Evaluation of the Notch, IL-1ß and Leptin Crosstalk Outcome (NILCO) signaling pathway in schizophrenia

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SUMMARY

Objective: In the nervous system, processes that require high organization, such as neuronal development, adaptation, and plasticity, are controlled by various signaling pathways. Investigating the disruptions in these signaling pathways in schizophrenia aims to reveal the etiology and so probable treatment focus options of the disease.

Method: In this study, which we designed as a step towards finding markers in schizophrenia, we evaluated the clinical findings, anthropometric parameters, and NILCO signaling pathway together in schizophrenia.

Results: Our results showed that NOTCH and leptin levels in patients with schizophrenia in our study were significantly higher than in healthy individuals, and IL-1B was lower than in controls. Among the parameters we examined, a positive correlation was found between NOTCH and fat mass, fat percentage, and BMI. Leptin had positive correlations between PANSS positive score, PANSS general, and total PANSS score.

Discussion: This study revealed changes in NOTCH, leptin, and IL levels in schizophrenia and that these markers have a significant relationship with each other and clinical parameters.

Key Words: Schizophrenia, Notch, leptin, Il-1ß, NILCO, PANSS

INTRODUCTION

People with SCZ move away from interpersonal relationships and realities and live an introverted life with significant inadequacies in their thoughts, feelings, behaviors, and professions (1). This multidirectional chronic disease usually begins before age 25 and can be seen in all social classes and populations, with approximately similar incidence and prevalence rates worldwide (2). The lifetime prevalence of SCZ is 4/1000, and (3) an estimated 0.5% of individuals are diagnosed with SCZ at some time in their lives (4). The main symptoms of SCZ can be listed as hallucinations, delusions, disorganized speech and behavior, inappropriate affect, loss of cognition, and deterioration in psychosocial functioning (5). Schizophrenia (SCZ) can also cause cognitive deficits and adversely affect global functionality due to its positive and negative symptoms (6).

Diagnosis of SCZ is made according to the criteria of DSM-5 (Diagnostic and Statistical Manual of Mental Disorders 5) (7) or ICD 10 (8) with observation of clinical features, and diagnosis through clinical interview may vary depending on the clinician's experience, training and adherence to the criteria. Misdiagnosis makes disease management and treatment difficult(9). Despite numerous studies, no proven biomarker has been found that can accurately predict or detect this disease at an early stage(10).

Schizophrenia is thought to be a neuro-inflammatory disease similar to Multiple Sclerosis (MS),

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Alzheimer's Disease, Parkinson and so (11). The vulnerability-stress model for schizophrenia has been proposed in the past, but this model has now turned into the vulnerability-stress-inflammation model as it has been determined that inflammation can be triggered by stress (12). According to a meta-analysis examining the relationship between schizophrenia and neuroinflammation, pro-inflammatory cytokines were found to be higher in schizophrenia patients than in the control group (13). Although the detected pro-inflammatory cytokines are not specific to schizophrenia, the interaction of cytokines and neurotransmitters may contribute to the pathophysiology of schizophrenia during brain development (14).

Notch signaling in the nervous system (15,16) is one of the central regulators of neural stem cells. It regulates neural development, such as neurogenesis, neural proliferation and differentiation, axonal growth, synaptogenesis, and apoptosis in adult brains (17). The Notch pathway plays a role in neural stem cell regulation and in the development of glial lineage cells that lead to the development of different neuronal cells and comprise more than 90% of the human brain in gliogenesis. The authors suggest two progenitors (cells that can differentiate into specific cells) originating from the primitive neural stem cell: P1, which develops into neurons, and P2, which develops into glial cells. Notch is initially responsible for inhibiting P2 from turning into neurons. After other differentiation signals begin, Notch directs the glial precursor to the glial fibrillary acidic protein (GFAP) astrocyte instead of oligodendrocyte development. Notch expression is seen both during the maintenance and proliferation of the glial precursors and in their differentiation into astrocytes, but transiently (18).

