DOPAMINE RECEPTOR D3R AND D4R MRNA LEVELS IN PERIPHERAL LYMPHOCYTES IN PATIENTS WITH SCHIZOPHRENIA AND ITS CORRELATION WITH SEVERITY OF ILLNESS

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ABSTRACT

Objective: This study aimed to assess D3R and D4R mRNA levels in patients with schizophrenia.

Subjects: Thirty six schizophrenia patients; 24 males (66.7%) and 12 females (33.3%) and 36 healthy individuals; 23 males (63.9%) and 13 females (36.1%) as control subjects.

Methods: All schizophrenia patients are thoroughly screened and diagnosed for schizophrenia using DSM-IV diagnostic criteria for schizophrenia.

Results: The mean values of D3 and D4 receptors mRNAs level among both studied cases and controls show a highly statistically significant difference (P <0.001) between both schizophrenia patients and their controls regarding levels of D3 and D4 mediators. D3 receptor mRNAs level influenced by PANS scale of schizophrenic patients, as level of D3 R increased in PBLs with decreased schizophrenia severity, and the difference was statistically significant (P <0.001), while the difference in D4 R level was not statistically significant (P >0.05).

Conclusion: This study reveals that the molecular biologically-determined dopamine receptors (DR3 and DR4 mRNA) of peripheral lymphocytes are reactive after taking antipsychotics, and that increased expression of dopamine receptor in peripheral lymphocyte has possible clinical significance for subgrouping of schizophrenia.

Key words: DR3: dopamine receptor 3, DR4: dopamine receptor 4, RT- PCR: real time polymerase chain reaction

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INTRODUCTION

Schizophrenia is a severe, chronic mental disorder, and it affects approximately 1% of the world's population [1]. For individuals who have a schizophrenic relative in her/his family, the chances of the individual having schizophrenia raises to 65–85% [2]. The etiology and pathophysiology of schizophrenia remain obscure, and its current diagnosis is based on complex clinical symptoms. The application of easily detectable peripheral molecular markers could substantially help the diagnosis of psychiatric disorders [3].

The dominant "dopamine hyperfunction hypothesis" was supported by molecular, pharmacological and clinical evidence for over 40 years [4]. Many of the signs and symptoms of schizophrenia can be reproduced in humans or animal models with dopaminergic drugs [5]. In addition, a recent meta-analysis was performed that was based on over 1000 association studies on schizophrenia, and this study highlighted 16 genes, which were mostly dopamine-related, including catechol-O-methyltransferase (COMT) and dopamine receptors D1, D2, and D4 (DRD1, DRD2 and DRD4) [6].

Dopamine is a monoamine catecholamine neurotransmitter that acts through its D1 and D2 classes of receptors present in the target cells. The D1 class of receptors includes the D1 and D5 subtypes, which increase intracellular cAMP on activation. In contrast, the D2 class of receptors, which includes D2, D3 and D4 subtypes, inhibit intracellular cAMP on stimulation [7]. DA reuptake mostly depends on the presence and activity of the DA transporter (DAT), a 80 kD glycoprotein belonging to the large Na+/Cl− dependent transporter family,

which includes norepinephrine, serotonin, GABA and glycine transporters [8].

Dopamine receptors are the key elements of the dopaminergic system. The dopamine receptors in PBLs may reflect the status of homologous brain receptors [9]. Analysis of dopamine receptors in PBLs is a useful tool for evaluating the functional properties of dopaminergic function that underlie the variation in complex psychological and psychopathological traits [10].

Based on the above studies, our present study aimed to assess D3R and D4R mRNA levels in patients with schizophrenia compared to controls and to determine the correlation between Dopamine receptor D3R and D4R mRNA levels in peripheral lymphocytes in patients with schizophrenia and the severity of symptoms and cognitive impairment.

SUBJECTS & METHODS

The study subjects included 72 adult subjects; 36 schizophrenia patients (group A) and 36 healthy control volunteers (group B), they selected from the attendants of Psychiatry Department, Zagazig University Hospitals, Zagazig, Sharkia, Egypt and informed consent obtained from each person.

Exclusion criteria: Participants with any physical or general medical condition, substance dependence for the last one month, history of present symptoms of any other psychiatric disorder and mental retardation.

Examination: All schizophrenia patients are thoroughly screened and diagnosed for schizophrenia using DSM-IV diagnostic criteria for schizophrenia.

DSM-V diagnostic criteria for schizophrenia:

A necessary (but not sufficient) diagnostic component of schizophrenia and schizoaffective disorder in the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM- V) is criterion A, which comprises five symptom types: delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior, and negative symptoms. Two or more of these are required for a diagnosis of schizophrenia [11].

Positive and Negative Syndrome Scale (PANSS):

The PANSS was developed in late 1980s to assess clinical symptoms of schizophrenia. Schizophrenia is a heterogeneous disorder with a wide range of symptoms. This extensive clinical variability poses a challenge for establishing accurate diagnosis and assessing treatment response. The Positive and Negative Syndrome Scale (PANSS) is one of the most widely used instruments to evaluate psychotic symptoms. It is composed of 30 items divided into three subscales - Positive Symptoms, Negative Symptoms, and General Psychopathology - developed to assess the severity of symptoms and measure general psychopathology and drug-related changes ***(12)***.

