Middle East Current Psychiatry

RESEARCH

Open Access

Serum S100B is related to insulin resistance and zinc-α2-glycoprotein levels in patients with chronic schizophrenia

Parinaz Kalejahi[1], Sorayya Kheirouri[2*] and Seyed Gholamreza Noorazar[2]

Abstract

Background Elevated serum levels of S100B may associate with insulin resistance and other metabolic complication in schizophrenia patients. The aim of this study was to investigate the association of serum S100B levels with cardiometabolic parameters, serum levels of zinc-α2-glycoprotein (ZAG), and the severity of schizophrenia symptoms in schizophrenic patients. We recruited 42 patients with chronic schizophrenia. The participant's body weight (BW), waist circumference (WC), and blood pressure (BP) were measured. Serum levels of low and high-density lipoprotein cholesterol (LDL-c and HDL-C), triglyceride (TG), cholesterol (CHOL), fasting blood glucose (FBG), insulin, S100B, and ZAG levels were determined. The Homeostatic Model Assessment (HOMA) was used to quantify insulin resistance (IR) and the severity of schizophrenia was measured using a positive and negative syndrome scale (PANSS) score.

Results The results showed that the mean serum S100B levels increased significantly with increasing HOMA-IR and ZAG levels ($\beta = 0.595$, 95% confidence interval (CI) (8.722 to 26.002), $p < 0.001$; and $\beta = 0.334$, 95% CI 0.067 to 0.525, $p = 0.013$ respectively). Patients under treatment with atypical antipsychotic medications (AAPM) had lower serum S100B levels ($p = 0.035$).

Conclusion Our results suggest that alteration in glucose metabolism and ZAG secretion may increase serum S100B levels in patients with schizophrenia.

Keywords Schizophrenia, S100B, Insulin resistance, HOMA-IR, ZAG

Background

Schizophrenia is a severe and debilitating mental disorder with a worldwide prevalence of about 1% [1]. Several studies have put forward hypotheses about the incidence of schizophrenia, one of which is the damage of glial cells, including astrocytes, oligodendrocytes, and microglia. S100 calcium-binding protein B (S100B) is produced by astrocytes and is involved in various intracellular and extracellular processes, such as the regulation of protein phosphorylation, glucose metabolism, and calcium homeostasis [2, 3].

S100B, depending on its concentration, can be considered a neurotrophic or neurotoxic factor [4]. Increased cerebrospinal fluid (CSF) and serum levels of S100B have been reported in a number of studies in schizophrenic patients [5, 6]; in this regard, verified dysfunction of glial cells might be presented as an important marker to the pathogenesis of schizophrenia [7]. In a meta-analysis study (including 13 studies, 420 patients with schizophrenia, and 393 healthy individuals), the levels of S100B were reported to be higher in patients with schizophrenia compared to healthy subjects [8]. In addition, a positive correlation between CSF and serum levels of S100B has been observed in animal and human studies [9, 10].

*Correspondence:
Sorayya Kheirouri
kheirouris@tbzmed.ac.ir
[1] Department of Nutrition, Faculty of Nutrition and Food Sciences, Tabriz University of Medical Sciences, Tabriz, Iran
[2] Research Center of Psychiatry and Behavioral Sciences, Tabriz University of Medical Sciences, Tabriz, Iran

The findings are contradictory regarding the relationship between serum levels of S100B and the severity of the patient's symptoms. In a study conducted by Rothermundt et al., it was found that serum levels of S100B were positively correlated with negative symptoms [11]; however, in some other studies, no relationship has been found between serum levels of S100B and schizophrenia severity. Furthermore, according to a study by Dev et al. (2013) on clozapine-treated schizophrenic patients, no significant association was found between serum S100B levels and symptom severity [12]. Except for the central nervous system (CNS), S100B is also expressed or secreted in other tissues, including adipose tissue [13]. The concentration of S100B in adipose tissue can be controlled by various factors, such as glucagon, adrenaline, and insulin [13]. According to the literature, metabolic disorders such as visceral obesity, diabetes, and peripheral/cerebral IR may have a role in elevated S100B serum levels in schizophrenia. ZAG, as a relatively new adiponectin, is a 41-kDa soluble glycoprotein implicating in IR and involved in body composition, energy balance, and metabolic homeostasis [14]. It was previously reported that ZAG is negatively associated with body mass index (BMI), fat mass, plasma insulin, and leptin, which also decreases plasma levels of glucose and triglycerides [15, 16].

