

RESEARCH ARTICLE

Could Transforming Growth Factor Beta and Target MicroRNA Dysregulation Serve as Biomarkers of Symptom Severity in Patients With Obsessive-Compulsive Disorder?

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ABSTRACT

Introduction: This study investigated the regulation of miRNA-132-3p on TGF- β levels and its association with OCD severity. We hypothesized that miRNA-132-3p and TGF- β influence OCD aetiology and severity, with their levels correlating with disease severity.

Methods: The study included 48 OCD patients diagnosed via SCID-5-CV per DSM-V and 48 matched healthy controls. Blood samples were analysed for miRNA-132-3p and TGF- β using RT-PCR and ELISA. Participants completed Y-BOCS, symptom list, HAMA, HAM-D, consent and sociodemographic forms.

Results: OCD patients had significantly lower TGF- β levels ($p=0.008$), negatively correlating with Y-BOCS scores ($r_s=-0.220$, $p=0.045$) and disease duration ($r_s=-0.473$, $p=0.002$). miRNA-132-3p levels were 1.92 times higher in OCD patients ($p=0.003$), positively correlating with Y-BOCS scores ($r_s=0.208$, $p=0.045$).

Conclusions: Altered TGF- β and miRNA-132-3p levels may contribute to OCD pathophysiology by affecting BDNF regulation, inflammatory responses (Th1/Th2, Th17/Treg balance) and synaptic plasticity-related genes.

1 | Introduction

Obsessive-compulsive disorder (OCD) is a psychiatric condition characterized by involuntary, repetitive obsessions and rigid, ritualistic compulsions that consume time (Goodman et al. 2014). Growing interest in psychoneuroimmunology research suggests that cytokine imbalances from Th1/Th2 cells play a role in various psychiatric disorders, including OCD (Furtado and Katzman 2015).

The TGF- β family is a multifunctional cytokine group involved in the development and pathogenesis of fibrotic, cardiovascular and oncological diseases (Suzuki 2018). Growing evidence highlights its role in neuroadaptations, drawing attention to TGF- β signalling in maladaptive cellular and behavioural plasticity in neuropsychiatric disorders (Mitra et al. 2022). microRNAs (miRNAs), ~22-nucleotide regulatory RNAs, modulate post-transcriptional gene expression (Chen et al. 2019). Circulating miRNAs are increasingly recognized for their role in the aetiology and

pathophysiology of psychiatric and neurodegenerative disorders, as well as their potential in advancing diagnostics and therapeutics (van den Berg et al. 2020). Notably, miR-132-3p regulates key neuronal plasticity pathways, including LTP, DNA methylation, CREB, NMDAR and BDNF signaling, underscoring its pivotal role in CNS pathophysiology (Qian et al. 2017).

Considering the role of miR-132-3p in neuronal differentiation, synaptic plasticity and neuroinflammation and the regulatory function of TGF- β in cell growth, differentiation and immune responses, it is vital to investigate their interactions in neuropsychiatric disorders including OCD. This study aims to elucidate the regulatory effect of miR-132-3p on TGF- β levels and its relationship with OCD severity. We hypothesize that miR-132-3p and TGF- β significantly contribute to the aetiology and clinical severity of OCD, and that serum TGF- β and miR-132-3p levels differ in OCD patients compared to healthy controls. In addition, a significant correlation is predicted between miR-132-3p levels and TGF- β levels with disease severity.

2 | Materials and Methods

This study compared miR-132-3p and TGF- β levels in 48 patients diagnosed with OCD using SCID-5-CV and 48 healthy controls. Conducted in psychiatry, medical biochemistry and medical genetics laboratories, the study received ethical approval from the relevant institutional ethics committee. All participants were thoroughly informed about the procedures and provided written consent. All controls underwent structured psychiatric interviews to rule out any psychiatric diagnoses, ensuring comparability with the patient group.

2.1 | Clinical Assessment

The Sociodemographic Data Form, Yale-Brown Obsessive-Compulsive Scale and Symptom Checklist (Goodman et al. 1989), Hamilton Depression Scale (Hamilton 1960) and Hamilton Anxiety Scale (Hamilton 1959) were administered to all participants. Individuals were excluded if they had intellectual disability, pregnancy, severe head trauma, substance use disorder, psychotic disorders, bipolar disorder, moderate-to-severe depression or anxiety, neurological, oncological or autoimmune diseases, severe endocrinopathy, active infections or immunosuppressant use.

