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RESEARCH ARTICLE

Investigating the effects of glucose and lipid metabolism on neuronal structure using optical coherence tomography in treatment-resistant schizophrenia

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ABSTRACT

Objective: The effects of metabolic changes on neural structures in the later stages of schizophrenia remain unknown. Alterations in glucose and lipid metabolism could impact disease progression. This study aims to investigate the effects of glucose and lipid metabolism on neuronal structures in treatment-resistant schizophrenia using optical coherence tomography (OCT), glycogenic proteins, and cholesterol values.

Method: The study included 39 schizophrenia patients with remission, 43 treatment-resistant schizophrenia (TRS) patients, and 40 healthy controls (HC). Optical coherence tomography (OCT) was performed on all participants. Serum samples were collected to determine fasting glucose, Low-Density Lipoprotein (LDL), High-Density Lipoprotein (HDL), triglycerides, total cholesterol, fasting insulin, and Insulin-like Growth Factor 1 (IGF-1) levels.

Results: IGF-1 levels in TRS patients were higher than those in the remission group. Additionally, the thickness of the inferior retinal nerve fiber layer (RNFL), superior RNFL, and global RNFL regions was significantly lower in the TRS group than in the HC group.

Conclusion: While OCT measurements and elevated IGF-1 levels indicate neural thinning in treatment-resistant schizophrenia, there was no observed effect from lipid and glucose metabolism on this phenomenon.

Keywords: Glucose metabolism, lipid metabolism, neurodegeneration, OCT, treatment-resistant schizophrenia

INTRODUCTION

Schizophrenia is a progressive, chronic mental disorder affecting approximately 1% of the population, usually first identified during late adolescence and young adulthood (1). In longitudinal follow-up studies spanning many years, around one-third of schizophrenic patients demonstrated positive development and functionality

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and improved familial and social adjustment. However, clinical exacerbations, such as suicide attempts, relapses, and poor prognosis, were observed in approximately 60% of patients, (2). Regrettably, the factors influencing clinical progress and treatment response in schizophrenia remain elusive. Treatment-resistant schizophrenia (TRS), sometimes termed unresponsive to treatment schizophrenia, characterizes individuals who do not exhibit significant improvement following standard treatment methods. Kane et al. (3) initially described the criteria for TRS, with updates provided by the Treatment Response and Resistance in Psychosis (TRRIP) group (4). Several hypotheses have been proposed to explain the neurobiological mechanisms underlying TRS. Among the most extensively studied are dopamine hypersensitivity, glutamatergic dysfunction, inflammation and oxidative stress, and serotonergic dysregulation. As the disease progresses, treatment response often diminishes, and the frequency of episodes or exacerbations increases. This pattern is typically indicative of treatment resistance (4). However, the root cause remains unidentified.

Diabetes mellitus poses a significant public health challenge, deteriorating the quality of life due to associated complications such as retinopathy, nephropathy, and neuropathy (5). Especially during the insulin resistance phase, neuropathy emerges as a prevalent consequence of diabetes mellitus. Multiple clinical studies have underscored insulin resistance as a central risk factor in developing diabetic retinopathy and neuropathy (6). Several clinical studies have shown that the neurodegenerative facet of diabetic retinopathy begins before the appearance of retinal vasculopathy symptoms in diabetes. Inflammatory processes play a pivotal role in this condition (7).

Besides its function as a neurotrophic factor, increased levels of Insulin-like Growth Factor 1 (IGF-1) are implicated in inflammatory processes, bolstering this progression (8).

There is growing evidence indicating that individuals with schizophrenia are at a higher risk of developing diabetes and metabolic syndrome compared to the general population. While the use of antipsychotic medications has traditionally been associated with these metabolic abnormalities, recent studies show that hyperinsulinemia, insulin resistance, and metabolic syndrome can also be observed in patients experiencing their first episode of psychosis who have not previously been treated with antipsychotic medication (9). Furthermore, another study reported elevated levels of insulin, C-peptide, and chromogranin-A in individuals during their first episode of schizophrenia. This suggests that alterations in insulin secretion and related markers may manifest early in the course of the illness (10).

Oxidative stress is widely recognized as a key mechanism in the development of neurodegenerative disorders. Hypercholesterolemia, characterized by elevated cholesterol levels, is known to contribute to oxidative stress. As a result, cholesterol is deemed a significant risk factor for numerous neurodegenerative conditions (11).