Accordingly, we assumed that serum S100B levels increase in schizophrenia; thus, we investigated the correlation between S100B levels and cardiometabolic parameters, serum levels of ZAG, and severity of symptoms to identify factors influencing the serum S100B level.

Material and methods

Study design and participants

This cross-sectional survey was conducted from June 2019 to January 2020. Forty-two patients were recruited from the Razi Hospital, Tabriz, Iran. The inclusion criteria were as follows: male patient diagnosed with schizophrenia using the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR) criteria, having PANSS score of 70 or higher and age 18–65 years old; the exclusion criteria included: subject with mental retardation (intelligence quotient of < 70), receiving nutritional supplements over the past year, the simultaneous onset of other major psychiatric disorders or changes in treatment and medication during the intervention.

Anthropometric, biochemical, and clinical assessment

For each patient, socio-demographic information was collected. Anthropometric data were collected through physical examination. BW, height, WC, and resting BP were made in duplicate and averaged. All the measurements were performed by one person to minimize the error rate. Body mass index (BMI) was collected as the weight in kilograms divided by the square of height in meters.

Participants' venous blood samples were collected after 8–12 h overnight fast. The samples were centrifuged and serums were isolated and stored at − 80 °C until analysis. Serum levels of LDL-c, HDL-C, TG, CHOL, and FBG were determined by enzymatic methods. Enzyme-linked immunosorbent assay (ELISA) kits (Bioassay Technology Laboratory) determined serum levels of S100B, ZAG, and insulin. The Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) was calculated according to the formula: fasting insulin (μU/mL) × fasting glucose (mg/dL)/405.

Dyslipidemia was defined as any one of TG ≥ 150 mg/dL, total CHOL ≥ 200 mg/dl, LDL- c ≥ 160 mg/dl, HDL-c < 40 mg/dL, and/or using cholesterol-lowering medicines during the last 2 weeks, diabetes mellitus as defined, FBG level of ≥ 126 mg/dl or drug use, overweight or obesity as defined BMI ≥ 25 (kg/m^2) and hypertension as defined ≥ 140/90 mmHg for SBP/DBP or drug use.

PANSS was used to determine the severity of the disorder. This tool is a 30-item scale composed of subscales to assess negative (seven items), positive (seven items), and general psychopathological (sixteen items) symptoms of schizophrenia; the sum of these three scores demonstrates the total score.

Statistical analyses

Data analysis was done using SPSS version 16.0 (SPSS Inc, Chicago, IL). The Kolmogorov–Smirnov test was employed to check the normal distribution of data. Data were presented as mean ± standard deviation (SD) and as median (inter-quartile range) for normally distributed variables and non-normal distributed variables, respectively. Independent samples *t*-test and Mann–Whitney *U* test were used to compare between groups. Univariate logistic regression analyses, univariate, and multivariate linear regression analyses were performed to determine the predictive factors of serum S100B levels. A p-value ≤ 0.05 was considered statistically significant.

Results

Forty-two schizophrenic patients were included in the evaluation. Demographic data, current medication, clinical characteristics and symptoms severity of the study population are presented in Table 1. The patients were divided into 2 groups based on the median value of serum S100B levels (57.200 ng/mL): S100B ranges

