sensation. Vitamin D deficiency is a risk factor that may cause depression. This study was aimed to evaluate the effects of vitamin D deficiency and its receptor gene polymorphisms in depression. This study consisted of 80 men depressed patients and 100 healthy men as a control. For each one age, weight and length were estimated and BMI was calculated. Blood samples were collected for 25-(OH) vitamin D level measurement and to determine VDR genotypes. Vitamin D level in the depressed patient was low compared with its level in the control group (P<0.01). According to VDR genotypes, our study didn`t confirm any association of these genotypes and depression. Conclusion: Vitamin D deficiency may be a risk factor for depression in Saudi men.

Keywords: depression, vitamin D receptor, gene polymorphisms

INTRODUCTION

Depression becomes a big problem distributed all over the world and may be the major cause of death in the future. It affects about 350 million persons worldwide(Hyman et al., 2006). Depression defines as a mental illness characterized by persistent low mood and despair sensation leading to a sad feeling, hopeless, frustrated and low self-esteem(Bertone-Johnson, 2009).In Saudi Arabia, the depressed patients are increased each year and the prevalence of all type between 15.3-22% (Simon et al., 1999). Depression usually appears as a sign of serotonin and dopamine depletion (Cass et al., 2006). Vitamin D plays autocrine, paracrine and endocrine functions through its receptor (Hendrix et al., 2005). Its deficiency now becomes a global public health in our sunny country. The previous study done showed that 98% of the studied population have a vitamin D deficiency (Alharbi, 2013). Several studies showed that vitamin D deficiency is associated with different diseases include obesity, diabetes and cancer (Holick, 2010). Two hydroxylations are responsible to convert vitamin D to its active form. The enzyme responsible for the second hydroxylation is present in the hypothalamus, and cerebellum (Obradovic et al., 2006).In addition to maintenance of bone strength, vitamin D also regulates the production of adrenaline,

noradrenaline and dopamine. It also protects against dopamine and serotonin depletion(Cass, 2006). These evidences show an importance of vitamin D in nervous system function. Previous epidemiological studies showed that vitamin D deficiency is associated with 50% of depression and suicide (Umhau et al., 2013). Vitamin D exerts its effect through binding to a receptor called vitamin D receptor (VDR). The VDR is expressed in many tissues including neurons and glial cells present in the thalamus and hypothalamus (Eyles et al., 2005). Association of these areas with depression gives another evidence about n association of vitamin D with depression. previously, a study reported that vitamin D maintain structure and concentration of neurons through detoxification mechanism and synthesis of neurotrophin (Garcion et al., 2002). Another study showed that vitamin D has a protective effect against serotonin and dopamine depletion induced by methamphetamine (Cass et al., 2006). Moreover, vitamin D induces the expression of tyrosine hydroxylase which plays important role in the biosynthesis of adrenaline, noradrenaline and dopamine by adrenal medulla (Puchacz et al., 1996). This study was aimed to determined vitamin D level and VDR gene polymorphisms in Saudi depressed men.

MATERIALS AND METHODS

Subjects:

This study was approved by Taif University Medical Ethics and done in communication with the outpatient department of Taif Psychiatry Health hospital. It consisted of 80 depressed patients aged between 20-52 years diagnosed in the outpatient department of Taif Psychiatry Health hospital according to Diagnostic and Statistical Manual of Mental Axis I disorders (DSM-IV) scale(Umhau *et al.*, 2013). All patients were under antidepressant therapy and didn`t use vitamin D supplementation. A hundred healthy men aged from 20-50 years were used as a control group.

Methods:

Demographic measurements were obtained from each individual and BMI was calculated. In addition, after an overnight fast, venous blood samples were obtained in EDTA tubes, separated immediately and stored at 20 C until the analysis. The plasma was used for measurement of 25-(OH) vitamin D by using ELISA technique.

Genotyping: The DNA was extracted from peripheral blood leukocytes collected in EDTA tube by using the Thermo SCIENTIFIC DNA isolation kit (Thermo SCIENTIFIC). Genomic DNA was amplified and analyzed for VDR genotype by restriction fragment length polymorphism-polymerase chain reaction (RFLP-PCR) for *BsmI, Taq1* and *ApaI*.

