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Dysregulation of Serum Serotonin–Melatonin Biosynthetic Pathway Markers in Patients with Obsessive-Compulsive Disorder: A Case-Control Study

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ABSTRACT

Objective: Obsessive-compulsive disorder (OCD) is a disabling neuropsychiatric disorder associated with disturbances in neurotransmitter systems. This study aimed to investigate serum levels of serotonin, melatonin, and selected enzymes involved in their biosynthetic pathway in patients with OCD, and to determine the correlations among these biochemical markers.

Methods and Materials: This case-control study included 50 patients with OCD diagnosed according to DSM-5 criteria and 15 age- and sex-matched healthy controls. Fasting venous blood samples were collected between 8:00 and 10:00 AM under controlled conditions. Serum concentrations of serotonin, melatonin, tryptophan hydroxylase-1 (TPH-1), aromatic amino acid decarboxylase (AADC), arylalkylamine N-acetyltransferase (AANAT), and acetylserotonin O-methyltransferase (ASMT) were measured using sandwich enzyme-linked immunosorbent assay (ELISA). Statistical analyses were conducted using SPSS version 26, with significance set at $p < 0.05$.

Findings: Serum levels of serotonin, melatonin, TPH-1, AANAT, and ASMT were significantly lower in patients with OCD than in healthy controls (all $p < 0.001$). AADC levels were also significantly reduced in the OCD group ($p < 0.05$). Furthermore, correlation analysis revealed significant positive associations among the studied biochemical parameters in patients with OCD, suggesting coordinated dysregulation within the serotonin–melatonin biosynthetic pathway.

Conclusion: Patients with OCD demonstrated significant reductions in serotonin, melatonin, and related biosynthetic enzymes. These findings support the possible involvement of altered serotonin–melatonin pathway activity in the pathophysiology of OCD and may provide a basis for future biomarker-oriented studies.

Keywords: Obsessive-compulsive disorder, serotonin, melatonin.

Introduction

Obsessive-compulsive disorder (OCD) is a neuropsychiatric condition marked by an overwhelming preoccupation with a specific demand, leading to abnormal compulsive behaviors exhibited by the individual. The triggers for obsessions and compulsive behaviors may vary among patients. The participants may incite an exacerbated state of irrationality; although they may acknowledge it, they are wholly incapable of controlling their desires (Goodman et al., 2021). Concerning the neuroanatomical and neuropathophysiological dimensions, research indicates that OCD primarily results from the dysfunction of the cortico-striato-thalamo-cortical (CSTC) loop, which plays a crucial role in regulating behavioral components of motivation, affectivity, sensory-emotional functions, and overall cognitive performance. Moreover, the connection between the cerebellum and the CSTC may be impaired, leading to spontaneous, uncontrolled activation of the circuitry during OCD-like behaviors (Stein et al., 2019).

Neurotransmitters are signaling molecules released by nerve cells to communicate. These neurotransmitters regulate mood, cognition, and behavior, and any imbalance among them can lead to psychological disorders (van Oudheusden et al., 2020).

Serotonin modulates physiological functions like appetite, mood, and sleep, as well as pathophysiological conditions such as depression, anxiety, schizophrenia, and obsessive-compulsive disorder (Pourhamzeh et al., 2022). Serotonin interacts with a variety of membrane receptors, including G protein-coupled receptors (GPCRs) (Bear et al., 2025). Numerous serotonergic medications, such as selective serotonin reuptake inhibitors (SSRIs), are available for the treatment of conditions believed to be associated with serotonin (Hatamnejad et al., 2022). They do not directly interact with serotonin receptors but inhibit serotonin reuptake into the synapse, thereby elevating extracellular synaptic serotonin concentration (Stahl, 2021). Consequently, the increased bioavailability of serotonin results in enhanced binding to serotonin receptors; however, it remains uncertain if this is the sole mechanism of action. Additionally, there are numerous adverse effects associated with the prescription of SSRIs.(De Deurwaerdère & Di Giovanni, 2020).