The PANSS includes 30 items on three subscales 7 items covering positive symptoms (e.g., delusions and hallucinations), 7 items covering negative symptoms (e.g., social withdrawal, flat affect, lack of motivation), and 16 items covering general psychopathology (e.g., anxiety, depression). The PANSS was conceived as an operationalized instrument that provides balanced representation of positive and negative symptoms, as well as mood and anxiety symptoms. The PANSS requires a clinician rater because considerable clinical judgment is required. The assessment consists of a semi-structured clinical interview and any available supporting clinical information, such as family member's reports or previous records. The ratings can be completed in 30–40 min. Each item is scored on 10 Rating Scales in Schizophrenia 211 a 7-point Likert scale ranging from 1 to 7. Therefore, the positive and negative subscales each range from 7 to 49, and the general psychopathology subscale from 16 to 112.

The PANSS has become an important instrument in schizophrenia research. It is one of the instruments most frequently used to assess efficacy of antipsychotic drugs, based on variation of its total score over time. It has been validated in several languages and used in the majority of the studies of new drugs for schizophrenia ***(13)***.

Laboratory Investigations:

Peripheral blood, collected between 10:00 a.m. and noon, was layered on Monopoly Separation Solution and separated into lymphocytes and granulocytes according to the manufacturer's instructions.

RT-PCR

For RT-PCR analysis, total RNA was isolated from lymphocytes using TRIzol (Invitrogen). Total RNA (0.5 μg) was reverse transcribed using Primescript reverse transcriptase (TaKaRa) and random 6-mers and oligo dT primer (TaKaRa) according to the manufacturer's instructions. The resulting complementary DNA fragments were amplified using Fast Start Universal Probe Master Mix (ROX reference dye) according to the manufacturer's instructions.

The test used quantitative reverse-transcription polymerase chain reaction (RT-PCR) to compare the mRNA levels of IFN-γ, TNF-α, IL-2, and IL-10 in peripheral blood mononuclear cells (PBMCs) between the schizophrenia patients and the matched healthy controls.

Method Details:

Whole blood samples were collected using Paxgene Blood RNA tubes (Becton Dickenson) and stored at −80° C. Total RNA was extracted using the Paxgene Blood RNA kit (Qiagen) according to the manufacturer's protocols. Complementary DNA was generated from 1 microgram of total RNA using oligo dT primers and Powerscript RT enzyme (BD Clontech) at 42° C for 60 minutes in a total volume of 20 μl. Two μl of cDNA (approximately 0.1 μg) was used to quantify gene expression by real-time PCR on an Mx3000P thermocycler (Stratagene) using Full Velocity SYBR Green 2× mix (Stratagene) and gene-specific primers for human DR3, DR4 and control gene .Following denaturation (10 minutes, 95°C), DNA was amplified using 50 cycles at 95°Cfor 10 sec, 55°Cfor 15 sec, and 72°Cfor 30 sec, then final extention at 72°c for 10 minutes. Results were normalized to HPRT1 using real time PCR method and are displayed as relative expression values.

RESULTS

Table 1: Demographic data of the studied cases and controls:

Variables	Mean ± SD		T-test	P-value
	Cases=36	Controls=36		
Age	**33.03±9.82**	**35.69±9.58**	1.17	0.247
	N	**%**	**N**	**%**	**X^2 test**	**P -value**
Sex						
Male	**24**	66.7	**23**	63.9	0.06	0.804
Female	**12**	33.3	**13**	36.1		

This table shows that both studied groups of cases and controls were matched as regard age and sex, so there is no statistical significant difference.

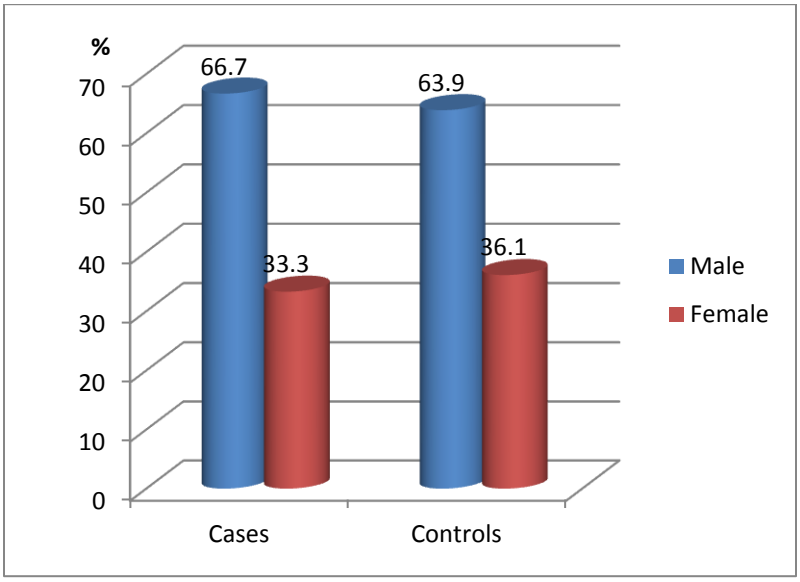

Figure (1): Sex distribution among both studied groups

Table (2): Clinical data of the studied schizophrenia patients.