Table 1 Demographic and clinical characteristics of the study's patients

Characteristics	
n	42
Age (years)	41.60 ± 8.64
Duration of illness (year)	5.50 (3.00,10.50)
Current smokers	29 (69%)
AAPM	13 (30%)
TAPM	20 (47.61%)
CAPM	11 (26.20%)
Body weight (kg)	72.21 ± 12.88
WC (cm)	87.55 ± 9.06
BMI (kg/m^2)	24.56 ± 3.92
Obesity	20 (47.60%)
TG (mg/dL)	158.71 ± 52.46
CHOL (mg/dL)	156.05 ± 24.04
HDL-c (mg/dL)	35.46 ± 5.02
LDL-c (mg/dL)	93.07 ± 15.37
Dyslipidemia	27 (64%)
HOMA-IR	1.80 (1.00,3.65)
FBG (mg/dl)	92.33 ± 8.92
HOMA-IR	1.80 (1.00,3.65)
Diabetes	3 (7%)
ZAG (ng/mL)	50.50 (31.15,75.20)
SBP (mmHg)	121.29 ± 8.01
DBP (mmHg)	77.61 ± 2.20
Hypertension	6 (14%)
PANSS-NSS	29.29 ± 4.80
PANSS-PSS	25.76 ± 4.91
PANSS-GPSS	58.07 ± 5.65
PANSS-TS	113.60 ± 11.53

Data are presented as mean ± SD, *n* (%) or median [percentile 25, 75]

AAPM atypical antipsychotic medications, *TAPM* typical antipsychotic medications, *CAPM* combined antipsychotic medications, *WC* waist circumference, *BMI* body mass index, *TG* triglyceride, *CHOL* cholesterol, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *FBG* fasting blood glucose, *HOMA-IR* homeostatic model assessment—insulin resistance, *ZAG* zinc alpha 2-glycoprotein, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *PANSS* Positive and Negative Syndrome Scale, *PANSS-NSS* PANSS negative subscale score, *PANSS-PSS* PANSS positive subscale score, *PANSS-GPSS* PANSS general psychopathology subscale score, *PANSS-TS* PANSS total score

below 57.200 ng/mL (22 patients, 50.30% of the population) and S100B higher than 57.200 ng/ml (20 patients, 49.70% of the population). Patients with high S100B had higher HOMA-IR and ZAG levels (1.17 (0.92, 1.86) vs 2.65 (1.25, 4.04), $p=0.037$) and 43.10 (27.35, 52.70) vs 72.25 (44.72, 127.95), $p=0.005$) and patients under treatment with AAPM had lower serum S100B levels $p=0.035$) (Table 2).

To find which factors might influence the serum S100B levels in schizophrenic patients, we performed univariate and multivariate regression analyses (Table 3). The results showed that the mean S100B levels increased significantly with increasing HOMA-IR and ZAG ($\beta=0.573$, 95% CI 8.956 to 24.412, $p<0.001$; and $\beta=0.469$, 95% CI 0.162 to 0.670, $p=0.002$ respectively). No other variables showed any influence on serum S100B level. To build a model of the serum S100B level, we used a stepwise forward inclusion and backward elimination procedure, in multivariate linear regression analysis, predictive factors for high serum S100B levels were HOMA-IR ($p<0.001$) and ZAG ($p=0.013$).

Discussion

In the present study, we evaluated the association between serum S100B levels, metabolic complications parameters, and severity of symptoms in chronic schizophrenic patients.

In accordance with the literature, a statistically significant positive correlation was observed between HOMA-IR and serum S100B levels. Insulin has been shown to downregulate S100B expression in the cerebral and peripheral targets [17]; while in contrast, IR or glucose intolerance appears to induce the expression and release of S100B [17]. Previous studies have shown that insulin signaling was disrupted in the dorsolateral prefrontal cortex in schizophrenic patients [18].

A study by Steiner et al. showed that S100B was elevated in both unmediated and medicated schizophrenic patients, and IR resulted in an increased release of S100B from the brain and adipose tissue [19]. Altered glucose homeostasis may be part of sedentary behaviors, unhealthy diets, smoking, and antipsychotic treatments in schizophrenic patients [20, 21].

To the best of our knowledge, this is the first study that shows a positive correlation between serum S100B and ZAG levels in schizophrenia. Although it may seem that these two substances may have different mechanisms (i.e., S100B is known as an inflammatory factor, while ZAG is known as a noninflammatory factor), there may be similarities between them. 3T3-L1 adipocytes are one of the main sources of S100B secretion [22], and, interestingly, these cells also synthesize ZAG [23]. The same synthesis origin may lead to connections between them.

