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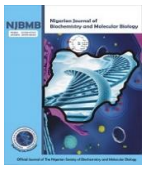

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Research Article

Evaluation of Thyroid Function Hormones Among Patients with Schizophrenia in a Neuropsychiatric Hospital in Nigeria: A Cross-Sectional Assessment

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ABSTRACT

Endocrine disorders including thyroid hormone deregulation has been associated with the pathogenesis of schizophrenia. The study evaluated the thyroid hormones of patients with schizophrenia receiving care at Federal Neuropsychiatric Hospital, Enugu. A total of 108 patients between the ages of 18 to 65 years were enrolled; 38 were antipsychotic naïve while 70 were on treatment with atypical antipsychotics. As control, 50 apparently healthy participants were included. Enzyme linked immunosorbent assay was used to evaluate the studied hormones. Among the patients on atypical antipsychotics, high concentrations of thyroid stimulating hormone (TSH) (4.82 ± 6.45 µIU/ml) and free triiodothyronine (FT3) (2.53 ± 0.40 pg/dL) were observed when compared to the concentrations among treatment naïve (TSH: 2.31 ± 2.46 µIU/ml and FT3: 2.36 ± 0.33 pg/dL) and the control (TSH: 1.88 ± 0.87 µIU/ml and FT3: 2.14 ± 0.76 pg/dL) participants. Patients with schizophrenia stand the risk of developing thyroid abnormalities which may be as a result of the disease associated stress or antipsychotic medication. Occasional examination of the thyroid function of persons with chronic schizophrenia and more research to unravel the relation between the thyroid and mental health are encouraged.

Keywords: *Thyroid stimulating hormone, free triiodothyronin (T3) and free thyroxine (T4), Schizophrenia*

INTRODUCTION

Schizophrenia is a chronic mental illness associated with significant health, social and financial burden (Oloniniyi *et al*., 2019). Persons with schizophrenia have a reduced life expectancy compared to the general population (Kahn *et al*., 2015). Non-psychiatric diseases such as diabetes mellitus, respiratory disorders and cardiovascular diseases are common among persons with severe mental illness including schizophrenia. These physical co-morbidities proceed unidentified in most instances owing to misinterpretation of symptoms, cognitive impairment, social isolation and poor social skills. Due to more attention given to the mental status and less to the physical health of the patients, psychiatrists often miss the presenting signs and symptoms of physical illnesses (De Hert *et al*., 2011; Telo *et al*., 2016).

The thyroid hormones triiodothyronin (T_3) and thyroxine (T_4) play essential roles in regulating the body metabolism, cellular growth and development, development and maturation processes of the brain. These hormones are also important for optimum functioning of

the matured brain (Alhilaly *et al*, 2018; Baksi and Pradhan, 2021). Functions of the thyroid hormones in maintaining the development and function of the brain include its involvement in myelination, cerebellum differentiation, axonal emigration, transportation of neurotransmitters such as dopamine (Lekurwale *et al* 2023). Alterations in the levels of thyroid hormones in the peripheral circulation may affect the cognitive ability of a person and has been associated with neuropsychiatric disorders (Alhilaly *et al*, 2018). Cognitive impairment, distress and sadness have been associated with hypothyroidism while agitations, psychosis have been described as manifestations of hyperthyroidism (Gyawali *et al*., 2015). Thyroid dysfunction refers to abnormal serum levels of TSH with normal or altered levels of the thyroid hormones (FT_3 and FT_4) (Saleh *et al*., 2017).

The thyroid hormones are synthesized in the thyroid gland from iodine and tyrosine. The thyroid gland secrets 93% of circulating T_4 and 7% of the circulating T_3. The more biologically active T_3 has a shorter half-life. The production and circulation of thyroid hormones are regulated by the thyroid stimulating hormone (TSH) secreted from the anterior pituitary gland. Alterations in the release or concentration of plasma TSH will in turn result in alterations of circulating T_4. The major biological function of T_4 is regulation of TSH release (Tost *et al*., 2019).