Variables	Mean ± SD (N =36)
Disease duration\year	**12.26±7.08**
Range	**1 year – 25 years**
PANS scale	**119.58±19.23**
Range	**73-162**

This table shows clinical data of studied schizophrenia cases regarding disease duration which ranged from 1 year to 25 years with mean duration of 12.26±7.08. Positive and negative syndrome scale which ranged from 73 to 162 and mean value of 119.58±19.23.

Table 3: The mean values and standard deviation (± SD) of D3 and D4 receptors mRNAs level among both studied cases and controls:

Variables	Mean ± SD		t-test	P-value
	Cases=36	Controls=36		
D3	**1.96±0.39**	**1.04±0.034**	**14.21**	**0.000****
D4	**0.98±0.105**	**0.898±0.081**	**3.94**	**0.000****

****p-value<0.001 (highly significant)** **D3R & D4R (µg)**

This table shows a highly statistically significant difference between both schizophrenia patients and their controls regarding levels of D3 and D4 mediators.

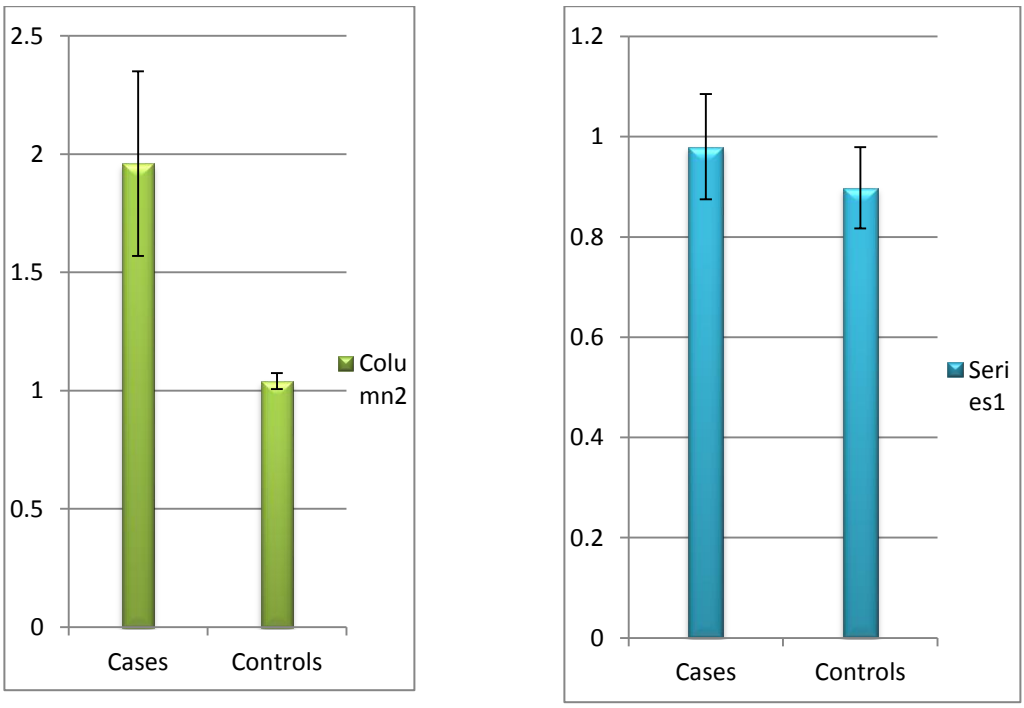

Figure (2): Difference in D3 and D4 receptors level among both studied cases and controls.

Table (4): The effect of demographic data on dopamine receptors mRNAs level among studied schizophrenia patients.

Variables	D3 R Mean±SD	Test of sig.	P-value	D4 R Mean±SD	t-test	
Sex						
Male (n=24)	**1.57±0.57**	MW*	0.142	**0.95±0.11**	0.61	0.544
Female (n=12)	**1.38±0.47**	1.49		**0.93±0.087**		
Age						
≤ 25 years (n=10)	**1.8±0.31**	t-test		**0.97±0.088**		
>25 years (n=26)	**2.02±0.401**	1.69	0.109	**0.99±0.11**	0.407	0.689

*Mann-whitney non parametric test of significance for not normally distributed data

This table shows that both dopamine receptors mRNAs level were not affected by age or sex of the studied schizophrenia cases, as the difference between groups was statistically not significant.

Table (5): The effect of PANS scale on dopamine receptors mRNAs levels among studied schizophrenia patients.