2.2 | Collection and Evaluation of Biological Material

All blood samples were collected in the morning under fasting conditions to minimize variability related to circadian rhythms and food intake.

2.2.1 | Measurement of microRNA Expression Levels

miRNAs were isolated from EDTA-anticoagulated venous blood of 48 OCD patients and 48 healthy controls using the SanPrep Column MicroRNA Mini-Prep Kit (Catalogue No.: SK8811) following the manufacturer's protocol. Complementary DNA synthesis was performed with the miRNA All-In-One cDNA Synthesis

Kit (Catalogue No.: G898) in two steps. Real-time PCR analysis was conducted using the Qiagen Rotor-Gene Q and BlasTaq 2X qPCR MasterMix (Catalogue No.: G891, G892). Samples were analysed in triplicate with U6-2 (Catalogue No.: MPH00001) and hsa-miRNA-132-3p (Catalogue No.: MPH02174). Gene expression was quantified using Rotor-Gene Q Software (Version 2.3.4) with ACTB as a reference gene. Relative miRNA expression was calculated using the $2^{-\Delta\Delta C_t}$ method.

2.2.2 | TGF-Beta (ng/mL) Level Measurement

Blood samples were collected from OCD patients and healthy controls in EDTA tubes, centrifuged at 1500 rcf for 10 min to separate the supernatant. Plasma was stored in capped Eppendorfs at -40°C until analysis. Prior to measurement, samples were thawed at $+4^{\circ}\text{C}$ and room temperature. TGF- β levels were measured using the Human TGF- β ELISA kit (Catalogue No.: 201-12-5480, SunRed Biotechnology, China) according to the manufacturer's instructions. The kit's measurement range is 0.2–60 ng/mL, with a sensitivity of 0.198 ng/mL, within-run CV < 10% and between-run CV < 12%.

2.3 | Statistical Analysis

Data were analysed using SPSS 25.0 (IBM, USA). Descriptive statistics are presented as number (N), percentage (%), standard deviation (SD), median (M) and percentiles (P). For non-normally distributed data, median values and 25th–75th percentiles were reported; normally distributed data are presented as mean and SD. Independent samples *t*-test was used for normally distributed data, while the Mann–Whitney *U* test was applied for non-normally distributed data. Spearman and Pearson correlation coefficients were used to assess relationships between quantitative variables, depending on the distribution. The chi-square test was used for categorical data. ROC analysis evaluated the diagnostic performance of TGF- β and miR-132-3p, with a 95% confidence interval and significance set at $p < 0.05$. Fold changes were calculated using $2^{-\Delta\Delta C_t}$ ratios based on median values.

3 | Results

The study included 48 OCD patients and 48 age- and gender-matched healthy controls. The mean age of OCD patients was 35.2 ± 12.3 years, while the mean age of controls was 37.0 ± 12.0 years. Among participants, 33 (68.8%) were female, and 15 (31.3%) were male. No significant differences were found in age ($p = 0.467$) or gender ($p = 1.0$) between the groups.

3.1 | Evaluation of TGF- β (ng/mL) Values and miRNA-132-3p Expression Rates

The median TGF- β levels in OCD patients (25th–75th percentiles) were 9.69 (5.82–17.13) ng/mL, while in healthy controls, they were 14.83 (8.43–32.22) ng/mL. A significant difference was observed between the groups ($p = 0.008$). The median miRNA-132-3p expression in OCD patients (25th–75th percentiles) was 0.48 (0.26–0.82), compared to 0.25 (0.13–0.51) in controls, with