Studies have shown that Notch is associated with learning and memory (19). Curiosity about the correlation between Notch and learning and memory disability arose from the relationship between Alzheimer's Disease and a protein called presenilin1. Later, conditions causing learning disabilities in Down Syndrome and Alzheimer's began to be investigated in terms of Notch signaling. Research is insufficient to understand the exact mechanisms in humans. However, the association of Notch signaling with learning abilities has also been demonstrated in some studies in Drosophila (20), C. elegans (21), and Notch mutant mice (22). Notch also plays a role in the relationship between immune cells and the brain in ischemic stroke (23). All these findings up to now, Notch can be considered to have a probable role in the pathogenesis of SCZ through neuroinflammation (24, 25). One of the subtypes of Notch, Notch 4, is most closely related to Sch, and the gene coding for Notch 4 is located in the major histocompatibility complex (MHC) region of 6p21.3 in humans (26).

Leptin is produced mainly by adipocytes (27) and in small amounts by the brain (28-30). The leptin produced by adipocytes and its related protein is also transmitted to the brain through the endocrine pathway (31). The literature reports that circulating leptin is associated with BMI, and antipsychotic drugs such as clozapine and olanzapine increase serum leptin levels (32-34).

Interleukin-1 (IL-1), a pro-inflammatory cytokine, has two types, IL-1a and IL-1b, whose biological activities are similar (35). Interleukin-1 (IL-1) is a central mediator of innate immunity and inflammation, and in inflammatory reactions, IL-1 affects many cell types, along with tumor necrosis factor (TNF). This cytokine's synthesis, release, and effects are highly controlled since the excess of IL-1, which benefits the body in appropriate amounts, causes harm (35).

IL-1β is one of the ligands of the IL-1 family with agonist activity (36). IL-1b is produced in response to TLR by hematopoietic cells such as blood monocytes, tissue macrophages, skin dendritic cells and brain microglia, activated complement components, and other cytokines such as TNF-a (37). Unlike the IL-1a precursor, the IL-1b precursor is inactive but cleaved by caspase-1, releasing the active cytokine into the extracellular space. High secretion of IL-1b is associated with inflammation in patients with auto-inflammatory diseases with specific mutations (36). In a study to investigate the pathophysiology of schizophrenia, the CSF concentration of well-characterized cytokines was analyzed in first-episode schizophrenia patients and healthy volunteers of the same age. IL-1β concentrations in patients were significantly higher than

controls in that study (38).

NILCO is an abbreviation for a complex signaling pathway defined between Notch, IL-1, and leptin, which initiates that pathway (Notch, IL-1, and leptin crosstalk outcome). It has been shown in the literature that leptin increases the expression of both Notch receptors and their ligands (39).

Although previous studies have been examined and there are studies examining the relationship between serum levels of leptin (40) and IL-1 β (41) and schizophrenia, there is no study examining the relationship between Notch-4 serum level and schizophrenia. Additionally, no other study has been found examining the relationship between the NILCO pathway and schizophrenia. Our study aims to examine the correlation between NILCO pathway hormones and their relationship with schizophrenia. Our hypotheses in this study are as follows: 1) Since schizophrenia is an inflammatory disease, IL-1 β serum level is expected to be higher than the control group. 2) The NILCO pathway is activated in schizophrenia disease. There is a relationship between positive symptoms of schizophrenia and NILCO pathway hormones. 3) The NILCO pathway is related to anthropometric parameters (weight, BMI) 4) There is a relationship between the hormones that make up the NILCO pathway.

METHOD

Study design

The study was planned as a cross-sectional study in the psychiatry inpatient clinic of our Medical Faculty Hospital. Ethics committee approval was obtained from the local ethics committee (15.02.2017/ 050.01.04/11). Patients hospitalized with acute psychotic symptoms and all patients have a diagnosis of schizophrenia according to DSM 5 criteria. These patients were evaluated and diagnosed by an experienced psychiatrist in the first week of their hospitalization. Inclusion criteria in the study are as follows: Patients who were diagnosed with schizophrenia between the ages of 18-65 and hospitalized with acute psychotic symptoms, patients whose consent has been obtained by themselves and their legal guardians, patients without organic disease, patients who do not have severe and chronic diseases diagnosed in the past. Exclusion criteria in the study are as follows: Patients under 18 years of age, patients with any additional neuropsychiatric disease in the past or present, and patients who did not agree to participate. The control group was included in the study by having a consent form signed by the participants who volunteered to participate.