Variables	D3 R Mean±SD	t-test	P-value	D4 R Mean±SD	t-test	P-value
PANSS						
≤ 118	**2.18±0.296**			**0.96±0.107**		
>118	**1.77±0.361**	**3.78**	**0.001****	**1.01±0.101**	1.24	0.224

p-value<0.001 (highly significant)

This table shows that D3 receptor mRNAs level influenced by PANS scale of schizophrenic patients, as level of D3 R increased with decreased schizophrenia severity, and the difference was statistically significant. While the difference in D4 R level was not statistically significant.

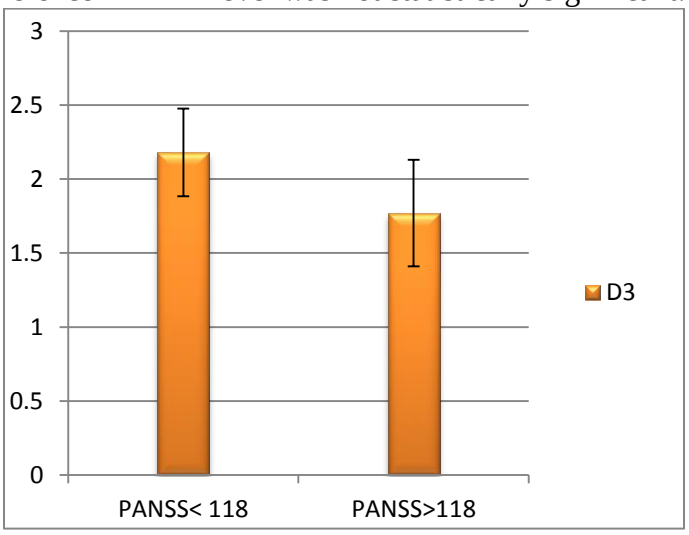

Figure (3): Difference in D3 receptors level according to PANS scale of the studied cases.

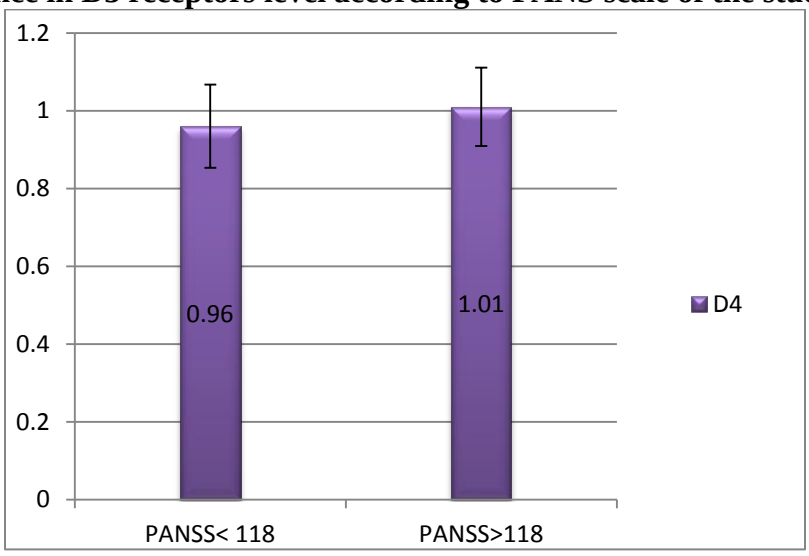

Figure (4): Difference in D4 receptors level according to PANS scale of the studied cases.

Table (6): Correlation between dopamine3 receptors mRNAs level and age, disease duration and PANS scale of studied schizophrenia patients.

Variables	D3	
	R	P-value
Age	0.273	0.107
Disease duration	**0.612**	**0.000****
PANS scale	**- 0.649**	**0.000****

**p-value<0.001 (highly significant)

This table shows a highly statistically significant negative correlation between D3 R and PANS scale of schizophrenia patients, also showed a highly statistically significant positive correlation with disease duration.