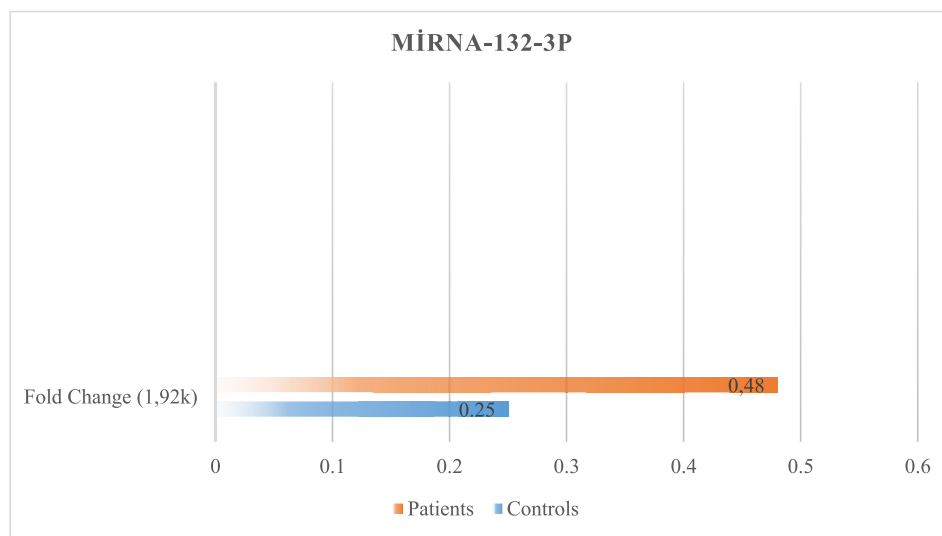


FIGURE 1 | miRNA-132-3p fold change rates of participants.

TABLE 1 | Clinical characteristics of participants.

		HAMA	p
Controls	Median (25th–75th percentiles)	1.00 (0–2.00)	<0.001
Patients	Median (25th–75th percentiles)	3.00 (2.00–5.00)	
		HAMD	p
Controls	Median (25th–75th percentiles)	1.00 (0–2.00)	<0.001
Patients	Median (25th–75th percentiles)	3.00 (0.25–4.00)	
		Y-BOCS obsession	
Patients	Mean ± SD	11.38 ± 3.75	
		Y-BOCS compulsion	
	Mean ± SD	10.98 ± 4.21	
		Y-BOCS total	
	Mean ± SD	22.35 ± 7.83	

a significant difference between groups ($p=0.003$). The fold change in miRNA-132-3p was 1.92 times higher in OCD patients than in controls (Figure 1).

3.2 | Correlation of TGF-β (ng/mL) Values and miRNA-132-3p Expression Rates With Clinical Characteristics of Participants

Spearman correlation analysis of TGF-β (ng/mL) values and Y-BOCS obsession scores showed no significant correlation ($r_s=-0.213$, $p=0.051$). However, significant negative

correlations were found between TGF-β levels and Y-BOCS compulsion scores ($r_s=-0.247$, $p=0.023$) and total scores ($r_s=-0.220$, $p=0.045$). A significant negative correlation was also observed between TGF-β and HAMA scores ($r_s=-0.227$, $p=0.038$), but no significant correlation was found with HAMD scores ($r_s=-0.184$, $p=0.095$). TGF-β levels did not correlate with participants' ages ($r_s=-0.124$, $p=0.261$), but a significant negative correlation was found with disease duration in OCD patients ($r_s=-0.473$, $p=0.002$) (Tables 1 and 2).

Regarding miRNA-132-3p expression, no significant correlation was found with Y-BOCS obsession scores ($r_s=-0.201$, $p=0.053$). However, significant positive correlations were observed with Y-BOCS compulsion ($r_s=0.235$, $p=0.023$) and total scores ($r_s=0.208$, $p=0.045$). miRNA-132-3p expression also showed significant correlations with HAMA ($r_s=0.243$, $p=0.019$) and HAMD ($r_s=0.250$, $p=0.016$) scores. No significant correlation was found between miRNA-132-3p expression and age ($r_s=-0.179$, $p=0.086$) or disease duration ($r_s=-0.162$, $p=0.278$) (Table 3). No significant correlation was found between TGF-β levels and miRNA-132-3p expression rates ($r_s=-0.091$, $p=0.414$).

3.3 | ROC Curve Evaluation of TGF-β (ng/mL) and miRNA-132-3p Levels

ROC curve analysis determined the cut-off values for TGF-β and miR-132-3p based on statistically significant differences between patient and control groups. For TGF-β, a sensitivity of 71.4% and specificity of 59.5% were found at a threshold of 10.44 ng/mL. For miR-132-3p, sensitivity was 61.7% and specificity was 67.4% at a cut-off of 0.39.

4 | Discussion

Studies indicate that genetic load, alongside familial factors, is higher in certain OCD subtypes with distinct symptom characteristics (Wang et al. 2024). Given the role of neuroimmunological factors in neuroplasticity and neurogenesis, along with

TABLE 2 | Correlation of TGF- β (ng/mL) with scale scores, disease duration and age of participants.