Schizophrenia and its management have been associated with various forms of endocrinopathies (Aina *et al*., 2004; Roh *et al*., 2007; Alhilaly *et al*, 2018). Thyroid hormones have been associated with the cognitive functioning of persons with schizophrenia (Zang and Li, 2020). Various researchers have recorded variable concentrations of the hormones of the pituitary-thyroid axis across various populations of persons with schizophrenia (Misiak *et al*., 2021; Kornetova *et al*., 2020; Zhang and Li, 2020). Alhillaly *et al* (2018) recorded high circulating levels of T_3 and T_4 with low TSH levels among patients with schizophrenia compared to the general population. This pattern of thyroid hormone in patients with schizophrenia may be associated with metabolic abnormalities and dietary pattern (Melamed, *et al*, 2020). Hypothyroidism which may be associated with exposure to antipsychotic medications have been observed among patients with schizophrenia (Saleem *et al*., 2015). The aetiology of thyroid dysfunction in persons with schizophrenia has been described to be multifactorial as there may be genetics contributions, following a family history of thyroid dysfunction or due to an interaction of the dopamine, serotonin, glutamate and GABA system with the pituitary-thyroid axis. The interaction of the pituitary-thyroid axis with myelin and pro-inflammatory response may also be associated with deregulation of the thyroid hormones of patients with schizophrenia (Samadi *et al*., 2020). Researchers have suggested that antipsychotic or neuroleptic medications may affect the metabolism of thyroid hormones through their effects on the expression of nuclear receptors and genes involved in the thyroid function (Bunevicius *et al*., 2014;Baksi and Pradhan, 2021).The ability of these psychotropic medications to prevent dopaminergic transmission may result in elevated TSH and a low T_3 and T_4 as has been reported among patients with schizophrenia (Chukwujekwu, 2019; Baksi and Pradhan, 2021). Given the importance of the thyroid function in the pathophysiology of psychiatric conditions and the possible influence of antipsychotics on the metabolism and synthesis of thyroid hormones, it is important to understand the thyroid function status of patients with severe mental illness. Studies on the thyroid hormone levels of patients with schizophrenia in Nigeria are limited. A better understanding of the thyroid function of persons with mental disorders will help inform proper planning management strategies. Therefore, the aim of this study was to assess the levels of TSH, FT_3 and FT_4 of antipsychotic naïve and antipsychotic experienced patients with schizophrenia enrolled in a tertiary hospital in south eastern part of Nigeria. We also compared the thyroid hormones of the different study group in order to assess any difference in the thyroid function of persons with schizophrenia and the healthy individuals.

MATERIALS AND METHODS

Study area and study population

The study was carried out in the Federal Neuropsychiatric Hospital Enugu, Nigeria. This is the only neuropsychiatric hospital in South-Eeastern part of Nigeria.

The study design was a cross sectional quasi experimental study design which employed a systematic sampling technique. The participants for this study were randomly recruited among the out-patients and in-patients of the hospital from April to August 2022. A total of 158 participants aged between 18 to 65 years were recruited for the study. The participants included 108 patients who were diagnosed with schizophrenia by consultant psychiatrists using the international classification of disease 11 (ICD-11) and 50 apparently healthy persons with no history of psychiatry condition or use of antipsychotic medications. The apparently healthy control participants were recruited from the hospital environs.

Selection criteria

Individuals who were diagnosed with Schizophrenia by consultant psychiatrists using the ICD-11 criteria and being managed at the Federal Neuropsychiatric Hospital, Enugu were included in the study. All participants included were between age 18-65years. The participants included were antipsychotic naïve patients and patients who had received treatment with atypical for at least six-month prior enrollment in the study.

We also included apparently healthy individuals with no history of mental illness or antipsychotic use as control participants.

We excluded persons with history of thyroid dysfunction prior to enrollment, patients who had lithium included in their treatment regimen or who were being managed with typical antipsychotic medications, pregnant women and people with chronic disorders.

Ethical clearance

Before the commencement of this study, ethical approval was sought and obtained from the Ethics and research Committee of Federal Neuropsychiatric Hospital, Enugu: reference number FHNE/TR/VOLII/03/023.