Multiple studies have demonstrated that individuals with schizophrenia have higher rates of obesity and hypercholesterolemia. These conditions are linked to factors such as the use of antipsychotic medications and living conditions, especially in relation to insulin resistance. Additionally, research focusing on first-episode psychosis has revealed discrepancies in Low-Density Lipoprotein (LDL) and High-Density Lipoprotein (HDL) values, indicating potential disturbances in lipid metabolism early in the course of the illness (12). However, the impact of metabolic dysfunctions that arise throughout the course of the disease on disease progression and neuronal structures remains unknown. Optical coherence tomography (OCT) offers a non-invasive, cost-effective, and efficient procedure, safe for individuals with schizophrenia, without any contraindications.

Given that the retina is embryologically derived from the diencephalon and is regarded as an extension of the brain, it is often referred to as a "window into the brain." As a result, retinal pathology can provide valuable insights into central nervous system diseases (13). OCT has been successfully used to assess various neurodegenerative diseases, including multiple sclerosis, Alzheimer's disease, and Parkinson's disease, yielding intriguing and consistent findings (14). In psychiatry, OCT studies have mainly concentrated on conditions like depression, bipolar disorder, and schizophrenia. Yet, these studies have frequently been limited by small sample sizes. Specifically, OCT research on individuals with schizophrenia has consistently demonstrated a significant decrease in retinal nerve fiber layer (RNFL) thickness compared to control groups (15). Numerous studies have investigated the application of OCT in patients with schizophrenia, reporting varying findings. For instance, Cabezon et al. and Lee et al. (16,17) both observed reduced overall retinal nerve fiber layer (RNFL) thickness. Additionally,

Cabezon et al. (16) specifically reported a decrease in the thickness of the superior quadrant, while Chu et al. (18) observed a reduction in the thickness of the right nasal quadrant of the RNFL in patients with schizophrenia. However, other studies found no significant differences in RNFL thickness or macular volume (MV) between individuals with schizophrenia and controls (18).

In the current study, we hypothesize that both glucose and lipid metabolism influence treatment-resistant schizophrenia, leading to a decrease in neuron thickness. We believe that this effect can be assessed using OCT. In this context, we aimed to investigate the impacts of both glucose and lipid metabolism on neuronal structure in treatment-resistant schizophrenia by employing OCT, glycogenic proteins, and cholesterol values.

METHOD

Study Participants

The current study comprised a cohort of 93 patients diagnosed with schizophrenia. These patients were admitted to outpatient clinics and met the criteria outlined in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). Among them, 45 patients met Andreasen's criteria for remission and constituted the remission patient group. The treatment-resistant schizophrenia (TRS) group included 48 patients classified as treatment-resistant based on the TRRIP group criteria. The control group (healthy control (HC)) comprised 44 healthy individuals who were carefully matched with the patients in terms of age, gender, and body mass index (BMI). All participants were aged between 18 and 50 years, with BMIs ranging from 18 to 25. Inclusion criteria ensured that all participants were literate and had no known mental disabilities that could hinder their study involvement. Moreover, none of the participants had a personal or family history of diabetes mellitus, chronic systemic diseases, or neuropsychiatric diseases (pertinent only to the HC group). Individuals with neurodegenerative or ophthalmological disorders, such as glaucoma, retinal disease, or refraction disorders, were excluded. None of the participants reported using drugs that might influence plasma insulin-like growth factor (IGF) levels.

Drug compliance was evaluated through clinical interviews and records. Patients who demonstrated non-compliance with medication within the previous six months, as well as individuals diagnosed with substance or alcohol use disorder according to DSM-5 criteria, were excluded from the study. To further ensure the exclusion of potential substance or alcohol abuse, urine tests were conducted on all participants.

The sample size was calculated by evaluating the effect size as 0.3, the α-error as 0.05, power as 0.85, and using G Power 3.1.9.2.

Study Procedure

Initially, we obtained OCT measures and blood samples from all participants. Subsequently, we conducted a comprehensive evaluation of all patients over a 13-month period to determine the accuracy of their diagnosis, categorizing them as either treatment-resistant or treatment-responsive based on Andreasen's remission criteria and TRRIPS resistance criteria. Our study involved assessing patients' symptoms on two separate occasions. To ensure accurate evaluation, we used various standardized scales, including the Brief Psychiatric Rating Scale (BPRS), Positive and Negative Syndrome Scale (PANSS), Clinical Global Impression Scale (CGI), and Global Assessment of Functioning (GAF). All assessments were conducted by an experienced psychiatrist. During the 13-month evaluation period, three patients experienced clinical exacerbation, leading to their exclusion from the remission patient group. Similarly, two patients showed a >25% decrease in PANSS scores, resulting in their exclusion from the TRS (treatment-resistant schizophrenia) group. The remaining patients were prescribed medications, and for consistency, we adjusted the dosage based on their calculated chlorpromazine equivalent (19).