The next hypothesis is about zinc as an essential micronutrient. In addition to calcium, S100B can form dimers with other divalent ions such as zinc. Zinc binding to S100B increases its affinity to calcium, target peptides, and proteins [24]. S100B also affects homeostasis and regulates the amount of zinc in the brain [25]. On the other hand, the molecular structure of ZAG has zinc-binding sites (one strong zinc-binding site and up to 15

Table 2 Patients' characteristics grouped by serum S100B concentration: demographic data

Characteristics	S100B lower than 57.200 (μg/L) (*n* = 22)	S100B higher than 57.200 (μg/L) (*n* = 20)	*p*
Age	42.23 ± 9.18	41.15 ± 8.43	0.695
Duration of illness	8.36 ± 5.19	6.15 ± 5.57	0.949
Current smokers	19 (42.55%)	12 (28.45%)	0.051
AAPM	10 (23.80%)	3 (7.0%)	0.035
TAPM	8 (19.0%)	12 (28.50%)	0.161
CAPM	6 (14.30%)	5 (11.20%)	0.079
Body weight (kg)	71.13 ± 15.21	73.40 ± 9.97	0.136
WC (cm)	86.84 ± 10.07	88.35 ± 7.98	0.452
BMI (kg/m^2)	24.08 ± 4.38	24.95 ± 3.50	0.490
Obesity	9 (21.50%)	11 (26.20%)	0.361
TG (mg/dL)	162.50 ± 53.51	153.55 ± 53.45	0.579
TC (mg/dL)	152.62 ± 22.17	160.10 ± 25.82	0.331
HDL-c (mg/dL)	35.66 ± 4.95	35.35 ± 5.27	0.843
LDL-c (mg/dL)	90.61 ± 13.78	95.80 ± 17.16	0.731
Dyslipidemia	15 (35.70%)	16 (38.0%)	0.384
FBG	90.61 ± 7.41	94.15 ± 10.35	0.530
HOMA-IR	1.17 (0.92,1.86)	2.65 (1.25,4.04)	0.037
Diabetes	2 (5.0%)	2 (5.0%)	0.952
ZAG (ng/mL)	43.10 (27.35,52.70)	72.25 (44.72,127.95)	0.005
SBP (mmHg)	121.76 ± 7.99	120.60 ± 8.63	0.652
DBP(mmHg)	77.66 ± 5.89	94.15 ± 10.35	0.215
Hypertension	3 (7.0%)	3 (7.0%)	0.948
PANSS-NSS	29.24 ± 5.25	29.35 ± 4.55	0.942
PANSS-PSS	25.48 ± 5.25	25.95 ± 4.75	0.764
PANSS-GPSS	58.71 ± 5.69	57.25 ± 5.76	0.418
PANSS-TS	113.86 ± 11.55	113.10 ± 12.05	0.833

Data were expressed as mean ± SD, median (percentile 25, 75), and *n* (%)

p values were reported based on independent samples *t*-test or Mann–Whitney *U* test

AAPM atypical antipsychotic medications, *TAPM* typical antipsychotic medications, *CAPM* combined antipsychotic medications, *WC* waist circumference, *BMI* body mass index, *TG* triglyceride, *TC* total cholesterol, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *FBG* fasting blood glucose, *HOMA-IR* homeostatic model assessment—insulin resistance, *ZAG* zinc alpha 2-glycoprotein, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *PANSS* Positive and Negative Syndrome Scale, *PANSS-NSS* PANSS negative subscale score, *PANSS-PSS* PANSS positive subscale score, *PANSS-GPSS* PANSS general psychopathology subscale score, *PANSS-TS* PANSS total score

weak zinc-binding sites), that regulate the homeostasis of ZAG in the body [26]. The effect on zinc may be a common denominator between S100B and ZAG.

Moreover, there is also evidence for the effects of hormones on S100B and ZAG levels., both S100B and ZAG are downregulated by circulating insulin; also, studies have shown an inverse relationship between plasma leptin and S100B and ZAG levels [27].