In the power analysis performed using the G*Power 3.1.9.7 program, it was found that the minimum subject level to obtain the required statistical significance at the 5% significance level and 95% confidence interval (EB=1.086) was 20 (case-control) subjects each for the case and control groups (total, n=40). However, to obtain data at a higher significance level and significant results in correlation analyses, the minimum number of cases was planned as 40 cases and 40 controls (42). All patients received treatment as usual (TAU) (antipsychotic, benzodiazepine, anticonvulsant). In this study, 42 healthy male volunteers and 45 male patients who both had a diagnosis of schizophrenia according to DSM 5 criteria and were hospitalized with acute psychotic symptoms were included in the study group (SG). Female subjects were excluded from the study to avoid the confounding effect of gender.

The samples were set as two groups: schizophrenic patients (SG, n = 45) and healthy individuals (HG, n = 42) who voluntarily participated in the study. All participants or legal guardians gave written informed consent.

Schizophrenia and control groups were selected only from male patients to avoid the confounding effect of gender. Anthropometric parameters, including body mass index (BMI), fat mass (FM), fat-free mass (FFM), height, weight, basal metabolic rate (BMR), fat percentage, and total body water (TBW) measurements, were determined using Tanita bioelectrical impedance analyzer TBF-300 (Tanita Corporation, Chicago, USA). Education status, duration of illness, length of hospital stay, mental status and presence of psychosis in the fa-mily, presence of suicide, presence of additional medical assistance and medications

used, height, weight, and demographic data (gender, age, etc.) were obtained and recorded. Positive and negative syndrome scale (PANSS), Clinic global impression scale (CGI), and Global Assessment of Function (GAF) Scale were applied. Patients went on to receive medications in the general manner of daily clinical practice including antipsychotics, anticonvulsants and benzodizepines, 'treatment as usual' in Sakarya University Training and Research Hospital Psychiatry Service (43).

Positive and Negative Syndrome Scale (PANSS): PANSS is a 30-item semi-structured interview scale with a seven-point severity rating. The scale was developed by Kay et al. in 1987 (44). Of those 30 psychiatric parameters in PANSS, seven belong to the positive syndrome subscale, seven to the negative syndrome subscale, and the remaining 16 belong to the general psychopathology subscale.

Clinic Global Impression Scale (CGI): The CGI was developed by Guy (45) to assess the course of all psychiatric disorders at all ages for clinical research purposes. The CGI has three subheadings ('severity of illness,' 'recovery,' and 'severity of side effects'), and it is filled in during a semi-structured interview to assess the treatment response of people with psychiatric disorders. In this study, the 'severity of illness' subscale (CGI-S) was used for the assessments (46).

Global Assessment of Function (GAF) Scale: Global Assessment of Function (GAF) score The GAF is a scale that assesses a person's general functioning over a period ranging from psychological or psychiatric illness to health. GAF is a general scale that helps monitor individuals' clinical course using a single measure. With GAF, only psychological, social, and occupational functionality can be graded, but functional impairments due to physical or environmental restrictions cannot be evaluated. In this scale, which is divided into ten equal intervals between 1 and 100, individuals below 70 indicate needing treatment. Outpatients usually score between 31 and 70, and inpatients often score below 40 (47).