Evaluation Instruments

Socio-Demographic and Clinical Data Form

Created by the researchers, this form collects two different sets of data for patients and healthy controls. It encompasses socio-demographic details such as age, gender, education level, marital status, and income level. Clinical attributes recorded include the duration of illness, number of hospitalizations, history of electroconvulsive therapy, height, weight, and body mass.

Brief Psychiatric Rating Scale (BPRS)

Developed by Overall et al. (20), the BPRS measures the severity and changes in psychotic and certain depressive symptoms in schizophrenia and other psychotic disorders. It is a semi-structured scale comprised of 18 items, each rated on a scale from 0 to 6. The total score is calculated by summing

up all the item scores. A score ranging from 15 to 30 suggests a minor syndrome, while a score of 30 or above indicates a major syndrome. The Turkish version of the scale was validated, and its reliability was assessed by Soykan (21).

Positive and Negative Syndrome Scale (PANSS)

The PANSS was administered to patients to gauge their condition's severity and determine if they were in remission or had treatment-resistant schizophrenia. Conceived by Kay et al. (22), this semi-structured interview scale comprises 30 items, each with seven-point ratings to evaluate symptom intensity. These 30 psychiatric parameters are categorized into three main categories: the positive symptom scale, the negative symptom scale, and the general psychopathology scale. The reliability and validity study of the scale in Turkish was conducted by Kostakoglu et al. (23).

Clinical Global Impression Scale (CGI)

Developed by Guy et al. (24), the CGI is designed to evaluate the course of psychiatric disorders across all age groups for clinical research purposes. It comprises three subscales that measure severity, global improvement, and side effects levels. It was formulated to assess patients during clinical studies and monitor changes resulting from treatment over time. In this study, the improvement subscale (CGI-I) was employed to measure the level of patient improvement. The severity values on the scale range from 1. Not mentally ill, 2. Borderline mentally ill, 3. Mildly ill, 4. Moderately ill, 5. Markedly ill, 6. Severely ill, to 7. Extremely ill.

Global Assessment of Functioning (GAF)

The GAF is a valuable metric for tracking the overall clinical trajectory of individuals using a single rating. It gauges mental, social, and occupational functioning. General functioning is rated on a scale from 0 to 100 (25).

The Body Mass Index (BMI)

BMI is determined by dividing an individual's weight in kilograms by the square of their height in meters (kg/m^2). This equation offers a standard measure to determine the degree of obesity and potential health repercussions.

Blood Samples

Patients were examined for fasting glucose, LDL, HDL, triglyceride, total cholesterol, fasting insulin, and IGF-1 levels. Blood samples were taken between 08:00 and 09:00 in the morning after a 12-hour fasting period. Additionally, blood pressure, weight (in kg), height (in m), waist circumference (in cm), and BMI (kg/m^2) were recorded for all participants. Participants from the TRS group (n=3), the remission group (n=3), and the healthy control (HC) group (n=4) who met the criteria for metabolic syndrome were omitted from the study. Insulin resistance was also evaluated using the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) score (26).

Upon collection, the blood samples were centrifuged at 3,400 rpm for ten minutes. The resulting supernatant (serum) was stored at -80 °C. The serum samples were then tested for insulin (µU/ml) using the radioimmunoassay (RIA) method (INSIK-5, Sorin, Saluggia, Italy) in duplicate. The kit displayed a sensitivity of 4.0 µU/ml, an inter-assay coefficient of variation of 5.9-6.3%, and an intra-assay coefficient of variation of 3.5-8.6%. Growth hormone (GH) levels in the serum (µg/l) were measured in duplicate using the ImmunoRadiometric Assay (IRMA) method (HGHCTK, Sorin, Italy), which had a sensitivity of 0.15 µg/l. Similarly, insulin-like growth factor 1 (IGF-I) levels in the serum (µg/l) were measured in duplicate by the RIA method (Nichols Institute of Diagnostics, San Juan Capistrano, CA, USA). To minimize potential interference caused by binding proteins, the samples were extracted with acid ethanol. The method had a sensitivity of 0.1 µg/l. The inter-assay and intra-assay coefficients of variation for IGF-I levels ranged between 8.8-10.8% and 5.0-9.5% at IGF-I levels of 79.6-766.4 µg/l, respectively. HDL-C, LDL-C, and serum glucose levels were measured using a glucose-oxidase autoanalyzer. Triglyceride levels were determined using a triglyceride-enzyme autoanalyzer, while total cholesterol was measured using a cholesterol-oxidase autoanalyzer (Dimension RxL, DADE Behring Inc., Newark, DE, USA).