Melatonin is produced from tryptophan, and the first step in the process is the synthesis of serotonin. Tryptophan (Trp) in cells is first hydroxylated by tryptophan hydroxylase (TPH), and then it is decarboxylated by aromatic amino acid decarboxylase (AADC) to bring about the production of serotonin. Two different TPH enzymes, namely TPH1 and TPH2, are required for the production of serotonin in the brain and in the peripheral nervous system, respectively. Following this, the enzyme N-acetylserotonin transferase (AANAT), the primary rate-limiting enzyme, converts serotonin to N-acetylserotonin (Gutknecht et al. 2012). At the end of the day, acetylserotonin O-methyltransferase is responsible for the conversion of nitric oxide (Gutknecht et al. 2012) to melatonin (Keszthelyi et al., 2009; Lv et al., 2020; Michalowska et al., 2015).

The pineal gland primarily releases the hormone and neurotransmitter melatonin. The circadian rhythm and the sleep-wake cycle are controlled by it. Some obsessive-compulsive disorder (OCD) symptoms may be alleviated by using melatonin, a medication that improves sleep and regulates circadian rhythms (Atmaca et al., 2025; Shokrani et al., 2023). According to prior research, peripheral biomarkers may be indicative of psychiatric disorders and dysregulation of brain circuits(Skorobogatov et al., 2021). There is a limited number of studies investigating the levels of melatonin, serotonin, and associated enzymes in patients with Obsessive-Compulsive Disorder in Iraq. This study aims to assess the levels of serotonin, melatonin, tryptophan hydroxylase-1, N-acetylserotonin transferase, aromatic amino acid decarboxylase, and acetylserotonin O-methyltransferase in patients with OCD.

Methods and Materials

Study Design

Blood samples were collected from 50 patients with OCD, both male and female, aged 20-60 years, in the period from September / 2023 to June/ 2025, after their diagnosis by psychiatrists and neurologists at outpatient clinics in Anbar. An additional 15 blood samples were collected from healthy individuals (control group), both male and female, of the same age range as the patients. Patients with OCD were diagnosed based on DSM-5 criteria. The duration of illness ranged from

approximately 1 to 3 years. The control groups were matched to patients by sex and age.

The inclusion criteria were: age between 20 and 60 years, clinical diagnosis of OCD, and willingness to participate. The present study excluded other psychiatric and neurological disorders, use of medications affecting serotonin or melatonin levels , such as medications (SSRIs, antipsychotics, mood stabilizers, melatonin supplements), chronic systemic diseases, and pregnancy or lactation.

Sample collection

After overnight fasting, serum samples were collected between 8:00 and 10:00. Collection was performed in low light to prevent melatonin breakdown. After allowing the materials to coagulate for half an hour, they were centrifuged at 3000 rpm for 10 minutes. The serum samples were briefly stored at -80°C before testing. The sample was subjected to a single freeze-thaw cycle before measurement to ensure stability.

Assessment of biochemical parameters

Biochemical tests were performed to analyze the biosynthetic pathways of serotonin and melatonin using Sandwich- ELISA (Serotonin, melatonin, TPH-1, AANAT, AADC, ASMT) using Sunlong Biotech assays, with catalogue numbers (SL1570Hu, SL1169Hu, SL4129Hu, SL4634Hu, SL4635Hu, SL4080Hu)

Ethical Considerations

The Declaration of Helsinki lays out the ground rules for conducting this study ethically. Following the review and validation of the study protocol and subject information by the local ethics committee, the patient provided verbal and written informed consent before sample collection (recorded under number 6800, dated 29/5/2025).