Laboratory analysis

Blood samples were taken from the patients and the control group in tubes without anticoagulant (BD Vacutainer K2 plus plastic tubes, Becton Dickinson, Franklin Lakes, NJ, USA) on the first day of their hospitalization, and these samples were allowed to clot completely at room temperature. The sera were then separated by centrifugation at 5,000x at four °C for 5 minutes and stored at -80°C until the day of biochemical analysis. For biochemical analysis, Notch-4 (Cusabio, Catalog no: CSB-EL015953HU, China); Leptin (Elabscience Biotechnology Co., Ltd, Catalog No: E-EL-H0113, USA) and IL-1 beta (Invitrogen, Catalog Numbers BMS224-2 or BMS224-2TEN, ThermoFisher Scientific, USA) commercial kits were applied. Following the incubation, elimination, and color reaction steps, the color change was observed and measured using the enzyme-linked immunosorbent assay (ELISA) method (BioTek ELX50 Reader, BioTek, Instruments, Winooski, VT, USA and BioTek ELX-800 Washer, BioTek Instruments). All biomarker samples were read at 450 nm in an ELISA reader (BioTek, Epoch). The results were expressed as pg/mL, considering the given sensitivity values, and calculated from the standard curve.

Statistical analysis

The study's data were evaluated using the SPSS for Windows 22.0 software package. Whether the continuous data conformed to the normal distribution was evaluated using skewness and kurtosis values (48). Descriptive statistics were used for sociodemographic variables. The chi-square test was used for categorical variables. The Student-t test was used to compare the mean of the variables that fit the normal distribution. The Mann-Whitney U test was used for the variables that did not fit the normal distribution in comparing the independent variables. The correlation was conducted for hormonal and clinical variables. Univariate linear regression was conducted to clarify variables that were found to be significant. Confidence interval, CI; 95%, $p < 0.05$, was considered statistically significant.

Table 1. Clinical properties of schizophrenia groups (n=45)

	mean–SD	min-max
Age of the onset of schizophrenia	24.75– 8.48	12-57
Total duration of illness (months)	166–142	6-564
Total number of hospitalizations	4.91–5.19	1-30
A mental illness in the families of our patients n (%)	15(%33)	
Psychosis in the families of our patients n (%)	8(%17)	
Suicide attempt	7(%15)	
PANSS positive score	25.88–7.04	12-43
PANSS negative score	18.40–9.34	7-43
PANSS general score	37.51–8.29	23-54
Total PANSS score	81.38–19.96	46-118
CGI score-Severity of illness	5.70–1.40	4-13
GAF score	32.77–12.32	5-65

PANSS: Positive and Negative Syndrome Scale, CGI: Clinical Global Impression, Global Assessment Scale (GAS / GAF)

RESULTS

General characteristics and clinical features of samples

Forty-two healthy male volunteers were included in the study as the control group (CG), and 45 male patients were diagnosed with acute schizophrenia as the study group (SG). In the CG, the mean age was found to be 39,071±9,261 years, and the body mass index (BMI) was found to be 24,71±0.77. Those parameters in the SG group were found as 39,11±1,93 years for age and 26.26±0.84 for BMI. No statistically significant difference was found between those groups ($p<0.05$) when compared in terms of age (t= -,016, p=0.987) and BMI(t=-1.150, p=0.254). The clinical properties of SG are given in Table 1.

Comparisons of the biochemical parameters

According to biochemical analysis, Notch 4 and leptin serum levels were significantly higher, but IL-1β lower in the SG group than in the control group (Table 2).

Correlation of hormonal levels and clinical features in patients with acute schizophrenia

Table 2. Comparison of the biomarkers in groups

Biochemical serum levels	Control Group mean–SD	Schizophrenia Group mean–SD	t value	p value
Notch4	-1.042–0.111	-0.953–0.188	-2.644	0.010*
IL-1	-1.187–0,060	-1.217–0,048	2.495	0,015*
Leptin	-0,773–0.297	-0.641–0.257	-2.217	0.029*

*$p< 0.05$, All hormone values were not normally distributed and were log-transformed to fit the normal distribution.