OCT Measurement

An Optovue RTVue Fourier domain OCT device (RTVue-100, 2007, version 3.0) was used to capture OCT images. All participants were examined by an experienced ophthalmologist at the ophthalmology outpatient clinic. The right eye underwent Retinal Nerve Fiber Layer (RNFL) analysis and Ganglion Cell Component (GCC) scanning protocols to map the optic nerve head. All tests were conducted by the same experienced OCT technician. The scanning protocol involved a 360˚ scan centered on the optic disc, with a 3.45 mm diameter around the optic disc.

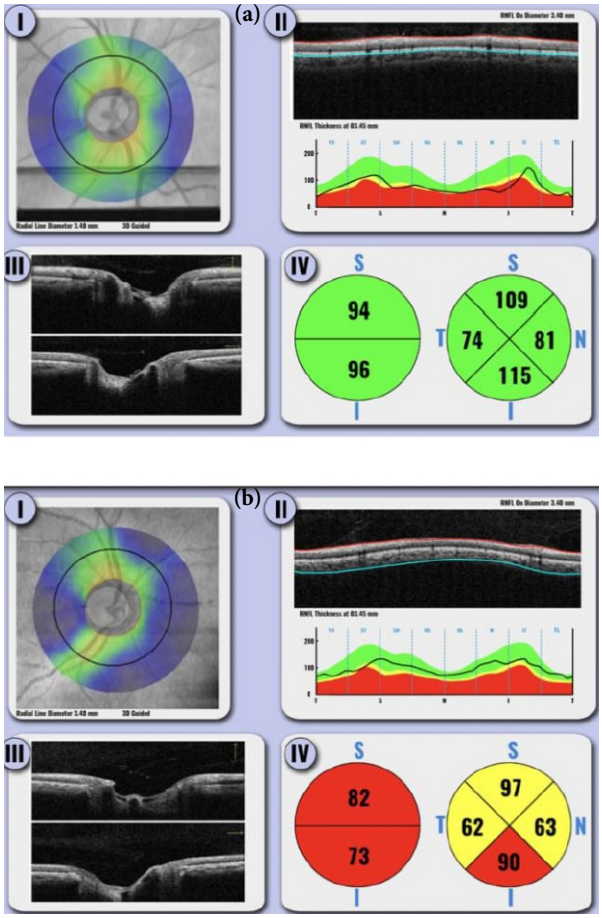

Figure 1. (a) Measurement of retinal nerve fibre layer (RNFL) thickness with OCT in healthy controls **(b)** Measurement of retinal nerve fibre layer (RNFL) thickness with OCT in patients. **I:** A circle which is to measure peripapillary rnfl thickness. **II:** A figure indicating the rnfl and rnfl thickness **III:** Extracted horizontal tomogram demonstrating regions assessed by RNFL scans, a picture indicating both GCC and RNFL thicknesses IV:Six measurements are performed for each eye.

RNFL thickness was evaluated using the rapid retinal nerve fiber thickness (RNFT) test. The average RNFT, measured in micrometers (µm), was automatically generated for all tested eyes. The mean volume of the GCC was calculated in mm^3 using the GCC scanning protocol (Fig. 1). The RNFL thickness and the GCC volume were compared between the patient group and the healthy control group using the generalized estimating equations (GEE) method. GEE is a well-established method for analyzing paired biological data, such as OCT data from the eyes of the same individual. This method allows the utilization of multiple data points from the same eyes while safeguarding against the inflation of statistical significance that can arise from using paired biological data from the same participant.

Statistical Analysis

Data were analyzed using the Statistical Package for Social Sciences for Windows (SPSS) version 25.0. A range of descriptive statistical methods, including frequency, percentage, mean, and standard deviation, were employed to evaluate the study data. The normal distribution of variables was assessed using the Kolmogorov-Smirnov test. Categorical variables were compared using the Pearson chi-square test. Independent samples t-test and one-way Analysis of Variance (ANOVA) were employed to compare groups of quantitative variables. The Levene test was used to assess the homogeneity of data distribution. In cases where data exhibited homogeneity, posthoc analyses were conducted using the Tukey test. The Pearson correlation test was used to examine correlations between variables. Logistic regression analysis was performed to identify significant predictors of treatment resistance in schizophrenia. A p-value of less than 0.05 was considered statistically significant.

RESULTS

Sociodemographic and Clinical Data

The study population comprised 79 (64.7%) males and 43 (35.3%) females, with an average age of 36.2±9.1 years. There were no significant differences observed in age (p=0.21), gender ratio (p=0.24), education level (p=0.13), smoking status (p=0.62), and BMI (p=0.72) between the study groups. Additionally, there were no significant differences in the chlorpromazine equivalent doses between the patient groups (Mean±SD in Remitted=782.6±34.74; Mean±SD in TRS=832.5±32.05, p=0.29). Detailed sociodemographic and clinical data can be found in Table 1.