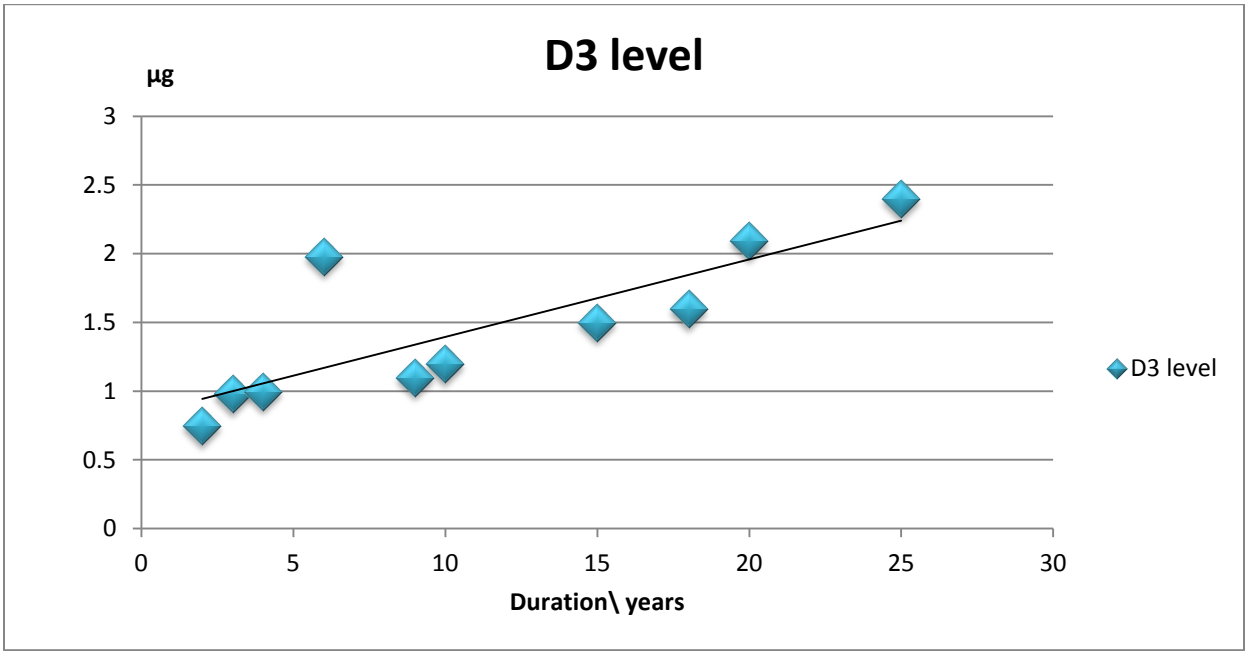

Figure (5): Positive correlation between D3 receptors level and disease duration among studied cases.

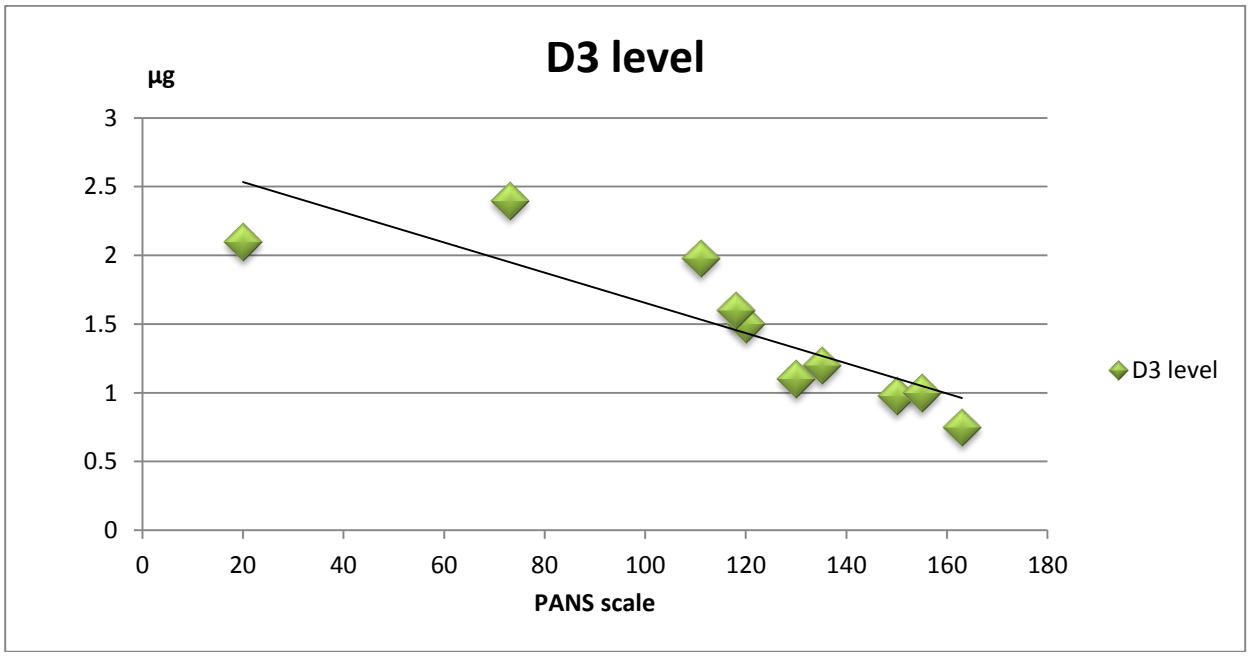

Figure (6): Negative correlation between D3 receptors level and PANS scale of the studied cases.

Table (7): Correlation between dopamine 4 receptors mRNAs level and age, disease duration and PANS scale of studied schizophrenia patients.

Variables	D4	
	r	P-value
Age	0.284	0.093
Disease duration	**0.425**	**0.01***
PANS scale	0.335	0.05

* p-value <0.05 (significant)

This table shows a positive correlation between D4 R and PANS scale of the studied schizophrenia patients but not reach significant level. While there was a statistical significant positive correlation between level of receptor and disease duration.