Analysis

SPSS version 26 was used for the statistical analysis. The Shapiro-Wilk test was used to assess normality, and Levene's test to assess homogeneity of variance. We used one-way analysis of variance (ANOVA) to compare the patient and control groups. Mean ± standard deviation (SD) is the way the results are presented. The researchers used Pearson's correlation coefficient to examine the direction and magnitude of relationships among the biochemical indicators analyzed. The Bonferroni adjustment was used to control the false discovery rate across the six analytes. For statistical purposes, a p-value below 0.05 was considered significant.

Findings and Results

The present study demonstrated a significant decrease in the level of Serotonin, Melatonin, trypyophan hydroxylase, acetyl serotonin o-methyl transferase, N-acetyl serotonin transferase in patient with OCD (62.30 ± 8.33, 63.88 ± 10.18, 18.84 ± 3.33, 65.30 ± 7.68, 4.60 ± 0.82) as compared with control groups (81.35 ± 16.81, 82.48 ± 9.34, 27.03 ± 3.86, 81.34 ± 16.81) at p-value <0.001. In addition, the level of Aromatic amino acid decarboxylase in OCD patients was lower than in controls (5.36 ± 1.62 vs. 6.73 ± 1.32), with a p-value <0.05. As shown in Table 1 and Figures 1, 2, 3, 4, 5, 6.

Table 1

Concentrations of enzymes in the serotonin and melatonin biosynthetic pathways for patients and the control group.

Variable	GROUP		
	patient (N=50)	control (N=15)	P.V
	Mean ± SD	Mean ± SD	
Serotonin (ng/ml)	62.30 ± 8.33	81.35 ± 16.81	<0.001
Melatonin (pg/ml)	63.88 ± 10.18	82.48 ± 9.34	<0.001
trypyophan hydroxylase-1 (TPH-1) (ng/ml)	18.84 ± 3.33	27.03 ± 3.86	<0.001
acetyl serotonin o-methyl transferase (ASMT)(pg/ml)	65.30 ± 7.68	81.34 ± 16.81	<0.001
Aromatic amino acid decarboxylase(AADC) (ng/ml)	5.36 ± 1.62	6.73 ± 1.32	<0.05
N-acetyl serotonin transferase(AANAT) (ng/ml)	4.60 ± 0.82	7.13 ± 1.08	<0.001

This study found that there was a strong positive correlation between parameters in patients with OCD, as shown in Table 2.

Table 2

Correlation between parameters in patients with OCD.

		ASMT	TPH-1	Melatonin	AANAT	Serotonin	AADC
ASMT	r	1	0.573**	0.743**	0.768**	0.989**	0.697**
	P		<0.05	<0.05	<0.05	<0.05	<0.05
TPH-1	r	0.573**	1	0.793**	0.721**	0.630**	0.775**
	P	<0.05		<0.05	<0.05	<0.05	<0.05
Melatonin	r	0.743**	0.793**	1	0.880**	0.777**	0.817**
	P	<0.05	<0.05		<0.05	<0.05	<0.05
AANAT	r	0.768**	0.721**	0.880**	1	0.805**	0.865**
	P	<0.05	<0.05	<0.05		<0.05	<0.05
Serotonin	r	0.989**	0.630**	0.777**	0.805**	1	0.748**
	P	<0.05	<0.05	<0.05	<0.05		<0.05
AADC	R	0.697**	0.775**	0.817**	0.865**	0.748**	1
	P	<0.05	<0.05	<0.05	<0.05	<0.05	