Our findings also indicate that patients treated with AAPM had lower serum S100B levels. Studies have shown that AAPM (such as clozapine, haloperidol, and risperidone) reduced S100B levels. This mechanism occurs through the inhibition of astrocytic dopamine D2 receptors (DRD2) [28, 29]. In the present study, no association was found between serum levels of S100B and other metabolic and clinical factors. The selected patients were hospitalized patients with chronic schizophrenia, all of whom had been treated with various antipsychotic drugs for many years, and, consequently, all had metabolic complications; this may be one of the reasons for the lack of correlation between other metabolic factors and serum S100B levels. There are some limitations in our study, including the relatively small sample size of patients; further, this study was observational, and

Table 3 Univariate linear regression analyses of factors that correlate with higher S100B levels

Variable	Coefficient	95% CI	*p*
Age (years)	−0.212	−3.775 to 0.723	0.178
Duration of illness (year)	−0.103	−4.823 to 2.468	0.518
Body weight (kg)	0.002	−1.534 to 1.555	0.989
WC (cm)	0.086	−1.597 to 2.778	0.588
BMI (kg/m^2)	−0.056	−5.591 to 4.176	0.725
TG (mg/dL)	−0.238	−0.652 to 0.082	0.129
CHOL (mg/dL)	0.147	0.438 to 1.190	0.353
HDL-c (mg/dL)	−0.043	−4.489 to 3.430	0.788
LDL-c (mg/dL)	0.122	−0.790 to 1.780	0.440
FBG (mg/dL)	0.280	−2.360 to 2.422	0.862
HOMA-IR	0.573	8.956 to 24.412	< 0.001
ZAG (ng/mL)	0.469	0.162 to 0.670	0.002
SBP (mmHG)	0.044	−2.134 to 2.824	0.780
DBP (mmHg)	−0.051	−4.431 to 3.202	0.746
PANSS-NSS	0.122	−2.526 to 5.695	0.440
PANSS-PSS	0.522	−3.388 to 4.703	0.744
PANSS-GPSS	0.739	−4.099 to 2.930	0.739
PANSS-TS	0.148	−0.907 to 2.505	0.349
Predictors of high serum S100B levels in multivariate linear regression analysis			
HOMA-IR	0.596	(8.722,26.002)	< 0.001
ZAG (ng/mL)	0.334	0.067 to 0.525	0.013

WC waist circumference, *BMI* body mass index, *TG* triglyceride, *TC* total cholesterol, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *FBG* fasting blood glucose, *HOMA-IR* homeostatic model assessment—insulin resistance, *ZAG* zinc alpha 2-glycoprotein, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *PANSS* Positive and Negative Syndrome Scale, *PANSS-NSS* PANSS negative subscale score, *PANSS-PSS* PANSS positive subscale score, *PANSS-GPSS* PANSS general psychopathology subscale score, *PANSS-TS* PANSS total score

it is impossible to account for all possible confounding factors.

Conclusion

The findings of our study demonstrate that high levels of plasma S100B in patients may contribute to IR and ZAG levels. However, further studies are needed to replicate our findings.

Abbreviations

ZAG	Zinc-α2-glycoprotein
BW	Body weight
WC	Waist circumference
BP	Blood pressure
HDL	High-density lipoprotein cholesterol
LDL	Low-density lipoprotein cholesterol
TG	Triglyceride
CHOL	Cholesterol
FBG	Fasting blood glucose
HOMA	Homeostatic Model Assessment
IR	Insulin resistance
PANSS	Positive and negative syndrome scale
CI	Confidence interval
AAPM	Atypical antipsychotic medications (AAPM)
CSF	Cerebrospinal fluid
BMI	Body mass index
SD	Standard deviation
CNS	Central nervous system
DRD2	Dopamine D2 receptors
ELISA	Enzyme-linked immunosorbent assay
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision

Acknowledgements

The authors would like to thank all the patients who participated in the study. This study was derived from a Doctoral thesis approved at the Ethics Committee of the Tabriz University of Medical Sciences, Iran (Ethical No: IR.TBZMED.REC.1397.1025, ID: 61676, https://ethics.research.ac.ir/ProposalCertificateEn.php?id=51890&Print=true&NoPrintHeader). All authors were involved in manuscript writing and they read and approved the final manuscript.

