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Implications of extrapolative factors and their interplay to develop thyroid dysfunction in newly diagnosed schizophrenics

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Abstract

Schizophrenia is a chronic and devastating mental sickness which may be caused by neurological and behavioral deformities. Disruption of thyroid hormones maybe involved in the progression of schizophrenia. Inflammatory markers (IL-6, TNF-α, MMP-9 and NO), Thyroid biomarkers (T4, T3, TSH, TgAb, TPOAb), Antioxidants include Vitamins (A,C,E,D,B6,B9,B12) and SOD, GPx, GRx, MDA and homocysteine were investigated among 40 schizophrenic females and 20 healthy individuals. Thyroid biomarkers T4 (18.26pmol/L) and TSH (5.29IU/L) values were calculated higher in diseased subjects as compared to controls (11.25pmol/L) and (3.26IU/L). T3 values (3.62µg/dl) seem less in schizophrenic females as compared to healthy controls (5.26µg/dl). Auto-antibodies demonstrate high levels in schizophrenics than normal controls TgAb (p=0.0139), TPOAb (p=0.0110). SOD (0.19U/ml), GSH (5.26µmol/L) and CAT (3.26U/L) have low levels in female schizophrenics as compared to healthy controls. GPx are elevated while GRx levels are reduced in disease state. The vitamins (VIT-A, VIT-C, VIT-E, VIT-D, VIT-B6, VIT-B9, VIT-B12) levels showed decreased trend in schizophrenic females rather than healthy controls. Oxidative markers IL-6, TNF-α, NO, MMP-9 and MDA are also concerned with the disease due to their increased levels (5.66pg/ml), (41.26pg/ml), (31.26µmol/L), (77.28ng/ml) and (1.69µmol/L) as compared to controls. The present study evident the association of thyroid hormones in schizophrenia. Pituitary-Thyroid hormone axis has interesting knot with dopaminergic, serotonergic, glutametergic and GAB Aergic systems in schizophrenia. Thyroid hormones along with increased oxidative stress and decreased antioxidant capacity have severe detrimental effects with the metabolic activity of mature brain.

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Introduction

Schizophrenia is a degenerative disorder and debilitating mental sickness that affects millions of people worldwide (Berna, 2005). Kraepelin and Bleuler stated that schizophrenia might have its roots in the development and growth of brain. In current years, the psycholinguistics and cognitive neuroscience have been upgraded by empirical, theoretical and methodological progress (Kraepelin, 1971). It is related to behavioral and psychological malformations in which delusions, hallucinations, cognitive derangements are involved (Santos *et al.*, 2012). Environmental and genetic factors are also considered in the etiology of schizophrenia (Pickard, 2011). Alcohol, cocain and amphetamine consumption provoke schizophrenia (Sagud *et al.*, 2006 and Smaha, 2014). It is the disastrous psychiatric disorder with a probable prevalence of 0.7-1.0% worldwide (Mcdonald and Schulz, 2009 and Du Toit and Manganyi, 2016). Peak periods of schizophrenia are late adolescence and early adulthood (Kapur, 2009). Percentage of schizophrenia to be diagnosed is 40% in men and 23% in women. Personality manifestations appears before the age of 19 (Cullen *et al.,* 2008). Factors involve in the development of schizophrenia are hereditary and ecological (Picchioni and Murray, 2007; Kapur, 2009).

Hypothalamus is the main precursor for the formation and then release of thyrotropin releasing hormone (TRH). Thyrotrope cells found in the anterior pituitary gland and stimulate the endocrine function of thyroid gland by the production of TSH. TSH having another name “thyrotropin” stimulates the thyroid gland to release thyroxine (T4) and triiodothyronine (T3). L-thyroxine (T4) and triiodo-L-thyronine (T3) are well-established to wield in energy metabolism (Magnus-levy, 1985 and Davis *et al.*, 2015). Prohormone thyroxine (T4) and the dynamic active metabolite 3,5,3-triiodothyronine (T3) taken by plasma or proteins of cerebrospinal fluid (CSF) (Cheng *et al.*, 2010) by using thyroid receptors network. In a fully developed brain, thyroid hormones become critical in growth. Various studies have mentioned the relation of thyroid hormones with schizophrenia that any deregulation in their performance attributes to schizophrenia (Santos *et al.*, 2012). Hypothyroidism might be found in those individuals that are under treatment with schizophrenia and treatment with antipsychotics.