Determination of *ApaI* genotypes:

The PCR mix was contained 5 µL of each primer; the forward 5'-CAGAGCATGG-ACAGGGAGCAAG-3' and the reverse 5'-GCAACTCCTCATGGCTGA-GGTCTCA-3' (10 pmol), 5 µL buffer, 1.5 µL MgCl2 (50 mM), 5 µL template DNA (50–100 ng), 5 µL dNTPs (2 mmol/L), Taq polymerase (MBI) 2 µL and H2O 26.5 µL. The DNA template was denatured at 95°C for 2 min. A total of 40 cycles of PCR were performed, consisting of denaturation step for 45 sec at 94°C, an annealing step for 45 sec at optimum temperature 67°Cand an extension reaction for 1 min at 72°C. A final extension step at 72°C for 2 min was added after the last PCR cycle. After amplification, the PCR products were digested by incubation with ApaI restriction enzyme in 37°C for 5 minutes to get its three genotypes on 1.5% agarose gel designated AA, Aa and aa.

Determination of *TaqI* genotypes:

The technique was similar to ApaI genotypes except that the forward primer was 5′-CAGAGCATGGACAGGGAGCAAG-3′ and the reverse was 5′- GCAACTCCTCATGGC-TGAGGTCTCA-3′. In addition, the products of PCR were incubated with TaqI enzyme for at 65°C for 4 hours produced TT, Tt and tt on 2.5% agarose gel.

Determination of *BsmI* genotypes:

Determination of BsmI genotypes also similar to ApaI methods except primer was used; forward 5′-AGTGTGCAGGCGATTCGTAG-3′ and reverse 5′-ATAGGCAGAACCATCT-CTCAG-3′. The products were incubated with BsmI enzyme at 65 °C for 15 min, then applied on 2% agarose gel to get its three genotypes BB, Bb and bb.

Statistical analysis: -

SPSS software version 16 (SPSS Inc., Chicago, IL, USA) was used in the performance of statistical analysis. The correlations were tested by using Spearman`s test. The t-test was used in comparisons performance. Both comparisons and

correlations were considered statistically significant when P < 0.05.

RESULTS

Demographic measurements and 2-(OH) vitamin D level represented by table 1 and comparisons in the table were done by using t-test. BMI showed significant differences between the two group with the higher value in depressed group (*P*=0.005). The vitamin D level in depressed group (17.81±3.85) showed a lower significant statistical difference compared with control group (32.55±6.33) with *P*=0.007. Table 2 represents the comparison of VDR genotypes and alleles between the depressed patient group with the control group by using t-test. *ApaI*, *Taq1* and *BsmI* genotypes and alleles didn`t show significant differences in its frequencies in the depressed patients compared with the control group.

Table1. Comparison of biometric measurement and vitamin D level between depressed patient group and control using t-test (Mean±SD):

	Control N= 100	Depressed patients N= 80	P value
Age	30.59±5.50	32.25±6.25	0.851
Weight (kg)	67.44±9.88	56.63±6.4	0.038*
BMI	30.48±5.04	25.7±2.65	0.005**
25-H-Vit-D (ng/mL)	32.55±6.33	17.81±3.85	0.007**

Table2. Comparison of *ApaI*, *TaqI* and *BsmI* genotypes and allelic frequencies between depressed patient group and control group:

Genotypes *ApaI*	Control (100) %	Depressed patient (80) %	*P* value
AA	33 (33%)	30 (37.5%)	0.806
Aa	41 (41%)	32 (40%)	0.902
aa	26 (26%)	18 (22.5%)	0.505
Allele A	107 (53.5%)	92 (57.5%)	0.768
Allele a	93 (46.5%)	68(42.5%)	0.659
Genotype *TaqI*			
TT	44 (44%)	37 (46.25%)	0.812
Tt	38 (38%)	22 (33.75%)	0.772
tt	18 (18%)	21 (26.25%)	0.093
Allele T	126 (63.00%)	96(60.00%)	0.837
Allele t	74 (37.00%)	64 (40.00%)	0.852
Genotypes *BsmI*			
BB	33 (33%)	25 (31.25%)	0.916
Bb	35 (35%)	29 (36.25%)	0.931
bb	32 (32%)	26 (32.50%)	0.952
Allele B	101 (50.50%)	79 (49.37%)	0.938
Allele b	99 (49.50%)	81 (50.63%)	0.971