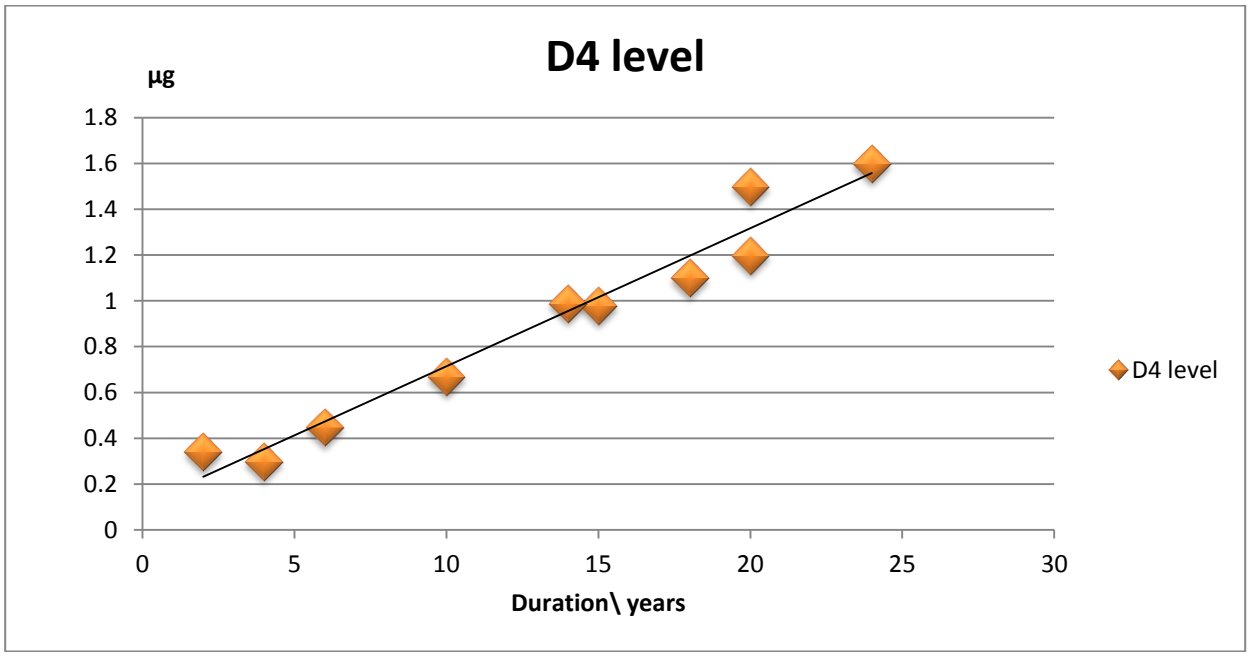

Figure (7): Positive correlation between D4 receptors level and disease duration among studied cases.

DISCUSSION

In this study, 36 schizophrenia patients; 24 males (66.7%) and 12 females (33.3%) and 36 healthy individuals; 23 males (63.9%) and 13 females (36.1%) as control subjects. Both groups are matched in age and sex, the mean age of the patient group was 33.03 ± 9.82 years and the mean age of the control group was 35.69 ± 9.58 years, where they are statistically non-significant (P > 0.05).

Clinically the disease duration ranged from one year to 25 years with mean duration of 12.26 ±7.08 years. Positive and negative syndrome scale which ranged from 73 to 162 and mean value of 119.58±19.23.

In this study, the mean values of D3 and D4 receptors mRNAs level among both studied cases and controls show a highly statistically significant difference (P <0.001) between both schizophrenia patients and their controls regarding levels of D3 and D4 mediators.

This study shows that both dopamine receptors mRNAs (D3 & D4) level in peripheral blood leukocytes (PBLs) were not affected by age or sex of the studied schizophrenia cases, as the difference between groups was statistically not significant.

In accordance with our study ***Ilani et al.*** [14] found in several representative patients, the signals for D_3 receptor mRNA were significantly higher in schizophrenic patients than in healthy controls. This increase was found to apply to the D_3 receptors specifically, because no significant differences in the intensities of D_4 receptor bands were detected between schizophrenic patients and healthy controls.

In contrast ***Urhan-Kucuk et al.*** [15] reported that when schizophrenia group was compared with the control group, there was no significant difference (P = 0.411) in DRD3 mRNA/b-actin mRNA levels. ***Ilani et al*** [14] measured the DRD3 cDNA band density in 14 schizophrenic patients and 11 healthy controls and found a significant increase in the levels of DRD3 mRNA levels in the blood lymphocytes of schizophrenic patients. They suggested that DRD3 mRNAs in blood lymphocytes could be used as a marker in diagnosis and monitoring of schizophrenia.

On the other hand, ***Van Der Weide et al.*** [16] studied in 8 schizophrenic and 8 healthy controls and did not observe an increase in the DRD3 PBL mRNA expression in schizophrenics, and suggested that antipsychotic medicines might decrease DRD3 products. They suggested that DRD3 mRNAs levels had a value in diagnosis of schizophrenia.