The use of antipsychotic drugs causes a basal TSH concentration might be elevated (Martinos *et al.*, 1986). The association of TH and schizophrenia is relevant (Bunevicius, 2009 and Mebis and Ven den Berghe, 2009). Numerous groups have considered TH concentrations and further thyroid parameters in schizophrenic individuals. Approximately 49% of psychiatric individuals reported the important modification in more than one TH concentrations (Roca *et al.*, 1990). In addition, clinically it is reported that hyperthyroid patients might have marked psychosis (Marian *et al.*, 2009). In schizophrenic individuals, positive symptoms have seen and hypothyroid patients also exhibit behavioural changes like less inspiration and more depressive symptoms (Macdonald and Schulz, 2009). FT3 concentrations in schizophrenic male and female individuals were considerably low in comparison with normal individuals (Palha *et al.*, 2010).

Even though a complicated analysis, methodological boundaries and patients heterogeneity as well as tough multifarious history of antipsychotic medication, in general annotations point out that variability in the concentration of TSH may have taken as clinical. These annotations are related to the communication among pituitary-thyroid axis and some systems like dopaminergic, serotonergic, glutamatergic and GAB Aergic; they are mutually associated with myelination and proinflammatory reaction which are applicable in schizophrenic individuals etiology (Geyer and Vollenweider, 2008 and Potvin *et al.*, 2008).

The current study reveals the association of markers of medical importance that may be involved in the pathogenesis of schizophrenia in the group of given population and it rules out the significance of these factors in the case of schizophrenia. Thyroid gland which is the most essential gland involved in the metabolism of the body.

Thyroid may be affected in number of cases such as if one is exposed to any of the pathophysiological disorder such as cognitive impairment and malformation can lead to the abnormality of thyroid gland by increasing or decreasing the secretions of thyroid gland.

Aim of the current study was to rule out the role of extrapolative factors and their significance in the thyroid dysfunction within newly diagnosed schizophrenics.

Materials and methods

The present study was conducted to evaluate the role of thyroid in the development of schizophrenia. For this, we have taken 40 blood samples of schizophrenic females with age range of (21-67Yrs) and 20 of healthy controls from University of Lahore teaching hospital to assess the oxidative stress markers, Thyroid biomarkers and antioxidants.

The experimental protocols were approved by the Research Ethical Committee of The Institute of Molecular Biology and Biotechnology, The University of Lahore. The venous blood up to five ml was taken from every individual. Serum were separated after centrifugation within one hour of sample collection and preserved at -70°C till assayed.

Inclusion Criteria

The inclusion criteria were based on the following points: 1) Patients age 20-40Yrs, 2) Only schizophrenic females were taken in this research.

Exclusion Criteria

Patients with the history of any medication i.e., drugs, alcohol etc. or any other complication were excluded out of the current study

Biochemical Analysis

Subsequent parameters were carried out by the methods of: TNF-α, IL-6 and MMP-9 was carried out by their Bio Vendor Human ELIZA Kits. Thyroid hormones T3, throxine (T4), TSH and auto-antibodies TPOAb and TG Ab all were detected by using ELIZA Kits (Gen Way Biotech). MDA was evaluated calorimetrically by using the method of Ohkawa *et al.*, 1979.

The levels of GSH were estimated by following methods proposed by Moron *et al.*, 1979. Catalase levels was detected by using Aebi preparations (Aebi, 1984), GPx by using spectrophotometer with the help of buffer/enzyme reagent (Aebi and Bergmeyer, 1983), and SOD was find out by the method of Kakkar (Kakkar,1984). David and Richard, 1983 has proposed the method of detecting GRx and NO by (Moshage *et al.*, 1995).

Homocysteine is the amino acid which was determined by Amino-acid analyzer (Biochrom). Vit-E was estimated by Rusenberg method (Rusenberg, 1992), Vit-A (Rutkowski *et al.*, 2006) and Vit-C was detected by using the method of Lowry *et al.*, 1945. Detection of Vit-D was done by ELIZA Kit method of ALBCO.USA (Heaney, 2010).

Statistical Analysis

SPSS (V16) was used for the statistical analysis of data and it is written as mean ±S.D. To evaluate the outcome from schizophrenic females group and healthy control Independent T-test was used as a practical. Pearson correlation was applied to compare variables correlation with each other. $P<0.05$ is measured to be statistically significant.