Authors' contributions

Sorayya Kheirouri and Parinaz Kalejahi: concept and design the study. Seyed Gholamreza Noorazar: diagnose and introduce patients. Parinaz Kalejahi: data collection and interpretation of the data. Sorayya Kheirouri, Parinaz Kalejahi, and Seyed Gholamreza Noorazar: wrote the manuscript with input from all authors. All authors discussed and approved the results and contributed to the final manuscript.

Funding

Tabriz University of Medical Sciences, IRAN supported this study. (Grant number: 61676).

Availability of data and materials

The datasets used or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The ethics committee of the Tabriz University of Medical Sciences approved the study protocol and the trial was registered with the Iranian Registry of Clinical Trials (code: IRCT20190313043039N1). Written informed consent was also obtained from a first-degree relative of each patient before the participant were enrolled in the study.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Received: 25 April 2023 Accepted: 9 May 2023
Published online: 11 August 2023

References

1. Charlson FJ, Ferrari AJ, Santomauro DF, Diminic S, Stockings E, Scott JG et al (2018) Global epidemiology and burden of schizophrenia: findings from the global burden of disease study 2016. Schizophr Bull 44(6):1195–1203
2. Dietz AG, Goldman SA, Nedergaard M (2020) Glial cells in schizophrenia: a unified hypothesis. Lancet Psychiatry 7(3):272–281
3. Bresnick AR (2018) S100 proteins as therapeutic targets. Biophys Rev 10(6):1617–1629
4. Rezaei O, Pakdaman H, Gharehgozli K, Simani L, Vahedian-Azimi A, Asaadi S et al (2017) S100 B: A new concept in neurocritical care. Iran J Neurol 16(2):83