****. Correlation is significant at the 0.01 level (2-tailed).**
P: p-value

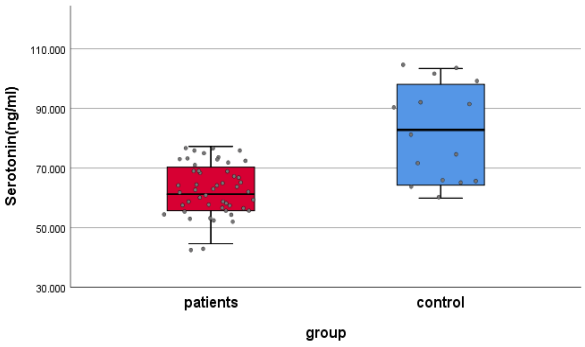

Figure 1

The average concentration of the Serotonin enzyme

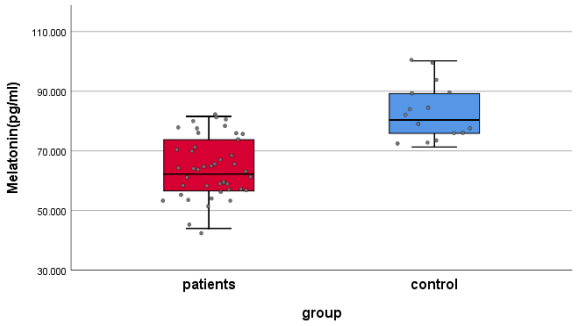

Figure 2

The average concentration of the Melatonin enzyme

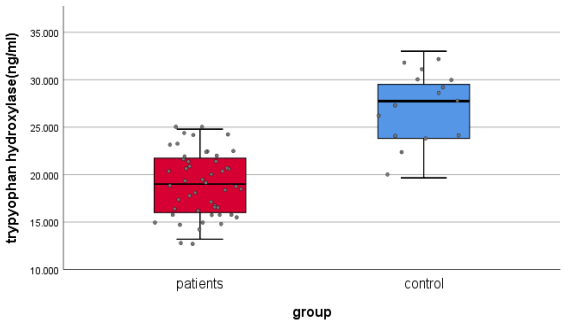

Figure 3

The average concentration of the tryptophan hydroxylase enzyme

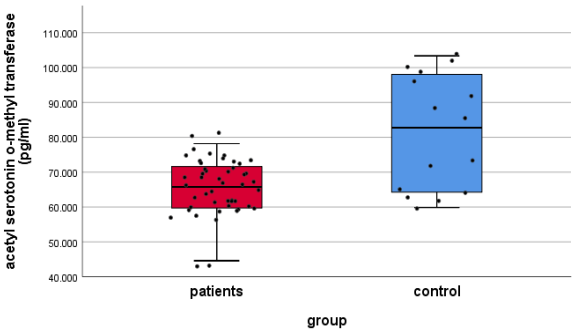

Figure 4

The average concentration of acetylserotonin O-methyltransferase

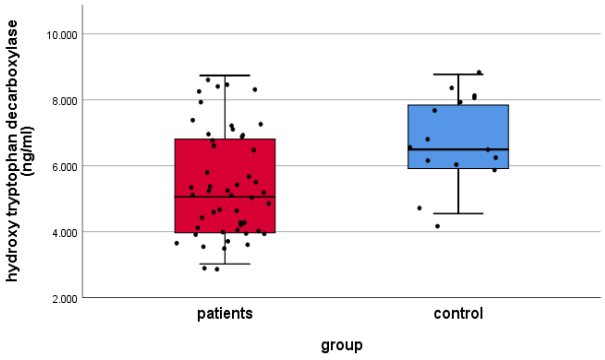

Figure 5

The average concentration of the hydroxy-tryptophan decarboxylase enzyme

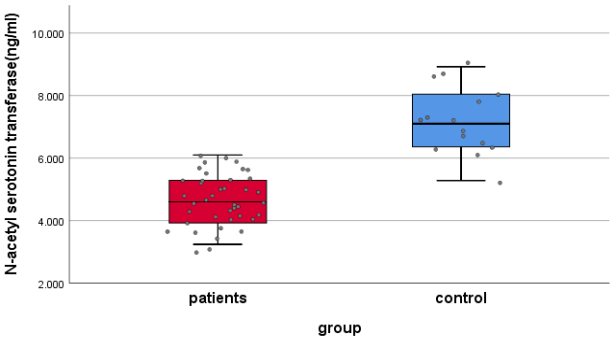

Figure 6

The average N-acetylserotonin transferase concentration

Discussion and Conclusion

Obsessive-Compulsive Disorder (OCD) is a neuropsychiatric condition marked by intrusive thoughts and compulsive actions, which severely diminish the quality of life for patients and impose substantial financial and emotional strains on family and society (Wang et al., 2025)