Results

Demographic and physical characteristics of schizophrenia in table 1. Observe no difference in the SBP (137.22mmHg vs. 120.21mmHg) and DBP (83.57mmHg vs. 80.99mmHg) values.

The data is specified in table 02 illustrates antioxidant profile of schizophrenics versus control. The mean value of SOD reduced in female schizophrenics (0.19±0.0015U/ml vs. 0.625±0.0011 U/ml) as compared to healthy ones.

While, GSH (5.26±1.55µmol/L vs. 8.06±1.26µmol/L) and CAT (3.26±0.16U/L vs. 4.26±0.016U/L) also have the same consequences showing lower values in diseased females as compared to healthy controls. GP x (8.59±0.68µmol/L vs. 6.26±0.22µmol/L) and GR x (1.58±0.044µmol/L vs. 4.26±0.0015µmol/L) are in contrast to each other, with the reduction of GR x values in schizophrenics, the concentration of GP x becomes increased in schizophrenic females as compared to healthy controls.

Lower values of VIT-A (3.26±1.08nmol/L vs. 6.01±0.78nmol/L), VIT-C (0.462±0.023nmol/L vs. 0.65±0.016nmol/L), VIT-E (0.29±0.0026nmol/L vs. 0.498±0.001nmol/L), VIT-D (15.26±2.06pmol/L vs. 22.26±2.26pmol/L), VIT-B6 (51.26±5.99nmol/L vs. 77.26±6.25nmol/L), VIT-B9 (1.99±0.0016nmol/L vs. 3.26±0.0018nmol/L),

VIT-B12 (128.9±8.26pmol/L vs. 226.25±8.26pmol/L) in schizophrenic females as compared to healthy controls. T4 (18.26±4.06 pmol/L vs. 11.25±2.25 pmol/L) and TSH (5.29±0.96IU/L vs. 3.26± 0.82IU/L). values were find higher in schizophrenic females as compared to healthy ones.

When auto-antibodies display their values more.
Than normal, they ultimately imitate auto-immune thyroid disorder (AITDS) in schizophrenics TgAb (p=0.0139), TPOAb (p= 0.0110). Faraway, IL-6 (5.66±0.48pg/ml vs. 3.73±0.76pg/ml) and TNF-α (41.26±7.26pg/ml vs. 21.25±4.25pg/ml), MDA (1.69±0.015µmol/L vs. 0.951±0.001µmol/L) and NO (31.26±3.98µmol/L vs. 23.26±2.26µmol/L).

Showed high levels as compared to healthy controls. MMP-9 levels are found to be high in diseased as compared to controls (77.28±4.15ng/ml vs. 41.26±7.26 ng/ml). Homocysteine.

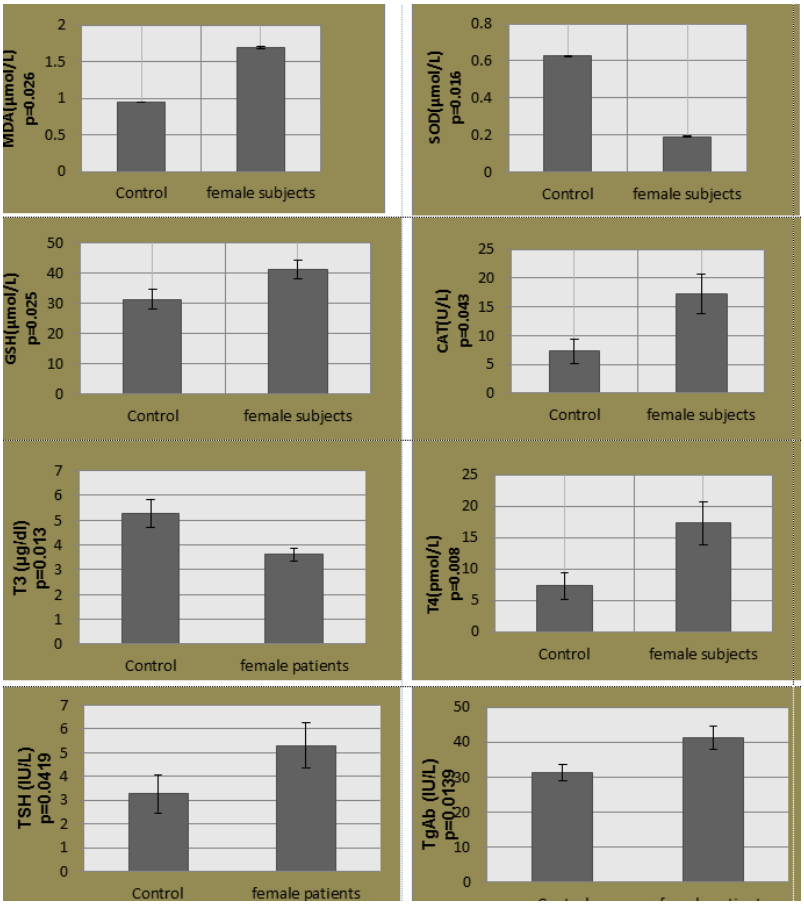
Which is an amino acid of Thiol group, showed increasing trend (17.26±3.42µmol/L vs. 7.26±2.15 µmol/L) in schizophrenic females which is compared with healthy controls.