Informed consent

Written and oral consent was obtained from the study participants and/ or their care givers. The details of the study were explained to the participants and their care givers. They were assured of the high confidentiality with which any information obtained during the course of the research will be treated. Only consenting participants were enrolled in the study.

Specimen collection and preparation

From each of the consenting participants, 4 millilitres (4 mL) of venous blood was drawn aseptically via venipuncture. The blood samples were dispensed into a plain sample container and allowed to sit at room temperature for 30 minutes to allow clotting. The clotted sample was spun at 2000 rpm for 5minutes and aliquots of the serum introduced into plain sample containers. The serum was stored at -20^{0}C until the time of sample analysis. The storage period did not exceed one week.

The processed samples were transported in cold chain to the Clinical Laboratory Department of Alex Ekwueme University Teaching Hospital, Abakaliki where all the laboratory analyses were done.

Laboratory methods

The laboratory evaluations of the studied parameters were done using enzyme linked immunosorbent assay (ELISA) technique. All reagents used for the laboratory analysis were commercially purchased from Monobind Inc Lake Forest, CA 92630, USA. The manufacturer's instructions were strictly adhered to during the course of the study. The manufactures reference limits of the hormones were TSH (0.4-6.0µIU/mL), FT3(1.4-4.2pg/mL) and FT4(0.8-2.2ng/dL).

Statistical analysis

Data obtained were analyzed using Statistical Package for Social Sciences (SPSS) version 25 (Inc., Chicago, Illinois, USA). The results were expressed as mean ± standard deviation (S.D). Data obtained from this study were analyzed using analysis of variance (ANOVA) and Chi-square. p-value was significant at values <0.05.

RESULTS

Table 1 shows the characteristics of the three groups of the study population. Total number of patients with schizophrenia enrolled were 108, 38 (35.2%) were antipsychotic naïve while 70 (64.8%) were on atypical antipsychotic medication. More males had schizophrenia; 26 (68.4%) for the treatment naïve group and 40 (57.1%) for the patients on antipsychotic as compared to 26 (36.0%) who made up the control group. The mean age of the participants was 36.84 ± 13.38 years, 33.80 ± 6.24 years and 31.54 ± 10.54 years treatment naïve, atypical antipsychotics experienced and control participants respectively.

Table 1. Demographic Characteristics of the Patients in Three Study Arms

Variable	Naïve N (%) (mean±SD)	Atypical N (%) (mean±SD)	Control N (%) (mean±SD)	F/x^2(p-Value)
Gender				
Male	26(68.4)	40(57.1)	26 (36.0)	2.454[a] (0.293)
Female	12(31.5)	30(42.9)	24 (64.0)	
Age Group				
<35years	19 (50.0)	40(57.1)	36 (72.0)	4.825[a] (0.090)
⩾35years	19(50.0)	30(42.9)	14(28.0)	
Age(years)	(36.84 ± 13.38) *	(33.80 ± 6.24)	(31.54 ± 10.54)	3.198[b] (0.04)

SD, standard deviation; n, sample size; *. value is significantly different compared to control; [a], F-values; [b], x^2 value

Table 2 presents the mean ± standard deviation (SD) serum levels of thyroid stimulating hormones (TSH), free thyroxine (FT4) and free triiodothyronine (FT3) among antipsychotic –naïve, antipsychotic –experienced patients with schizophrenia and apparently healthy control participants. The TSH of the antipsychotic naïve patients (2.31±2.46µlU/mL) was significantly low compared to the values of the antipsychotic experienced patients (4.82±6.40µlU/mL), p =0.006 but not when compared to that of the control participants (1.88±0.87µlU/mL) p = 0.655. The TSH of the patients on antipsychotics was significantly high compared to control participants, p = 0.001. On comparing the FT3 levels, the participants on atypical antipsychotics had significantly high levels compared to control, p = 0.000. The fT4 levels of the control participants had no significant difference compared to that of the patients with schizophrenia and the control participants (p <0.05), however, the fT4 of the treatment naïve group had significantly high fT4 compared to that of the patients on atypical antipsychotics (p =0.012).