Kwak et al. [17] examined D3R mRNA expression in peripheral lymphocytes of schizophrenic patients with and without antipsychotic medication. They observed that in drug-free schizophrenics D3 dopamine receptor mRNA expression of peripheral lymphocytes significantly increased compared to that of controls and drug-medicated schizophrenics. When schizophrenia group compared with controls according to the DRD3 mRNA/b-actin mRNA ratio and significant difference (P = 0.030). Among schizophrenia subgroups, results of dual multi comparison showed that, there was a significant difference between disorganized schizophrenia and paranoid schizophrenia groups (P = 0.021). As there was a relation between schizophrenia subgroups and PBL DRD3 mRNA expression, this expression could be used a peripheral marker in schizophrenia subtyping. In spite of studies for long years, schizophrenia diagnosis is still based on clinical criteria and needs at least a period of 6 months and this cannot define subtypes. For this reason, researches on the question whether some blood markers including PBL dopamine receptors mRNA expression levels can operate as peripheral diagnostic markers for schizophrenia or for sub-typing of illness are highly important. Further studies will help in understanding of categorical determination in diagnosis of schizophrenia and other neuro-psychiatric illnesses [15].

We study the effect of PANS scale on dopamine receptors mRNAs levels among studied schizophrenia patients. D3 receptor mRNAs level influenced by PANS scale of schizophrenic patients, as level of D3 R increased in PBLs with decreased schizophrenia severity, and the difference was statistically significant (P <0.001), while the difference in D4 R level was not statistically significant (P >0.05). The study also found a correlation between dopamine receptors mRNAs level and age, disease duration and PANS scale of studied schizophrenia patients. It shows a highly statistically significant negative correlation between D3 R and PANS scale of schizophrenia patients (P <0.001), while it was in positive correlation with D4 R but not reach significant level (P <0.01). Dopamine receptors mRNAs level showed a positive correlation with disease duration which was statistically significant.

Glick et al. [18] assessed the association between both the PANSS total and subscale scores and psychiatric hospitalization. Their principal findings are first that lower initial PANSS total scores and reductions in these scores during a three-month period are associated with a significantly lower risk for psychiatric hospitalization. On average, those who experience a 10-point decrease in PANSS total score during three months are expected to reduce their number of psychiatric

hospitalizations by 0.02 (95% CI, 0.012 to 0.027) and their predicted nights in the hospital by 0.24 (95% CI, 0.07 to 0.41). Maintaining this reduction for a year is expected to reduce psychiatric hospitalizations by 0.10 (95% CI, 0.08 to 0.13) and nights hospitalized by 1.4 (95% CI, 0.9 to 1.9). Their finding of no significant association between neurocognitive function and risks for hospitalizations provides evidence of discriminant validity for the findings and reconfirms the separation of neurocognitive performance and its correlates from clinical symptoms and their treatment with antipsychotic medications [19].

Though the Positive and Negative Syndrome Scale (PANSS) is widely used to measure the severity of schizophrenia, some limitations exist. First, according to the original operational definition of the ratings, some patients' clinical conditions cannot be precisely matched to a specific score [20]. Second, different ratings for some items of the PANSS were related to different interpretations of the psychological symptoms by dissimilar geo-cultural groups [21]. Finally, these results should be interpreted in light of some limitations. Although several methods could be used, ***Higuchi et al.*** [22] chose factor analysis because it was the most widely used technique for analysis of the factor structure of PANSS in previous studies, allowing comparing the findings to those obtained in other countries/populations and generate convergent validation. Their sample was composed of individuals recruited from three different centers, from all stages of the disorder, under various antipsychotic treatment regimens, and assessed by different psychiatrists, which resembles the clinical reality of schizophrenic patients and reinforces the strength and validity.

Some limitations of this study should be taken into account such as we do not differentiate between acute and chronic schizophrenia as dopamine receptor may differ for both D3 and D4 [23]. Also we did not subtypes of schizophrenia as disorganized schizophrenia and paranoid schizophrenia that may show variations in dopamine receptors as mentioned in some studies [17].

CONCLUSION

From this study it is concluded that the DRD3 and DRD4 mRNA levels in PBLs were correlated with positive symptoms in schizophrenia patients, and DAT mRNA levels in PBLs of medicated schizophrenia patients were over-expressed. It is well-known that the analysis of dopamine receptors in PBLs is a useful tool for evaluating the functional properties of dopaminergic function that underlie the variation in complex psychological and psychopathological traits.