Evaluation of Biochemical Markers

When comparing biochemical markers between the two patient groups (TRS/remitted patients) and the healthy control (HC) group, no significant differences were found in insulin levels (p=0.06), HDL levels (p=0.21), and total cholesterol levels (p=0.18) among the groups. The remitted patient group exhibited significantly higher fasting blood glucose levels (p=0.008) and significantly lower triglyceride levels (p=0.03) compared to the HC group. However, these parameters did not show statistically significant differences between the remitted patients and the TRS group. Moreover, the remitted patient group demonstrated significantly higher plasma LDL levels compared to both the TRS and HC groups (p=0.01).

Table 1: Comparison of sociodemographic and clinical data among remitted schizophrenia patients, treatment-resistant schizophrenia patients, and healthy controls (mean±SD)

	Healthy control (n=40)	Remitted patients (n=39)	Treatment-resistant patients (n=43)	df	p
Age	37.40±10.1	35.90±8.2	34.30±8.8	2	0.21
Gender (%)	Male: 23 (57.5%)	Male: 26 (66.6%)	Male: 30 (69.7%)	2	0.24
	Female: 17 (42.5%)	Female: 13 (33.3%)	Female: 13 (30.3%)		
Education level (year)	11.80±3.95	10.70±4.9	9.25±3.36	2	0.13
Smoking (%)	Yes: 22 (55%)	Yes: 17 (43.5%)	Yes: 21 (48%)	2	0.62
	No: 18 (45%)	No: 22 (56.5%)	No: 22 (52%)		
Marital status (%)	Married: 20 (50%)	Married: 10 (25.6%)[a]	Married: 8 (18.6%)[a]	2	**0.003***
	Other: 20 (50%)	Other: 29 (74.4 %)	Other: 35 (82.6%)		
BMI	23.6±2.12	22.9±2.04	23.3±2.01	2	0.72
Age of disease onset (year)		27.1±8.8	23.1±6.4[b]	56	**0.047***
Duration of illness (year)		9.02±9.2	11.4±7.4	56	0.29

*: p<0.05; Students t-test; One-way ANOVA test, and Chi-Square tests were performed; BMI: Body mass index. For One-Way ANOVA, homogeneity was evaluated using the Levene test. The LSD test was applied if the data showed a homogeneous distribution, and Tamhane's T2 post-hoc tests were chosen if the data did not show a homogeneous distribution. In pairwise comparisons of data with significant differences in the Chi-square test, Bonferroni correction was applied, and the p-value was adjusted to 0.017. a: p<0.05 or p<0.017 (when compared with healthy control); b: p<0.05 or p<0.017 (when compared with remitted patients with schizophrenia).

Table 2: Comparison of biochemical markers and optical coherence tomography (OCT) measurements among treatment-resistant, remitted patients with schizophrenia, and healthy controls

	Healthy control (n=40)	Remitted patients (n=39)	Treatment-resistant patients (n=43)	df	p
IGF-1	137.86±35.82	174.37±45.04[b]	160.74±48.36	2	**0.01***
Insulin	6.27±4.31	10.35±10.91	11.32±10.98	2	0.06
Fasting glucose	100.77±12.75[a]	96.16±9.11	92.51±7.71	2	**0.008***
HDL	56.15±10.13	48±12.48	53.23±18.3	2	0.21
LDL	129.92±32.53[a]	109.61±27.63[b]	108.94±29.67	2	**0.01***
Total cholesterol	198.59±36.12	179.46±33.69	189.88±38.15	2	0.18
Triglyceride	86.81±25.77[a]	115.76±61.21	117.35±57.96	2	**0.03***
Inferior RNFL	124.14±9.67	120.66±15.16[a]	130.97±11.67	2	**0.006***
Superior RNFL	120.11±12.60	119.30±10.88[a]	125.47±10.45	2	**0.04***
Global RNFL	100.62±7.93	99.70±9.20[a]	104.50±6.79	2	**0.02***
Temporal RNFL	76.81±11.26	77.80±9.03	76.66±7.56	2	0.84
Nasal RNFL	81.77±10.85	80.86±11.90	84.41±9.62	2	0.22
Global GCC	98.77±6.95	97.53±7.47	100.86±5.55	2	0.15
Inferior GCC	99.92±7.46	98.23±7.73	101.75±6.63	2	0.16
Superior GCC	97.70±7.04	96.96±7.47	99.97±5.11	2	0.19

*: p<0.05, One-way ANOVA test was performed. HDL: High density lipoprotein; LDL: Low density lipoprotein; IGF: Insulin-like growth factor; GCC: Ganglion cell complex; RNFL: Retinal nerve fiber layer thickness. For the One-Way ANOVA test, homogeneity was evaluated using the Levene test. The LSD test was applied if the data showed a homogeneous distribution, and Tamhane's T2 post-hoc test was chosen if the data did not show a homogeneous distribution. Tukey's test was used in the post-hoc analysis of data showing homogeneous distribution. a: p<0.05 (compared with healthy controls); b: p<0.05 (compared with treatment-resistant patients with schizophrenia).