Spearman correlation		TGF-B (ng/mL)
HAMA scores	r_s	-0.227
	p	0.038
HAMD scores	r_s	-0.184
	p	0.095
Y-BOCS obsession scores	r_s	-0.213
	p	0.051
Y-BOCS compulsion scores	r_s	-0.247
	p	0.023
Y-BOCS total scores	r_s	-0.220
	p	0.045
Age	r_s	-0.124
	p	0.261
Duration of illness	r_s	-0.473
	p	0.002

Note: r_s : Spearman correlation coefficient.

TABLE 3 | Correlation of miRNA-132-3p expression rates with scale scores, disease duration and age of participants.

Spearman correlation		miR 132-3p
HAMA scores	r_s	0.243
	p	0.019
HAMD scores	r_s	0.250
	p	0.016
Y-BOCS obsession scores	r_s	0.201
	p	0.053
Y-BOCS compulsion scores	r_s	0.235
	p	0.023
Y-BOCS total scores	r_s	0.208
	p	0.045
Age	r_s	-0.179
	p	0.086
Duration of illness	r_s	-0.162
	p	0.278

Note: r_s : Spearman correlation coefficient.

the genetic basis of OCD (Brum et al. 2021), our study aimed to investigate miRNA-132-3p, which negatively regulates gene expression, and TGF- β , involved in immune and inflammatory regulation in the CNS. We also explored the relationship between disease severity and miRNA-132-3p and TGF- β levels in OCD patients compared to healthy controls. In this study, we found that OCD patients exhibit lower TGF- β levels and higher

miRNA-132-3p expression, with TGF- β negatively correlating and miRNA-132-3p positively correlating with symptom severity.

Existing literature highlights the role of TGF- β in the pathogenesis and treatment of neuropsychiatric disorders (Derynck and Akhurst 2007; Hiew et al. 2021; Liu 2006). Cytokine levels differ in these diseases compared to healthy controls, and their balance shifts before and after treatment (Sutcgil et al. 2007). To our knowledge, no studies have examined TGF- β levels in adult OCD patients, making our study the first to do so. We found significantly lower serum TGF- β levels in OCD patients compared to healthy controls. Brain-derived neurotrophic factor (BDNF), a neurotrophin, is crucial for synaptic plasticity, neurotransmitter production and long-term learning and memory (Carter et al. 2002; Aas et al. 2019). BDNF, stored in platelets and circulating in plasma, shows a strong correlation with TGF- β 1 in healthy individuals (Lommatzsch et al. 2005), suggesting a dual relationship between TGF- β and BDNF regulation. Our findings of lower TGF- β levels in OCD patients imply that BDNF levels may also be reduced. Additionally, a significant negative correlation was observed between TGF- β levels, Y-BOCS compulsion and total scores and disease duration, indicating a link between TGF- β and disease severity.

TGF- β 1 plays a key role in inflammation by stimulating regulatory T cells (Tregs) with anti-inflammatory effects and Th17 cells with pro-inflammatory effects (Takatori et al. 2008). IL-17 produced by Th17 cells disrupts the blood-brain barrier and promotes CNS inflammation (Kebir et al. 2007). In paediatric OCD patients, elevated IL-17A serum levels were found, though no correlation with symptom severity or duration was observed (Simsek et al. 2016). Another study found higher Th17 cell levels and lower Treg cell percentages in paediatric OCD patients, with a positive correlation between Th17 cells and OCD severity and a negative correlation between Treg cells and disease duration (Rodríguez et al. 2019). These findings suggest TGF- β 's role in maintaining the Th17/Treg balance, and, consistent with our results, alterations in TGF- β levels may contribute to OCD's aetiology and severity. The disrupted cytokine balance in OCD patients, indicated by lower TGF- β levels, suggests that TGF- β could serve as a biomarker for diagnosing OCD and assessing disease severity and treatment response.

Studies have suggested that the interaction between TGF- β and miRNAs influences cell behaviour and disease pathogenesis, particularly in oncology (Abukiwan et al. 2019). TGF- β is induced by miRNA-132 activation in non-small cell lung cancer (Zhang et al. 2016), and miRNA-132 functions as a tumour suppressor in bladder and cervical cancers by targeting Smad2 (Wei and Lv 2019). A reciprocal regulatory relationship between TGF- β signaling and miRNA-132 has been proposed, as both are involved in the modulation of inflammatory responses, cytokine release and immune regulation (Guo et al. 2016). However, to date, this potential interplay has not been systematically investigated in neuropsychiatric disorders, including OCD. In our study, although we did not observe a significant correlation between miRNA-132 and TGF- β levels, this finding may reflect complex, nonlinear regulatory mechanisms involving intermediate molecular pathways that simple correlation analyses may fail to detect. Such complexity may arise