5. Deng H, Kahlon RS, Mohite S, Amin PA, Zunta-Soares G, Colpo GD et al (2018) Elevated plasma S100B, psychotic symptoms, and cognition in schizophrenia. Psychiatr Q 89(1):53–60
6. Yelmo-Cruz S, Morera-Fumero AL, Abreu-González P (2013) S100B and schizophrenia. Psychiatry Clin Neurosci 67(2):67–75
7. Rothermundt M, Falkai P, Ponath G, Abel S, Bürkle H, Diedrich M et al (2004) Glial cell dysfunction in schizophrenia indicated by increased S100B in the CSF. Mol Psychiatry 9(10):897–899
8. Aleksovska K, Leoncini E, Bonassi S, Cesario A, Boccia S, Frustaci A (2014) Systematic review and meta-analysis of circulating S100B blood levels in schizophrenia. PLoS ONE 9(9):e106342
9. Steiner J, Bielau H, Bernstein H, Bogerts B, Wunderlich M (2006) Increased cerebrospinal fluid and serum levels of S100B in first-onset schizophrenia are not related to a degenerative release of glial fibrillar acidic protein, myelin basic protein and neurone-specific enolase from glia or neurones. J Neurol Neurosurg Psychiatry 77(11):1284–1287
10. Koh SX, Lee JK (2014) S100B as a marker for brain damage and blood–brain barrier disruption following exercise. Sports Med 44(3):369–385
11. Rothermundt M, Missler U, Arolt V, Peters M, Leadbeater J, Wiesmann M et al (2001) Increased S100B blood levels in unmedicated and treated schizophrenic patients are correlated with negative symptomatology. Mol Psychiatry 6(4):445–449
12. O'Connell KE, Thakore J, Dev KK (2014) Pro-inflammatory cytokine levels are raised in female schizophrenia patients treated with clozapine. Schizophr Res 156(1):1–8
13. Gonçalves CA, Leite MC, Guerra MC (2010) Adipocytes as an important source of serum S100B and possible roles of this protein in adipose tissue. Cardiovasc Psychiatry Neurol. 2010:790431. https://doi.org/10.1155/2010/790431.
14. Namkhah Z, Naeini F, Ostadrahimi A, Tutunchi H, Hosseinzadeh-Attar MJ (2021) The association of the adipokine zinc-alpha2-glycoprotein with non-alcoholic fatty liver disease and related risk factors: A comprehensive systematic review. Int J Clin Pract. 75(7):e13985. https://doi.org/10.1111/ijcp.13985.
15. Marrades M, Martinez J, Moreno-Aliaga M (2008) ZAG, a lipid mobilizing adipokine, is downregulated in human obesity. J Physiol Biochem 64(1):61–66
16. Yang M, Liu R, Li S, Luo Y, Zhang Y, Zhang L et al (2013) Zinc-α2-glycoprotein is associated with insulin resistance in humans and is regulated by hyperglycemia, hyperinsulinemia, or liraglutide administration: cross-sectional and interventional studies in normal subjects, insulin-resistant subjects, and subjects with newly diagnosed diabetes. Diabetes Care 36(5):1074–1082
17. Steiner J, Myint AM, Schiltz K, Westphal S, Bernstein H-G, Walter M et al (2010) S100B serum levels in schizophrenia are presumably related to visceral obesity and insulin resistance. Cardiovasc Psychiatry Neurol. 2010:480707. https://doi.org/10.1155/2010/480707.
18. Bernstein H-G, Ernst T, Lendeckel U, Bukowska A, Ansorge S, Stauch R et al (2009) Reduced neuronal expression of insulin-degrading enzyme in the dorsolateral prefrontal cortex of patients with haloperidol-treated, chronic schizophrenia. J Psychiatr Res 43(13):1095–1105
19. Steiner J, Walter M, Guest P, Myint A, Schiltz K, Panteli B et al (2010) Elevated S100B levels in schizophrenia are associated with insulin resistance. Mol Psychiatry 15(1):3–4
20. Mackin P, Watkinson H, Young A (2005) Prevalence of obesity, glucose homeostasis disorders and metabolic syndrome in psychiatric patients taking typical or atypical antipsychotic drugs: a cross-sectional study. Diabetologia 48(2):215–221
21. Yogaratnam J, Biswas N, Vadivel R, Jacob R (2013) Metabolic complications of schizophrenia and antipsychotic medications-an updated review. East Asian Arch Psychiatry 23(1):21–28
22. Fujiya A, Nagasaki H, Seino Y, Okawa T, Kato J, Fukami A et al (2014) The role of S100B in the interaction between adipocytes and macrophages. Obesity 22(2):371–379
23. Xiao X-H, Qi X-Y, Wang Y-D, Ran L, Yang J, Zhang H-L et al (2018) Zinc alpha2 glycoprotein promotes browning in adipocytes. Biochem Biophys Res Commun 496(2):287–293
24. Ostendorp T, Diez J, Heizmann CW, Fritz G (2011) The crystal structures of human S100B in the zinc-and calcium-loaded state at three pH values reveal zinc ligand swapping. Biochim Biophys Acta 1813(5):1083–91
25. Hagmeyer S, Cristóvão JS, Mulvihill JJ, Boeckers TM, Gomes CM, Grabrucker AM (2018) Zinc binding to S100B affords regulation of trace metal homeostasis and excitotoxicity in the brain. Front Mol Neurosci 10:456
26. Kumar AA, Hati D, Miah L, Cunningham P, Domene C, Bui TT et al (2013) Strong and weak zinc binding sites in human zinc-α2-glycoprotein. FEBS Lett 587(24):3949–3954
27. Hendouei N, Hosseini SH, Panahi A, Khazaeipour Z, Barari F, Sahebnasagh A et al (2016) Negative correlation between serum S100B and Leptin levels in schizophrenic patients during treatment with clozapine and risperidone: preliminary evidence. Iran J Pharm Res 15(1):323
28. Steiner J, Schroeter ML, Schiltz K, Bernstein H, Müller U, Richter-Landsberg C et al (2010) Haloperidol and clozapine decrease S100B release from glial cells. Neuroscience 167(4):1025–1031
29. Nardin P, Tramontina AC, Quincozes-Santos A, Tortorelli LS, Lunardi P, Klein PR et al (2011) In vitro S100B secretion is reduced by apomorphine: effects of antipsychotics and antioxidants. Prog Neuropsychopharmacol Biol Psychiatry 35(5):1291–1296

Publisher's Note