Leptin had positive correlations between PANSS positive score (p=0.005, r=0.409), PANSS general (p=0.012, r=0.373) and total PANSS score (p=0.009, r=0.389). A positive correlation was found between NOTCH between fat percentage and BMI (Table 3). There was no significant relationship between age of the patient, duration of illness, duration of hospitalization and total number of hospitalizations, and hormonal levels ($p>0.05$ for all)

Regression model

Finally, we constructed a univariate linear regression model to evaluate the effect of hormone level and clinical variables on three different PANSS scores, the ones with significant results up to here, as dependent variables (positive, general, and total). We used the backward method, in which all

Table 3: Correlation of hormonal levels and clinical features in patients with acute schizophrenia

		NOTCH	IL-1	Leptin
NOTCH	r		,127	,247
	p		,434	,115
IL-1	r	,127		-,011
	p	,434		,945
Leptin	r	,247	-,011	
	p	,115	,945	
PANSS positive score	r	,276	-,014	0.406
	p	,076	,927	0.006
PANSS negative score	r	-,124	-,121	0.174
	p	,433	,438	0.206
PANSS general score	r	-,061	,032	0.423
	p	,701	,841	0.004
Total PANSS score	r	-,022	-,073	0.391
	p	,892	,648	0.009
CGI score-Severity of illness	r	-,010	,011	-,033
	p	,950	,944	,834
GAF score	r	-,053	-,109	-,300
	p	,738	,487	,045
BMI	r	,326	-,102	-,005
	p	,010	,424	,968
BMR	r	,134	,207	,086
	p	,402	,189	,581
Fat percentage	r	,343	-,053	-,060
	p	,028	,738	,697
Fat mass	r	,308	-,022	,000
	p	,050	,888	,999
TBW	r	,106	,193	,136

Table 4. Linear regression models for PANSS scores

PANSS Positive	B	Std. Error	Beta	t	p	95.0% CI for B	
						Lower	Upper
Constant	18,899	17,365		1,088	0,286	-16,732	54,530
Number of hospitalization	-0,661	0,163	-0,498	-4,054	0,000	-0,995	-0,326
Leptin	10,299	3,065	0,367	3,360	0,002	4,010	16,588
GAF	-0,503	0,073	-0,788	-6,,882	0,000	-0,653	-0,353
Age	0,174	0,061	0,307	2,830	0,009	0,048	0,300
IL1B	-17,063	14,377	-0,124	-1,187	0,246	-46,562	12,436
BMI	0,211	0,136	0,160	1,554	0,132	-0,68	0,490
PANSS General							
Constant	66,531	6,146		10,825	0,000	53,979	79,083
GAF	-0,270	0,098	-0,365	-2,739	0,010	-0,471	-0,069
Leptin	15,816	4,341	0,486	3,643	0,001	6,951	24,682
BMI	-0,373	0,195	-0,245	-1,918	0,065	-0,771	0,024
PANSS Total							
Constant	143,743	15,821		9,085	0,000	111,431	176,054
GAF	-0,729	0,253	-0,401	-2,877	0,007	-1,247	-0,212
Leptin	35,324	11,175	0,441	3,161	0,004	12,502	58,146
BMI	-0,590	0,501	-0,157	-1,178	0,248	-1,614	0,433

significant variables and crucial ones according to previous literature were included, and eight variables (leptin, hospitalization number, BMI, NOTCH, GAF, IL-1β, age, age of the onset of schizophrenia) were added at the first step for all dependent variables linear regression analyses.

PANSS positive score (dependent); SPSS program suggested five models. The model that included six variables (leptin, IL-1β, hospitalization number, GAF, age, and BMI) was the most appropriate one with the highest adjusted R2. This model was statistically significant (F= 12.663, p: 0.000, CI; %95) and explained % 68.0 of the variance (Adjusted R2; 0.680). The variables had no autocorrelation and multicollinearity (Durbin-Watson; 1.965 max VIF score: ±1.551). Leptin, GAF, hospitalization number, and age were significant (CI; %95, $p<0.05$) (Table 4).

PANSS general score (dependent); SPSS program suggested six models. The model that included three variables (leptin, GAF, and BMI) was most appropriate with the highest adjusted R2. This model was statistically significant (F= 11.179, p: 0.000, CI; %95) and explained %48.1 of the variance (aR2; 0.481). The variables had no autocorrelation and multicollinearity (Durbin-Watson; 1.8719 max VIF score: ±1.127). Leptin and GAF were significant (CI; %95, $p<0.05$) (Table 4).