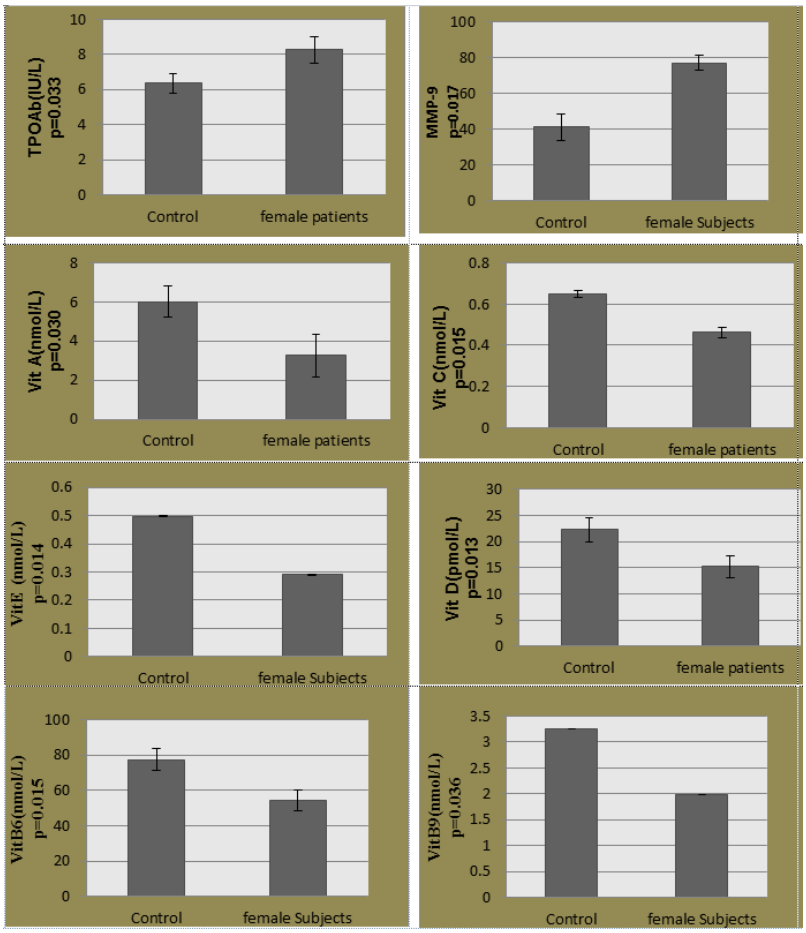
Table 1. Demographic/Physical Characteristics of Schizophrenics and Control.

Characteristics	Schizophrenics(n=40)	Control(n=20)
Age(Yrs)	21-67	15-70
Weight(Kg)	48-76	59-73
SBP(mmHg)	137.22	120.21
DBP(mmHg)	83.56	80.99

Table 2. Antioxidative profiles of schizophrenics versus controls.