Table 3 presents the number of participants with serum levels of thyroid hormones levels within or outside the normal values. TSH level was high among 17 (22.9%) of antipsychotic –experienced and 2(5.3%) of –naïve participants. Low TSH was recorded among 4(10.5%) of the antipsychotic naïve patients. The TSH levels pattern was significantly different among the various study groups (p <0.001). The levels of fT4 were low among 2(5.3%) and 8(11.4%) antipsychotic -naïve and –experienced groups respectively. While 2(4.0%) of the control group had low fT4

levels. High concentration of fT4 was recorded among 8(21.1%). 2(2.9%) and 4(4.0%) of the treatment naïve, antipsychotic treated and the control group respectively. The pattern of fT4 among the groups varied significantly (p = 0.004). Values of the FT3 for all participants fell within the normal range (1.4 – 4.2 pg/dL), except for the control group where fT4 above the normal range was recorded in 1(2.0%) of the participants. The pattern of fT3 did not vary significantly across the groups p = 0.337.

Table 4 presents the gender comparison of TSH. fT3 and fT4 among the studied population.

The mean TSH of the male patients who were treatment naïve patients (2.645 ± 2.907 µIU/mL) was not significantly different when compared to the concentration of the female patients (1.585 ± 0.606 µIU/mL), p = 0.085. Similarly, the fT3 of the male treatment naïve patients (2.356 ± 0.331 pg/dL) and their fT4 (1.668 ± 0.726 ng/mL) were not significantly different compare to respective values of the females (2.378 ± 0.323 pg/dL) and (2.200 ± 1.854 ng/mL), p = 0.848 and 0.355 respectively.

The gender wise comparison of the antipsychotic patients similar to that of the naïve patients did not show statistical difference in the concentration of TSH (p = 0.309), fT3(p = 0.304) and fT4 (p = 0.571) when the concentrations of the male patients (5.496 ± 6.716 µIU/mL, 2.589 ± 0.324pg/dL and 1.384 ± 0.661ng/mL, respectively) compared to the concentration of the female group (3.914 ± 5.944 µIU/mL, 2.589 ± 0.324pg/dL and 1.466 ± 0.518ng/mL, respectively).

Table 2. Serum Levels of TSH, FT3 and FT4 of Patients in the Three Study Groups

Variable	Naïve (mean±SD)	Atypical (mean±SD)	Control (mean±SD)	F (P-Value)	Post hoc test p-value		
					Control vs naïve	Control vs atypical	Atypical vs naive
TSH (µlU/mL)	2.31 ± 2.46	4.82 ± 6.40	1.88 ± 0.87	7.508 (0.001)	0.655	0.001	0.006
FT3 (pg/dL)	2.36 ± 0.33	2.53 ± 0.40	2.14 ± 0.76	7.772 (0.001)	0.058	0.000	0.116
FT4 (ng/mL)	1.83 ± 1.20	1.42 ± 0.60	1.51 ± 0.71	3.299 (0.040)	0.068	0.529	0.012

TSH, thyroid stimulating hormone; FT3, Free throxine; FT4, tetraiodothyronine

Table 3. Distribution of Thyroid Hormones among Antipsychotic –Naïve and –Experienced Persons with Schizophrenia

Variable	Naïve N (%)	Atypical N (%)	Control N (%)	F/x^2(p-Value)
TSH				
Low (<0.4 µlU/mL)	4(10.5)	0(0.0)	0(0.0)	
Normal (0.4 –6.0µIU/mL)	32(84.2)	54 (77.1)	50(100.0)	29.448 (<0.001)
High (>6/0µIU/mL)	2(5.3)	16 (22.9)	0(0.0)	
FT3				
Low (<1.4 pg/dL)	0 (0.0)	0 (0.0)	0(0.0)	
Normal (1.4 – 4.2 pg/dL)	38(100.0)	70(100.0)	49(98.0)	2.174 (0.337)
High(>4.2 pg/dL)	0 (0.0)	0 (0.0)	1(2.0)	
FT4 Group				
Low (<0.7 ng/mL)	2 (5.3)	8(11.4)	2(4.0)	
Normal (0.7 – 2.2 ng/mL)	28 (73.7)	60(85.7)	46(92.0)	15.325(0.004)
High (>2.2 ng/mL)	8 (21.1)	2 (2.9)	2(4.0)	