PANSS total score (dependent); SPSS program suggested seven models. The model that included six variables (leptin, GAF, BMI) was most appropriate. This model was statistically significant (F= 9,385 p: 0,000, CI; %95) and explained % 43,3of the variance (R2; 0.433). The variables had no autocorrelation and multicollinearity (Durbin-Watson; 2.091 max VIF score: ±1.132). Leptin and GAF were significant (CI; %95, $p<0.05$) (Table 4).

DISCUSSION

Several main findings were found at the end of this study. First, schizophrenia patients have higher NOTCH and leptin and lower IL-1β serum levels compared to the control group. Second, a positive correlation exists between positive and general PANSS scores and leptin levels. Third, a positive correlation was found between NOTCH, fat percentage, and BMI. In the linear regression analysis, leptin remained a significant predictor of PANSS scores.

In our study, serum Notch was found to be higher in patients with schizophrenia compared to controls. Previous research conducted by Hoseth EH et al. presented evidence that attenuated Notch activity in patients with bipolar disorders and schizophrenia compared to controls. In this study, they detected an increase in DLL1 level, a potential inhibitor for Notch signaling, and genetic expression changes impair intracellular Notch signaling in patients with schizophrenia (25).

The relationship between Notch and lipid metabolism has yet to be well known. The interaction of Notch and leptin and the effect of body

composition on this have been shown in a few publications. In a study conducted on the Ad-NICD (Notch intracellular domain) mice, it was shown that increased Notch signal in mouse adipocytes leads to enlargement of white adipose tissue and ectopic lipid accumulation. Ad-NICD male mice overexpress the NICD, specifically in adipocytes. It is also noteworthy that the leptin levels of 3-month-old Ad-NICD mice in that publication were six times lower than the levels of 1-month-old mice of the same genotype (49). There are publications reporting that the Notch signal increases with increasing fatty diet in PVAT (perivascular adipose tissue), and thus, the Notch signal promotes adipogenesis and lipid accumulation. In our study, a non-strong correlation was found between fat percentage and BMI and Notch. Although this does not indicate a causal relationship, it can be considered as a finding that encourages further research in the clinical population. Leptin is perceived as a feeding-control parameter. There are studies showing that medication, especially olanzapine use, increases leptin levels compared to pre-treatment. Circulating ghrelin concentration increases under conditions of negative energy balance, such as starvation and anorexia nervosa. Circulating ghrelin is reduced in conditions of positive energy balance, such as nutrition and obesity. Ghrelin provides a peripheral signal to the hypothalamus to stimulate food intake and adiposity in rodents. Adipocyte-derived circulating leptin informs the hypothalamus of the state of fat stores, preventing food intake and further fat accumulation. In a study comparing schizophrenic patients using risperidone with a GAF score above 70 and healthy individuals, leptin levels were found to be higher in schizophrenic patients using risperidone (50). Although the association of antipsychotics with leptin elevation is known, there are conflicting results on the association between leptin and SCZ. Fortunately, a meta-analysis on that issue suggests that leptin levels are higher in the SCZ (51). In our study, leptin levels were significantly higher in the schizophrenic group compared to the healthy group, which supports this meta-analysis (Table 3).

The leptin and cholesterol levels were found to be low in patients with major depressive disorder but high in schizophrenic patients in a study. The results of that study also showed positive correlations between serum cholesterol or leptin levels and the length of illness in schizophrenic patients. In the same study, plasma leptin levels were found to be higher in the schizophrenia group and lower in the major depressive group compared to the healthy group. The results of that study suggest that leptin may play a role in the pathophysiology of schizophrenia (52).

NOTCH is a critical signaling pathway in neurodevelopment and adult brain homeostasis. In a study (25), the activity of the Notch signaling pathway was investigated in bipolar disorder, schizophrenia, and healthy controls by measuring plasma levels of Notch ligands. That research found significantly higher Notch ligand levels in plasma in both SCZ and bipolar disorder compared to healthy controls, indicating that the Notch signaling pathway is impaired in both schizophrenia and bipolar disorder.