	Control	Female subjects	P<(0.05)
MDA (µmol/L)	0.951±0.001	1.69±0.015	0.026
SOD(U/ml)	0.625±0.0011	0.19±0.0015	0.016
GSH(µmol/L)	8.06±1.26	5.26±1.55	0.025
CAT(U/L)	4.26±0.016	3.26±0.16	0.043
IL-6(pg/ml)	3.73±0.76	5.66±0.48	0.032
TNF-α(pg/ml)	21.25±4.25	41.26±7.26	0.0235
NO(µmol/L)	23.26±2.26	31.26±3.98	0.033
GPx(µmol/L)	6.26±0.22	8.59±0.68	0.000
GRx(µmol/L)	4.26±0.0015	1.58±0.044	0.041
Homocysteine(µmol/L)	7.26±2.15	17.26±3.41	0.011
Vit A(nmol/L)	6.01±0.78	3.26±1.08	0.030
Vit C(nmol/L)	0.65±0.016	0.462±0.023	0.015
Vit E(nmol/L)	0.498±0.001	0.29±0.0026	0.014
Vit D(pmol/L)	22.26±2.26	15.26±2.06	0.013
Vitamine-B6(nmol/L)	77.26±6.25	51.26±5.99	0.015
Vitamine- B9(nmol/L)	3.26±0.0018	1.99±0.0016	0.036
Vitamine-B12(pmol/L)	226.25±8.26	128.09±8.26	0.15
T4(pmol/L)	11.25±2.25	18.26±4.06	0.008
T3(µg/dl)	5.26±0.56	3.62±0.26	0.013
TSH(IU/L)	3.26±0.82	5.29±0.96	0.0419
TgAb(IU/L)	31.25±2.26	41.26±3.22	0.0139
TPOAb(IU/L)	6.35±0.56	8.25±0.78	0.0110
MMP-9 (ng/ml)	41.26±7.26	77.28±4.15	0.017


MDA(µmol/L) p=0.026
Control
female subjects
SOD(µmol/L) p=0.016
Control
female subjects
GSH(µmol/L) p=0.025
Control
female subjects
CAT(U/L) p=0.043
Control
female subjects
T3 (µg/dl) p=0.013
Control
female patients
T4(pmol/L) p=0.008
Control
female subjects
TSH (IU/L) p=0.0419
Control
female patients
TgAb (IU/L) p=0.0139


TPOAb(IU/L) p=0.033
Control
female patients
MMP-9 p=0.017
Control
female Subjects
Vit A(nmol/L) p=0.030
Control
female patients
Vit C(nmol/L) p=0.015
Control
female patients
VitE (nmol/L) p=0.014
Control
female Subjects
Vit D(pmol/L) p=0.013
Control
female patients
VitB6(nmol/L) p=0.015
Control
female Subjects
VitB9(nmol/L) p=0.036
Control
female Subjects

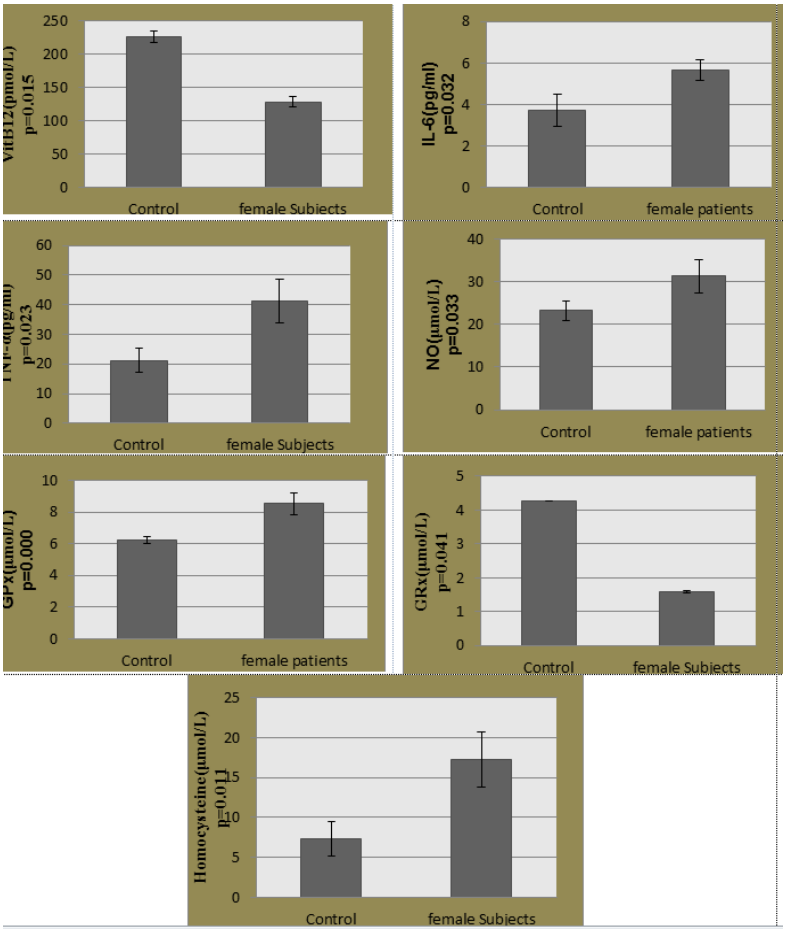


Fig. 1. Graphical representation of ant oxidative profiles of schizophrenics versus controls.