Additionally, the remitted patients had significantly lower serum IGF1 levels than the TRS group (p=0.01), but the difference with the HC group did not reach statistical significance. For more detailed information, please refer to Table 2.

Evaluation of OCT Measurements

When comparing the parameters derived from OCT measurements within the three study groups, significant differences were noted in the thickness of the inferior retinal nerve fiber layer (RNFL) (p=0.006),

Table 3: Investigating the relationship between optical coherence tomography (OCT) measurements and biochemical markers

	Global GCC	Superior GCC	Inferior GCC	Global RNFL	Superior RNFL	Nasal RNFL	Inferior RNFL	Temporal RNFL
Glucose	0.01	0.02	0.01	-0.10	-0.09	-0.21	-0.10	-0.14
IGF-1	-0.05	-0.07	-0.05	0.008	-0.04	0.02	-0.04	-0.01
LDL	-0.11	-0.09	-0.12	0.007	-0.03	0.13	-0.03	-0.03
HDL	0.08	0.14	0.44	0.14	0.13	0.01	0.13	0.13
Cholesterol	0.00	0.02	-0.01	0.09	0.01	0.15	0.05	0.04
Insulin	-0.11	-0.09	-0.10	-0.005	0.01	0.02	-0.009	-0.02
TGA	-0.05	-0.03	-0.05	-0.03	-0.01	0.05	-0.04	-0.10

Spearmen (rho) corelation analysis test was performed. HDL: Highdensity lipoprotein; LDL: Low density lipoprotein; IGF: Insulin like growth factor; GCC: Ganglion cell complex; RNFL: Retinal nerve fiber layer thickness.

Table 4: Investigation of biochemical and clinical variables and OCT measurements to predict treatment resistance in patients with schizophrenia using multivariate logistic regression analysis

Independent variables	Exp (B)	95.0% CI for β coefficient	p	Nagelkerke R Square
IGF-1	1.033	1.012–1.053	**0.002***	
Duration of illness	1.074	0.976–1.182	0.146	
RNFL	0.960	0.91–1.012	0.127	0.524
LDL	0.968	0.94–0.99	**0.013***	
Fasting glucose	0.965	0.88–1.048	0.39	

*: p<0.05. Multivariate logistic regression analysis was performed. RNFL: Retinal nerve fiber layer thickness; LDL: Low density lipoprotein; IGF-1: Insulin-like growth factor.

superior RNFL (p=0.04), and global RNFL (p=0.02) regions between the TRS group and the healthy control (HC) group. These regions exhibited markedly lower thickness in the TRS group compared to the HC group. There was no noteworthy difference in RNFL thickness identified between the TRS and remitted patient groups. The variations in the thickness of the inferior ganglion cell component (GCC) (p=0.016), superior GCC (p=0.19), global GCC (p=0.15), temporal RNFL (p=0.84), and nasal RNFL (p=0.22) did not reach statistical significance among the three study groups. These findings are detailed in Table 2.

Correlation of OCT Measurements and Biochemical Markers

No significant relationship was observed between glucogenic proteins lipid values and retinal thickness. The statistical evaluation of the relationship between OCT Measurements and biochemical markers is provided in Table 3.

Predictive Evaluation of Biochemical, Clinical, and OCT Features in Schizophrenia Diagnosis and Treatment Resistance, and Inter-correlation

The biochemical parameters, clinical features, and OCT measurements used for predicting treatment resistance are outlined in Table 4. A multivariate logistic regression model indicated that serum levels of IGF1 and LDL were significant predictors of treatment resistance. However, the duration of illness, RNFL thickness, and blood glucose levels did not influence treatment resistance. Conversely, the linear regression model presented in Table 5 demonstrated that lipid values and glycogenic proteins did not impact neural thinning.