DISCUSSION

Depression becomes the second major cause of disability by the year 2020. In Saudi Arabia, depression prevalence becomes a highest one worldwide and in the future, the figure is expected to increase and worsen (Umhau et al., 2013). Besides depression, vitamin D deficiency becomes a problem affects many people worldwide. Our country Saudi Arabia is a sunny area along four seasons. Previously, a study done on Saudi male showed that 98% of individuals included in the study suffering from vitamin D deficiency and insufficiency (Alharbi et al., 2013). Vitamin D promotes the synthesis of neurotropic factors so it may affect chemical change in the nervous system (Groves et al., 2013). Several studies were done previously to determine the association between vitamin D deficiency and many chronic diseases. Our group has two studies that showed an association of vitamin D deficiency with obesity and type 2 diabetes mellitus (Al-hazmi et al., 2017). The current study was aimed to confirm the association between vitamin deficiency and depression. Previously a study showed that vitamin D supplementation is a benefit in the treatment of depression (Milaneschi et al., 2010). In 2014, a study done by concluded that biological plausibility and epidemiological studies indicate vitamin D has therapeutic effects on depression. In addition, more than 50% of patients with resistance against antidepressant medication showed low vitamin D level (Bertone-Johnson, 2009).In 2008, Hoogendijk et al., found that low vitamin D level is associated with deterioration in cognitive function and depressive mood (Hoogendijk et al., 2008). Moreover, a large study found that people who had active depressed symptoms had lower vitamin D levels (Dilmec et al., 2010). Our results in consistency with these studies and showed that depressed patients have vitamin D deficiency and when compared with the healthy control it has a lower level of this vitamin. On the other hand, some study didn`t confirm this phenomenon and it described the low levels of vitamin D in depressed patients as a result of low motivation, lack of sun exposure and loss of appetite. So low vitamin D level in depressed patients is a symptom rather than a cause of depression (Lee et al., 2011). Another study didn`t agree about this description and it concluded that the low vitamin D level is a factor that causes depression, largely independent of several lifestyles and health factors (Fernandes et al., 2009). Vitamin D exerts its effect through binding to VDR located at large scale of cell lines and recently the association of this receptor with cognitive function become a hot study area. The VDR gene is located at 12q13 chromosomal region and its responsive elements are present in serotonin and tryptophan hydroxylase receptors promoter regions. Deleterious mutations in this gene leading to 1,25-dihydroxyvitamin D resistance rickets. There are many polymorphisms in this gene that occur frequently in the different population. Previously, several studies conclude that ApaI genotype and A allele are risk genes in Alzheimer's disease, schizophrenia and mild cognitive impairment in elderly. Little studies focus in the association of VDR gene polymorphisms with depression. In 2014 Kabinuer and his colleague study showed that, the AA genotype of ApaI and A allele had higher frequencies in depressed patients than control. Our results as Yalamanchili and Gallagher who didn`t confirm this association between TaqI genotypes and depression in 2012. About BsmI genotypes, Both Kuningas et al., and Kabinuer et al., studies confirmed the association of BB genotype and B allele with mild cognitive impairment, but our study didn`t confirm this association. Finally, about TaqI genotypes, our study is in accordance with previous studies that didn`t confirm this genotype as a risk factor of depression.

CONCLUSION

This is a small size study; a large sample study is recommended to confirm the association between VDR gene polymorphisms and depression. In addition, a supplementation of vitamin D is recommended for preventing complications. Also, a study that shows the effect of vitamin D supplementation on depression symptoms is recommended. We can conclude that vitamin D deficiency may be a risk factor for depression in Saudi men.

CONFLICT OF INTEREST

The authors declared that present study was performed in absence of any conflict of interest.

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AUTHOR CONTRIBUTIONS

Dr. AA, SA, MA, SA and Dr AA designed the study and wrote the manuscript, Dr. AA, Dr SA and Mr AA analyzed PCR results, Mr. MH collected samples, Mr. AA, Mr. MS and Mr. AA performed PCR experiment. Dr AE, Dr.BR and Dr AS performed the data analysis. All authors read and approved the final version

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