Discussion

Schizophrenia is a multifarious neuro-developmental and genetic problem. Thyroid hormones (T3, T4, TSH) are essential for the normal growth and maturity of brain. Any change in the concentration of thyroid hormones throughout different stages of growth may cause psychaitric symptoms. The communication of pituitary-thyroid-axis with schizophrenia genetically, with neurotransmitters (serotonin, GABA and glutamate) has highlighted. With increased deiiodenase-3 activity and local deprivation of T3, Schizophrenia-thyroid hormone inflammation interconnected in places of local inflammation (Boelen *et al.*, 2005). Thyroid hormones involvement as neurotransmitter is obvious in the Pathophysiology of schizophrenia when thyroid hormones (Dratman *et al.*, 1976). Thyroid gland secretes hormones T3, T4, TSH and play enormously to encourage astrocytes, intervenes cerebellar astrocytes, propagation of neuronal ions and the development of ECM molecules along with astrocytes (Trentin *et al.*, 2006; Mendes *et al.*, 2008). With the decarboxylation of T4 or rT3 (reverse T3) 3-iodothyronamine has produced (Scanlan *et al.*, 2009). Elevated levels of T3 receptors are found in amygdale and hippocampus. Thyroid hormones perform specific function in the development of central nervous system and continuation of homeostasis (Heinrich and Grahm, 2003). T3 levels are lower in schizophrenic patients as compared to healthy ones which are concurrent with the study of Palha *et al.* 2010. The description of each hormone in schizophrenia and thyroid hormone levels especially TT4 and FT4, triiodothyronine (TT3 and FT3) and thyroid stimulating hormone (TSH) has been presented (Rao, 1990).

Reactive oxygen species (ROS) increased when antioxidant unable to compensate the destructive effects of free radicals that causes waste of cell and its efficiency leading to oxidative stress (McGinnis, 2004).

Prooxidant ratio disturbs with the raised level of free radicals, which might be considered as essential factor in schizophrenia pathogenesis (Sarivastava, 2001; Akyol, 2004). With the decrease in GPx, SOD performance also goes down but lipid peroxidation is enhanced in RBC of schizophrenics (Sarivastava, 2001).

Some lipid peroxides are produced during lipid peroxidation process. Increasing ROS production and lipid peroxidation lead to the oxidative stress that causes mitochondrial derangement; therefore it is related to neuro-developmental disorder (Sogut, 2003). Certain verifications show linkage of oxidative stress and glutathione insufficiency in the pathogenesis of schizophrenic individuals (Gysin *et al.*, 2007). Various studies, for example, genetic and evaluation of glutathione levels of brain and on postmortem tissues have proposed that the disorder of GSH metabolism that involves in the development of schizophrenia (Do *et al.*, 2007; Yao *et al.*, 2006).

Levels of GSH decreased in CSF and in the prefrontal cortex of schizophrenics (Do *et al.*, 2000). Role of GSH as antioxidant helps to continue intracellular redox reactions and keep cells safe from oxidative stress (Soltaninassab *et al.*, 2000). However, the proposition of GSH assimilates different well known characteristics of schizophrenia (Do *et al.*, 2000). In present study, the levels of all enzymatic antioxidant sch as SOD, CAT, GSH and GR x decreases as compared to control group while GP x has been shown to be significantly increased due to the compensatory effects.