The relationship between NOTCH, leptin and SCZ as a mechanism can be summarized as follows based on the literature. Notch signal in adipocytes increases lipid accumulation, leading to enlargement of white adipose tissue (49). Adipocyte-derived leptin released into the circulation affects the hypothalamus in an inhibitory way against food intake (50). In light of this information, it can be deduced that the leptin molecule is released more in individuals with high adipocyte amounts. Both our study and the literature showed that leptin is higher in SCZ individuals than in healthy individuals (50-52). Unlike other studies, our study evaluated the relationship between NOTCH and leptin levels and body composition. According to our data, of these parameters, Notch, in particular, is closely related to body fat mass, fat percentage, and BMI. Leptin is a well-known metabolic hormone today and is directly proportional to the amount of fat in the body. In our study, the correlation of the leptin hormone with the scales used to measure the symptom severity of Schizophrenia patients, especially with positive symptoms such as delusions, conceptual disorganization, and excitement, suggests that this pathway may be one of the new therapeutic approaches in schizophrenia.

It is known that neuroinflammation has a crucial

role in the pathogenesis of schizophrenia (11). For this reason, although the level of Il-1ß, which is a marker of inflammation, was expected to be high, it was found to be lower than the control group. The results of studies on this topic are conflicting. IL-1β exerts a pro-inflammatory effect by promoting leukocyte recruitment to areas of inflammation and/or activating inflammatory cells (53). In a study comparing schizophrenic patients and healthy individuals, IL-1β was not found to be statistically different between healthy individuals and people with schizophrenia (54). However, some publications also report that IL-1β changes significantly in people with schizophrenia. IL-1β levels measured by ELISA in plasma are found to be higher in schizophrenia patients than in controls (10). Contrary to many studies suggesting an increase in IL-1ß levels, in a study Potvin et al. conducted in 2008, no significant change was detected in IL-1ß levels in vivo and in vitro studies (53). No significant increase has been reported in chronic patients with disease duration longer than six years (55). A recent study found that IL-1ß levels decreased in psychosis patients with a disease duration of less than two years, who had a first episode, and who did not use medication (FEDN) (56). In our study, we did not find any significant relationship between the age of the patients, duration of illness, duration of hospitalization, and total number of hospitalizations with hormonal levels. These findings contrast with expectations and previous research. Therefore, further investigation is warranted to elucidate the underlying mechanisms responsible for these contradictory results. Additional studies with larger sample sizes and more comprehensive methodologies may provide clarity on the factors influencing hormonal levels in relation to patient demographics and healthcare variables.

Our study results show a positive correlation between leptin and PANSS scores. Also, according to regression analyses, serum leptin level remained a significant predictor of the PANSS scale. A study reported that positive symptom severity inversely correlated with serum leptin levels in SCZ patients (57), but another study reported positive relations similar to our study (58). Although the results of the studies show a possible association between serum leptin levels and positive symptoms in schizophrenia, more research is needed to confirm the findings and understand the underlying mechanism.

This study acknowledges several limitations that warrant attention. Among the most significant are the small sample size, absence of subgroups for different medications, hindering the ability to assess medication effects, and the inclusion of only male patients, which restricts the generalizability of the findings. Moreover, confounding factors such as gender, obesity, smoking, medication use, and waist circumference measurements, as well as infectious diseases affecting IL-1β levels, were not thoroughly addressed. Consequently, the observed associations may be influenced by these factors, making it difficult to determine their specific effects. To mitigate these limitations and derive more robust conclusions, future studies necessitate larger and more diverse samples, comprehensive medication usage data, and meticulous control of confounding variables.

This study showed the relationship between NOTCH and lipid metabolism in a clinical population. This study shows that NOTCH and the leptin IL-1β pathway (NILCO) are affected in schizophrenia patients. We found lower levels of IL-1β in schizophrenia patients than in controls. Addionally leptin levels predicted PANSS scores in our study suggesting that serum leptin levels can be associated with particularly positive symptoms in schizophrenia.

The relationship identified between body fat mass, fat percentage, BMI, and Notch in our study suggests a potential avenue worth further investigation. However, conducting additional research with meticulous control of confounding variables is imperative to validate and better understand these findings.

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