from feedback mechanisms in which TGF- β signaling regulates miRNA expression while being influenced by miRNAs in return, forming dynamic molecular loops that maintain cellular balance. In addition, context-dependent transcriptional control shaped by factors such as inflammation, stress or neuronal activity can modulate the interaction between miRNA-132 and TGF- β under different physiological states. Finally, cell-type-specific signaling within neurons, glial cells, and immune cells may lead to diverse expression patterns and functional outcomes, making their relationship inherently nonlinear and difficult to capture through simple correlation analyses (Gill and Gomer 2025; Yan et al. 2018). Future studies employing larger sample sizes, longitudinal designs and integrative molecular analyses (e.g., transcriptomic or pathway-based approaches) could help clarify the dynamic and possibly bidirectional role of miRNA-132 in TGF- β signaling and its relevance to OCD pathophysiology.

The relationship between OCD and BDNF levels, along with the interaction between miRNA-132 and BDNF, suggests that miRNA-132 may contribute to the aetiology, symptom severity, and treatment resistance of OCD. Only one study, by Yue et al., has assessed miRNA-132 expression in OCD patients, finding higher levels in patients compared to controls, though no correlation was observed with clinical severity (disease duration, HAMA, HAMD and Y-BOCS) (Yue et al. 2020). In our study, consistent with Yue et al., higher miRNA-132-3p levels were observed in OCD patients, but these levels were downregulated (below 1) in both groups. A significant correlation was found between miRNA-132-3p and Y-BOCS compulsion and total scores, marking the first report of miRNA-132-3p's link to OCD symptom severity. Our findings suggest that elevated miRNA-132-3p in OCD patients may contribute to the disease's aetiology and severity by inhibiting neuronal differentiation and reducing BDNF levels. Previous studies in rodents have shown that high miRNA-132 reduces BDNF by affecting *Nurr1* expression (Lungu et al. 2013). Furthermore, miRNA-132 suppresses Methyl-CpG binding protein 2 (MeCP2) levels, and blocking this suppression restores MeCP2 and BDNF levels (Klein et al. 2007). Additionally, neurotrophins like BDNF promote miRNA-132 expression (Vo et al. 2005). Thus, miRNA-132 plays a crucial regulatory role in CNS functions such as neuronal activity, synaptic plasticity and neurodevelopment. Its upregulation may contribute to OCD pathogenesis and severity by disrupting homeostasis. These findings position miRNA-132-3p as a potential diagnostic and therapeutic target for neurodegenerative diseases, including OCD. Targeting miRNA-132-3p to reduce its activity could offer a new treatment approach.

A limitation of our study is that almost all OCD patients were using at least one psychotropic drug. Therefore, studies measuring microRNA and cytokine levels before and after treatment are crucial for understanding the impact of psychotropic drugs on these markers. Additionally, while miRNA-132-3p and TGF- β levels were measured from peripheral blood serum or plasma, it remains uncertain whether these levels accurately reflect the brain's condition.

In conclusion, our study highlights the importance of neurobiological factors in the aetiology and clinical severity of OCD and provides direction for future research. Although the exact

relationship between TGF- β and miRNA-132-3p levels and OCD is not fully understood, these factors likely contribute to the disease's aetiology and symptomatology through molecular and genetic mechanisms. This study also suggests that TGF- β and miRNA-132-3p could serve as potential diagnostic and therapeutic targets. Future studies involving larger, diverse populations, different body fluids and consideration of drug resistance and treatment response will further advance our understanding of OCD's neurobiology.

Author Contributions

Conceptualization: S.A., N.D. and T.K. Investigation: S.A., N.D., A.S.A. and H.B. Data curation: O.B. and S.A. Formal analysis: O.B. and S.A. Original draft preparation: S.A. and N.D. Review: O.B., A.S.A. and H.B. Editing: S.A., N.D. and T.K. All authors have read and agreed to the published version of the manuscript.

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Ethics Statement

The study received ethical approval from the Balikesir University Faculty of Medicine Clinical Research Ethics Committee (Decision No: 2022/54, March 30, 2022). All participants were thoroughly informed about the procedures and provided written consent.

Consent

All participants were thoroughly informed about the procedures and provided written consent. The authors are grateful to the participants and contributors who participated in this research.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author, S.A., upon reasonable request.

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