Table 4. Gender Based Comparison of the Thyroid Hormone of the Studied Participants

Variables	Naive			Atypical		
	Male	Female	t(p-value)	Male	Female	t(p-value)
TSH (µIU/mL)	2.645 ± 2.907	1.585 ± 0.606	4.065(0.085)	5.496 ± 6.716	3.914 ± 5.944	0.690(0.309)
fT3 (pg/dL)	2.356 ± 0.331	2.378 ± 0.323	0.016(0.848)	2.488 ± 0.453	2.589 ± 0.324	2.795(0.304)
fT4 (ng/mL)	1.668 ± 0.726	2.200 ± 1.854	6.689(0.355)	1.384 ± 0.661	1.466 ± 0.518	0.387(0.571)

DISCUSSION

In this present study, 61.1% of the patients with schizophrenia recruited were males while 38.9% were females. A recent study in similar geographical area reported that the prevalence of schizophrenia was more among male correspondents (60%) compared to females (Chukwujekwu. 2019). The mean age of the patients with schizophrenia were 36.84±13.57years and 33.80±6.24years for the antipsychotic -experienced and –naïve patients with schizophrenia respectively (table 1). More respondents (81%) were below the age of 40years; for the participants with schizophrenia who had been treated with antipsychotic 57.1% were below 35years and 42.9% were above equal to or greater than 35years. Among the antipsychotic naïve participants, 50.0% were less than 35years. This is consistent with the reports of Balarabe *et al* (2022) and Lekurwale *et al*., (2023).

Schizophrenia has been described as a disease with early age of onset (Campbell *et al*., 2015).

The serum TSH concentration of patients on atypical antipsychotics was significantly high compared to antipsychotic naïve and the healthy control group p = 0.005 (table 2). Previous studies have reported high concentrations of TSH among antipsychotic experienced patients with schizophrenia (Misiak *et al*., 2021). Findings of our study also showed that 22.9% of patients on atypical antipsychotic medication had significantly high concentration of TSH while 5.3% of the antipsychotic naïve patients had high levels of TSH. TSH is the most important biomarker for the assessment of thyroid function (Haarburger, 2012; Li *et al*., 2014). High serum concentration of TSH in the presence of normal of low levels of T3 and/or T4 is an indicator of hypothyroidism (Koulouri and Gurnell, 2013). The findings of this study is similar to the report of Radhakrishnan *et al* (2013). Previous researchers have recorded the hypothyroidism potentials of atypical antipsychotic medication among schizophrenic patients (Thanoon *et al*., 2011; Haarburger 2012; Faisal *et al*., 2013). Faisal *et al* (2013) studied the serum levels of TSH, FT3 and FT4 among patients with schizophrenia before commencement of antipsychotic medications and 4 weeks and 8 weeks after initiation of treatment with atypical antipsychotics. Their findings recorded significant elevation of TSH after 8weeks of antipsychotic therapy. The effect of antipsychotics on TSH may be a reflection of the high percentage (22.9%) of patients on atypical antipsychotics with elevated TSH levels as recorded in the present study. Although the dysregulation of thyroid hormones have been implicated in psychiatric conditions (Ainapur *et al*., 2022), the use of antipsychotic medications may contribute to thyroid dysfunction by altering the expression of genes and nuclear receptors which participate in the functioning of the thyroid hormones (Bunevicius *et al* 2014). Many antipsychotic medications are capable of obstructing transmission of dopamine, resulting in high levels of TSH (Baksi and Pradhan, 2021). The record of high TSH among 22.9% of the antipsychotic experienced patients in the current study is different from 2.7% recorded by Ainapur *et al* (2022). The difference may be due to the difference in the characteristics of the study populations. Ainapur *et al* (2023) study included 15 persons with schizophrenia and was conducted among Indian population. The difference in the proportion of hypothyroidism among the population studied may be due difference variation in the demographic characteristics.