Serotonin may play a role in the pathophysiology of obsessive-compulsive disorder (OCD) because of the anti-obsessional effect of SSRIs (Van Dijk et al., 2008). The present study showed a decreased level of serotonin and melatonin in OCD patients. This result agrees with (Catapano et al., 1992), who showed a decreased level of melatonin in OCD patients. The impairment of melatonin release in OCD patients mostly involves a diminished increase typically observed in darkness, potentially indicating a decreased sensitivity of pineal adrenergic receptors. The release of melatonin by the pineal gland is primarily regulated by β-adrenergic receptors and, to a lesser extent, by α-adrenergic receptors situated on the membranes of pinealocytes (Reiter, 1991). Consequently, an elevated noradrenergic tone in individuals with OCD may have prompted a downregulation of postsynaptic noradrenergic receptors, resulting in less melatonin secretion from the pineal gland. Conversely, the diminished melatonin secretion from the pineal gland in our patients may indicate a specific impairment in noradrenergic transmission along the sympathetic pathway innervating the gland (Jain et al., 2024).

Serotonin levels and signaling are modulated by various mechanisms, including the serotonin transporter and essential biosynthetic enzymes such as tryptophan hydroxylase (TPH) (Nakamura & Hasegawa, 2007). The current investigation revealed a reduced quantity of tryptophan hydroxylase in persons with OCD. This work may pertain to the function of tryptophan hydroxylase in serotonergic biosynthesis. TPH primarily affected serotonin production and modified serotonergic neurotransmission (Gutknecht et al., 2012).

Acetyl serotonin-O-methyltransferase (ASMT) is a crucial enzyme in melatonin production, and its activity is unaffected by diurnal rhythms. Furthermore, it is situated in the final stage of melatonin production and may be linked to conditions such as depression and mood disorders (Kurtulus Dereli et al., 2018). The current investigation revealed a reduced level of ASMT in patients with OCD. This suggests a correlation between decreased melatonin levels and the disruption of circadian rhythms, as well as the brain regulation of anxiety and obsessive thoughts.

Hydroxytryptophan decarboxylase, also known as Aromatic amino acid decarboxylase (AADC) or DOPA decarboxylase, is responsible for converting 5-HTP to serotonin (5-HT). Therefore, a decrease in this enzyme's activity may reduce serotonin synthesis rates in the central nervous system. It is consistent with Fatima-Shad (2024), who highlighted the contribution of the AADC enzyme to the biosynthesis of neurotransmitters such as dopamine and serotonin, and that its deficiency causes severe neurological disorders.

The present study demonstrated decreases in serotonin, melatonin, tryptophan hydroxylase-1, N-acetylserotonin transferase, Aromatic amino acid decarboxylase, and acetylserotonin O-methyltransferase in patients with OCD. In addition, a strong correlation between parameters in OCD patients. Limitation: The limitation is that patients were not classified according

to OCD severity, and the duration or onset of the disorder was not systematically recorded. In addition, measurements were conducted in peripheral blood, which may not completely represent CNS neurotransmission.

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Declaration of Interest

The authors of this article declared no conflict of interest.

Ethical Considerations

The study protocol adhered to the principles outlined in the Declaration of Helsinki, which provides guidelines for ethical research involving human participants. Ethical considerations in this study were that participation was entirely optional.

Transparency of Data

In accordance with the principles of transparency and open research, we declare that all data and materials used in this study are available upon request.

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Authors' Contributions

All authors equally contribute to this study.

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