REFERENCES

1. Lopez AD and Murray CC (1998): The global burden of disease, 1990–2020. Nat Med 4: 1241–1243.
2. Ohara K, Nagai M, Tani K, Nakamura Y, Ino A, et al. (1998): Functional polymorphism of -141 Ins/Del in the dopamine D2 receptor gene promoter and schizophrenia. Psychiatry Res 81: 117–123.
3. Zvara A, Szekeres G, Janka Z, Kelemen JZ, Cimmer C, et al. (2005): Over-expression of dopamine D2receptor and inwardly rectifying potassium channel genes in drug-naive schizophrenic peripheral blood lymphocytes as potential diagnostic markers. Dis Markers 21: 61–69.
4. Zhan L, Kerr JR, Lafuente MJ, Maclean A, Chibalina MV, et al. (2011): Altered expression and coregulation of dopamine signalling genes in schizophrenia and bipolar disorder. Neuropathol Appl Neurobiol 37: 206–219.
5. Peleg-Raibstein D, Knuesel I, Feldon J (2008): Amphetamine sensitization in rats as an animal model of schizophrenia. Behav Brain Res 191: 190–201.
6. Allen NC, Bagade S, McQueen MB, Ioannidis JP, Kavvoura FK, et al. (2008): Systematic meta-analyses and field synopsis of genetic association studies in schizophrenia: the SzGene data-base. Nat Genet 40: 827–834.
7. Missale C, Nash SR, Robinson SW, Jaber M, Caron MG (1998): Dopamine receptors: from structure to function. Physiol Rev 78: 189–225.
8. Buttarelli FR, Fanciulli A, Pellicano C, Pontieri FE (2011): The Dopaminergic System in Peripheral Blood Lymphocytes: From Physiology to Pharmacology and Potential

Applications to Neuropsychiatric Disorders. Curr Neuropharmacol 9: 278–288.
9. Rollins B, Martin MV, Morgan L, Vawter MP (2010): Analysis of whole genome biomarker expression in blood and brain. Am J Med Genet B Neuropsychiatr Genet; 153B: 919–936.
10. Wonodi I, Hong LE, Stine OC, Mitchell BD, Elliott A, et al. (2009): Dopamine transporter polymorphism modulates oculomotor function and DAT1 mRNA expression in schizophrenia. Am J Med Genet B Neuropsychiatr Genet 150B: 282–289.
11. McLean D, Thara R, John S, Barrett R, Loa P, McGrath J, Mowry B (2014): DSM-IV "criterion A" schizophrenia symptoms across ethnically different populations: evidence for differing psychotic symptom content or structural organization? Cult Med Psychiatry; 38(3):408-26.
12. Kay SR, Fiszbein A, Opler LA (1987): The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull.; 13:261-76.
13. Kinon BJ, Chen L, Ascher-Svanum H, Stauffer VL, Kollack-Walker S, Sniadecki JL, et al. (2008): Predicting response to atypical antipsychotics based on early response in the treatment of schizophrenia. Schizophrenia Res.; 102:230-40.
14. Ilani T, Ben-Shachar D, Strous RD, Mazor M, Sheinkman A, Kotler M, Fuchs S (2001): A peripheral marker for schizophrenia: Increased levels of D3 dopamine receptor mRNA in blood lymphocytes. Proc Natl Acad Sci USA; 98(2):625-8.
15. Urhan-Kucuk M, Erdal ME, Ozen ME, Kul S, Herken H (2011): Is the dopamine D3 receptor mRNA on blood lymphocytes help to for identification and subtyping of schizophrenia? Mol Biol Rep.; 38(4):2569-72.
16. Van Der Weide J, Steijin LSW, Van Der Geld M, De Groot PA (2003): D3 dopamine receptor mRNA expression in lymphocytes: a peripheral marker for schzophrenia? Acta Neuropyschiatrica 15:91–93.
17. Kwak YT, Koo MS, Choi CH, Sunwoo IN (2001): Change of dopamine receptor mRNA expression in lymphocyte of schizophrenic patients. BMC Med Genet 2(3):471–478.
18. Glick HA, Li P, Harvey PD (2015): The relationship between Positive and Negative Syndrome Scale (PANSS) schizophrenia severity scores and risk for hospitalization: an analysis of the CATIE Schizophrenia Trial. Schizophr Res.; 166(1-3):110-4.
19. Bowie CR and Harvey PD (2005): Cognition in schizophrenia: impairments, determinants, and functional importance. Psychiatr. Clin. N. Am.; 28 (3): 613–633.
20. Nielsen J (2007): eLetter. PANSS scale — are you disoriented? Br. J. Psychiatry 19081; Jan. http://dx.doi.org/10.1192/bjp.190.1.81a
21. Khan A, Yavorsky C, Liechti S, Opler M, Rothman B, DiClemente G, Lucic L, Jovic S, Inada T, Yang L (2013): A rasch model to test the cross-cultural validity in the positive and negative syndrome scale (PANSS) across six geo-cultural groups. BMC Psychol.; 1 (1): 5.
22. Higuchi CH, Ortiz B, Berberian AA, Noto C, Cordeiro Q, Belangero SI, Pitta JC, Gadelha A, Bressan RA (2014): Factor structure of the Positive and Negative Syndrome Scale (PANSS) in Brazil: convergent validation of the Brazilian version. Rev Bras Psiquiatr.; 36(4):336-9.
23. Liu L, Yuan G, Cheng Z, Zhang G, Liu X, Zhang H (2013): Identification of the mRNA expression status of the dopamine D2 receptor and dopaminetransporter in peripheral blood lymphocytes of schizophrenia patients. PLoS One; 8(9):e75259.