Findings of this research recorded low serum FT4 among 2(5.3%) of treatment naïve and 10(14.3%) of antipsychotic experienced patients. Though antipsychotic use may have inhibitory effects on the production and secretion of thyroid hormones (Bunevicius *et al*., 2014; Vargas *et al*., 2017), the exact cause of deregulated thyroid hormones among schizophrenic patients is not known. The cause of alterations in the thyroid hormone of antipsychotic naïve patients remains elusive. Abnormalities of thyroid hormone in treatment naïve group may be characterized by disturbed negative feedback between the pituitary TSH and the thyroid hormones as is common with non-thyroidal illness syndrome (Li *et al*., 2014).

We recorded high levels of FT4 among 26.3% and 8.6% of patients who were antipsychotic -naïve and -experienced respectively. Compared to the FT4 levels of antipsychotic experienced and control group, treatment naïve group had higher level of FT4, though the mean difference was not statistically significant (p = 0.141). High levels of serum FT4 have been associated with acute psychotic symptoms. High serum concentration of FT4 with relatively normal concentration of TSH has been reported in schizophrenic patients with acute psychotic episodes (Baumgartnar *et al*., 2000; Zhu *et al*., 2020). Similarly, increased levels of FT4 was recorded among patients with schizophrenia who had agitations compared to those without agitation and healthy control (Li *et al*., 2021). High concentrations of FT4 among these patients may be attributed to stress secondary to psychotic episode and not due to abnormality of the thyroid gland. Helal *et al* (2013) demonstrated that exposure of laboratory animals to stress led to overproduction of thyroid hormones and decreased production of TSH. Glucocorticoid has the potential of supressing the thyroid hormones. During stressful conditions, the secretion of glucocorticoid is up-regulated (Ranabir and Reetu, 2011; Xiang *et al*., 2019). We did not however consider the symptoms or clinical scoring of our study participants. The FT3 levels among all the study participants were observed to be normal and there was no significant difference in the mean when compared across the various study groups, p= 0.064 (table 2). Similar finding was recorded by Thanoon *et al* (2011) who recorded mean difference of T3 healthy control and patients with schizophrenia before and after treated to be not significantly different.

There was no gender associated difference in the studied hormones among the population studied. Little studies have assessed the gender associated difference in the thyroid levels of patients with schizophrenia. Similar to the present study, Huang *et al* (2023) reported no difference in the levels of thyroid hormones among male and female patients with depression disorder.

The interpretation of data generated from this study may not be generalized to all patients with schizophrenia as the research was conducted in a single centre. The inability to relate the studied hormones to the clinical scoring of the patients also limits the interpretation of the data from this study. The research area requires more investigation with consideration role of thyroid function hormones in monitoring symptoms of schizophrenia.

This study however observed strict control throughout the pre-analytical, analytical and post analytical phases of the study. The study design and data collection were carefully planned and implemented.

CONCLUSION

Thyroid hormone abnormalities are significant among persons with schizophrenia. The most significant abnormal hormone recorded by this study being TSH which was

significantly high among the study population. Though the exact mechanism is not very understood, it may be stress induced or related to the use of antipsychotic medications which interferes with dopamine transmission. It is recommended therefore the thyroid function of patients be assessed before initiation of antipsychotic treatment and periodically during the cause of management of the patients.

AUTHORS' CONTRIBUTIONS

Conceptualization: UAU and DOO. Methodology: UAU. Validation: MNI. Analysis and laboratory investigations: UAU, DOO and DAO. Resources: All authors. Data curation: MEK and UAU. Writing-original draft preparation: DOO. Writing review and editing: UAU and MEK. Supervision: MNI. Project administration: DOO. All authors have read and agreed to the published version of the manuscript.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest

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