DISCUSSION

The present study aimed to investigate the influence of glucose and lipid metabolism on neural structure in the context of treatment response in schizophrenia. OCT measurements, glucogenic proteins, and cholesterol panels were utilized to evaluate these parameters in patients with treatment resistance, remitted patients, and healthy control individuals. A notable finding of this study was the higher IGF-1 levels observed in patients with treatment-resistant schizophrenia compared to those with remitted schizophrenia. Furthermore, both treatment-resistant schizophrenia patients and remitted schizophrenia patients exhibited thinner Inferior RNFL, Superior RNFL, and Global RNFL in comparison to the healthy

Table 5: Investigation of the effect of glucose and lipid metabolism on retinal thickness

	Model coefficients – Global RNFL			
Independent variables	**SE**	**t**	**95.0% CI for β coefficient**	**p**
Intercept	10.43	10.52		≤**0.001***
LDL	0.02	0.23	-0.19 - 0.25	0.81
Triglyceride	0.01	-0.93	-0.33 - 0.11	0.35
Fasting glucose	0.08	-0.86	-0.32 - 0.12	0.39
IGF-1	0.02	-0.05	-0.23 - 0.22	0.95

*: p≤0.05; LDL: Low density lipoprotein; IGF: Insulin-like growth factor; RNFL: Retinal nerve fiber layer thickness. Multivariate linear regression analysis test was performed.

control group. However, no significant correlation or relationship was established between lipid profiles, parameters of glucose metabolism, and retinal thickness.

IGF-1 has been implicated in activating neuroprotective and anti-apoptotic signaling pathways that influence both prenatal and postnatal brain development (27,28). Additionally, brain volume has been shown to correlate with IGF-1 levels (29). So far, varied results have been obtained from studies investigating IGF-1 levels in patients with schizophrenia. While some studies reported higher IGF-1 levels (30), others found either lower levels (29–31) or no difference (32,33) in schizophrenia patients compared to healthy controls. The current study identified no difference in IGF-1 levels between schizophrenia patients and healthy controls. However, significantly higher IGF-1 levels were identified in the TRS group compared to the remitted schizophrenia patient group. Recent studies from our research group support these findings (34). We can elucidate these outcomes with three possible mechanisms. Firstly, it is established that dysfunction in IGF-1 can contribute to the pathogenesis of neurodegenerative diseases. Higher IGF-1 levels were detected in the early stages of neurodegenerative conditions such as Alzheimer's, Parkinson's, and Huntington's diseases. Hence, IGF-1 levels may rise during the initial phases of neurodegenerative diseases in response to IGF-1 resistance, aiming to counteract neurodegeneration, and decrease during the advanced stages of the disease (35,36). While the current study's results do not unequivocally support the neurodegenerative disease hypothesis of schizophrenia, the fact that a regression analysis indicated IGF-1 levels significantly predict treatment resistance in schizophrenia might suggest a potential role of IGF-1 in neurodegenerative processes during treatment resistance. Secondly, neuroinflammation is widely implicated in the etiology of schizophrenia.

Pro-inflammatory markers such as cytokines and interleukins are known to increase across all phases but may particularly peak during disease exacerbation (37). Furthermore, IGF-1 is recognized for its anti-inflammatory role (38). Interestingly, an animal model of schizophrenia induced by intrauterine inflammation exhibited elevated IGF-1 levels in the dorsolateral prefrontal cortex (DPFC) (38). The treatment-resistant phase of schizophrenia coincides with symptomatic manifestation, potentially leading to heightened inflammatory marker levels. Consequently, IGF-1 levels might escalate during this period to mitigate active inflammation.

Furthermore, although we did not observe a significant difference between the remitted group and the healthy control group, IGF-1 levels were at their lowest in the remitted group within this study. Unlike the treatment-resistant group, the remitted group responded positively to antipsychotic treatment. This might be attributed to the anti-inflammatory effects of antipsychotics (39), which result in decreased inflammation levels and consequently lower IGF-1 levels. The third and final potential mechanism is receptor resistance, akin to the insulin resistance seen in Type-2 diabetes mellitus (T2DM). Higher insulin levels are detected in the early stage of T2DM due to the suboptimal response of insulin receptors to the ligand (40). Similarly, treatment-resistant schizophrenia may be associated with a suboptimal response of IGF-1 receptors in the brain, eventually increasing IGF-1 levels over time. Pro-inflammatory signaling can be one of the factors contributing to this deregulation. Ultimately, our results suggest that elevated levels of IGF-1 may more effectively support neural thinning and indirectly bolster the neurodegenerative hypothesis in treatment resistance in schizophrenia.

Neuroimaging studies have demonstrated loss of gray matter and white matter density and volume reduction in almost all brain regions

among schizophrenia patients. These findings have intensified interest in the neurodegenerative hypothesis for schizophrenia (41). This drive has led to the application of methods like OCT, commonly used in neurodegenerative disorders, to be employed in schizophrenia patients (14). Numerous studies have aimed to measure retinal thickness in schizophrenia patients using OCT. The overall outcome of most studies is generally consistent, albeit with some variations. Several studies have reported thinner RNFL and MV, or solely thinner RNFL, in schizophrenia patients (16,17,41), while a minority of studies have found no discernible differences between schizophrenia patients and healthy controls.