Vitamins are antioxidants (A, E and C) and their plasma levels decreases in schizophrenic subjects as compared to normal persons. In case of oxidative damage and worsening of neurological problems in schizophrenia, vitamins (E, C, beta carotene) are usually recommended in the management (Souza and Souza, 2003). In the skin, a cholesterol metabolite transforms into vitamin D3 (cholecalciferol) by the action of Ultraviolet-B (UVB) radiations. After hydroxylation, it is converted into 25-hydroxyvitamin and then to seco-steroid hormone 1, 25-dihydroxyvitamin D3 (1,25OHD) which is much active form. (1,25OHD) is the constituent of nuclear family which combine with vitamin D receptor. Vitamin D is regarded as neuro-steroid hormone and play crucial role in the growth of brain and its function. A ligand receptor complex of vit D arbitrates a large number of biological roles of Vit D that is instituted all over the body and CNS. Vit D has its biological importance, if any ways it is reduced or insufficient in individual leads to rigorous psychological sickness in which schizophrenia is more common. Quite a few aspects for the occurrence of schizophrenia including birth period, liberty and immigration, all associated with Vit D deficit (John *et al.*, 2017). Vitamin B complex (folate, cobalamin, pyridoxine and riboflavin) is essential in the metabolism of homocysteine. Higher homocysteine values illustrate an evidence of underlying role in the development of schizophrenia (Muntjewerff *et al.*, 2006). The homocysteine catabolism becomes more competent in the presence of folate, vitamin B12 and vitamin B6. First of all, trans-sulfuration process gives rise to cysteine, which then converts into glutathione by the action of enzymes cystathionine beta synthase (CBS) and cystathionase. Multiple reactions are involved under different enzymes in the transformation of homocysteine in to methionine consisting of Homocysteine methyltransferase, methionine synthase (MS), methionine synthase reductase (MTRR) and meth ylenetetrahydrofolate reductase (MTHFR) (Scott and Wier, 1998). This has been proved that sentimental derangements are associated with low levels of serum folate (Shorvon *et al.*, 1980). The current study expresses the affiliation of homocysteine concentration in schizophrenia and depression which is concurrent with the study of Levine *et al.* 2002. However, homocysteine has negative correlation with folate and vitaminB12 in schizophrenic patients (Bouaziz *et al.*, 2010).

NO is a signaling molecule derived from enzyme neuronal nitric oxide synthase (nNOS). nNOS is found in sub cellular region having C-terminal oxygenase domain that convert L-arginine in to L-citruline causing the production of NO, as it is present all over the brain in cerebellum, basal ganglia,

hippocampus, frontal cortex and some other regions (Blum-Degen *et al.*, 1999; Snyder and Ferris, 2000; Bernstein *et al.*, 2011). The formation of NO is increased in schizophrenic individuals as compared to healthy ones (Karson *et al.*, 1996).

These results supported the finding of present study that showed the elevated levels of nitric oxide in schizophrenic patients. During the breakdown of arachidonic acid and PUFAs, an end product produced known as Malondialdehyde (MDA). The current study showed that MDA levels are severely elevated in schizophrenic subjects than healthy ones because of enduring oxidative damage which is concurrent with the study of Dahake *et al.,* 2016. As the result of infections and further physiological affronts like tissue damage or stress, the primary defense system of innate immunity is inflammation (Gallin *et al.*, 1999). IL-1β, IL-6 and tumour necrosis factor (TNF)-α are the constituents of inflammatory cytokines, receiving inflammatory response through febrile reactions. Various factors are responsible for inflammation by the activation of phagocytes, increasing their vascular permeability and discharge of inflammatory mediators (Meyer, 2013).

Glutamate receptors are stimulated and controlled by Matrix metalloproteinase-9 (MMP-9) which is at synapse excited by glutamate and adapted the physiological synaptic plasticity. It is analyzed from the theory based on MMP-9 involves in the development of synaptic plasticity in schizophrenia. The performance and appearance of MMP-9 in brain constitutes zinc-containing proteases, but they are found immobile as pro-enzymes on the outer surface of proteolysis splitting site (Huntly, 2012). MMP-9 is the greatest exemplify MMP that is found in central nervous system. It is situated in mature brain and glial cells and articulate by neurons. To increase the neuronal performance, they are secreted under physiological and pathological state (Huntly, 2012). MMP-9 has its effects upon the areas of brain like hippocampal and prefrontal cortical (Okulski *et al.*, 2007; Wilczynski *et al.*, 2008). Prefrontal cortex derangement is an important pathological result (Bunney and Bunney, 2000).

However, some proteins have association in schizophrenia development along with MMP-9 or its proteins including brain-derived neurotrophic factor (BDNF) and N-methyl-D-aspartate (NMDA) receptors (Je *et al.*, 2012).

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Conflict of interest

Authors declare no conflict of interest.

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