Using a cohort of schizophrenia patients with recent illness episodes (RIE) and non-recent illness episodes (NRIE), Ascaso et al. (42) reported thinner RNFL compared to the healthy control group. The same study also indicated RNFL thinning exclusively in the NRIE group. Segregating schizophrenia patients based on treatment response revealed decreased macular and RNFL thickness in schizophrenia patients, while no significant difference could be ascertained in the GCC between schizophrenia patients and healthy controls. Furthermore, the same researchers reported reduced GCC thickness within the non-treatment response patients group (43). Discrepancies in OCT findings were also noted in studies that did not separate patients according to specific characteristics. However, two separate studies failed to identify significant differences in OCT findings between healthy controls and schizophrenia patients (19,42). In the present study, we observed decreased RNFL thickness in schizophrenia patients. Moreover, we observed more pronounced RNFL thinning in TRS patients than in healthy controls. However, the difference did not attain statistical significance while RNFL was thinner in TRS patients than in remitted patients. No differences in GCC thickness were identified among the three evaluated groups. The more peripheral location of the GCC compared to the retinal layer may contribute to its delayed susceptibility. It is also known that factors like metabolic syndrome, obesity, systemic disorders, smoking, and prescription drug usage can impact OCT measurements (15).

In addition, studies reporting notable differences in GCC thickness between treatment and control groups did not exclude these underlying conditions that can influence OCT thickness. Our study excluded patients with these underlying conditions, which may have mitigated any GCC thickness differences. The neurodegenerative hypothesis of schizophrenia is rooted in factors like heightened inflammation, aberrant apoptosis, and synaptic pruning (44) and is supported by neuroimaging findings (45). This hypothesis is also reinforced by observations of reduced RNFL thickness in schizophrenia patients, akin to individuals with neurodegenerative diseases (15). However, in the current study, although RNFL thickness could predict schizophrenia, it did not serve as a predictor of treatment resistance in schizophrenia patients. Additionally, cholesterol and glucose metabolism were not found to significantly influence retinal nerve thinning; the impact of cholesterol and glucose metabolism appeared to be independent. Clearly, numerous more studies employing diverse methodologies encompassing neuroimaging, blood protein measurement, and OCT are imperative to elucidate the intricate pathogenesis of schizophrenia.

A negative correlation between LDL and disease severity was evident, a relationship supported by existing literature highlighting patients responding well to treatment with elevated LDL levels. While the precise mechanism linking increased serum lipids and improved schizophrenia symptoms during antipsychotic treatment remains unclear, elevated serum lipids may positively influence treatment (46). This phenomenon could be elucidated through two distinct mechanisms: 1) Serving as a physiological reservoir for the drug, enabling a continuous release akin to depot forms of antipsychotics; 2) Facilitating enhanced drug distribution by aiding easier penetration of the blood-brain barrier through passive diffusion or receptor-mediated processes.

The current study has certain limitations that warrant consideration when interpreting the results. Firstly, despite patients in the study using medications from a common category, the potential for drug interactions cannot be entirely dismissed due to variations in medication types and dosages. Secondly, the study did not explore other possible biomarkers that could shed light on the neurodevelopmental process. Lastly, it is important to note that the study solely relied on OCT for assessing neural structure, and the absence of an additional independent imaging method capable of evaluating neurodegeneration presents another limitation. These factors should be acknowledged in interpreting the findings. The design of new studies combining various techniques will contribute to obtaining more comprehensive results.

CONCLUSION

In conclusion, this study furnishes evidence that alterations in glucose and lipid metabolism correlate with the disease severity in schizophrenia. Moreover, our findings underscore that OCT measurements and IGF-1 levels hold potential as indicators of neural thinning in treatment-resistant schizophrenia, while the influence of lipid and glucose metabolism on this neural thinning seems insubstantial. These results enhance our comprehension of the implications of metabolic dysfunctions in schizophrenia. Nevertheless, further research is imperative to delve into the underlying mechanisms and potential therapeutic applications, thereby advancing our comprehension and management of this complex disorder.

Contribution Categories		Author Initials
Category 1	Concept/Design	U.H.Y., O.S.O.
	Data acquisition	D.F.G.
	Data analysis/Interpretation	U.H.Y., O.S.O., O.P.A.A.
Category 2	Drafting manuscript	U.H.Y.
	Critical revision of manuscript	U.H.Y., N.K.
Category 3	Final approval and accountability	U.H.Y., N.K.
Other	Technical or material support	I.U.O.
	Supervision	N.K.

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