Schizophrenia Research 267 (2024) 223–229

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Cellular adhesion molecules in drug-naïve and previously medicated patients with schizophrenia-spectrum disorders

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ARTICLE INFO

Keywords:
Schizophrenia-spectrum disorders
Non-affective psychosis
Neuroinflammation
Endothelial inflammation
Cellular adhesion molecules
PANSS

ABSTRACT

Background: Endothelial inflammation may be involved in the pathogenesis of schizophrenia, and cellular adhesion molecules (CAMs) on endothelial cells may facilitate leukocyte binding and transendothelial migration of cells and inflammatory factors. The aim of the present study was to assess levels of soluble cellular adhesion molecules, including intercellular adhesion molecule (ICAM)-1, vascular adhesion molecule (VCAM)-1, mucosal addressin cell adhesion molecule (MADCAM), junctional adhesion molecule (JAM-A) and neural cadherin (N-CAD) in patients with schizophrenia compared to healthy controls.

Methods: The study population consists of 138 patients with schizophrenia-spectrum disorder, of whom 54 were drug-naïve, compared to 317 general population controls. The potential confounders age, gender, smoking and body mass index (BMI) were adjusted for in linear regression models.

Results: The total patient group showed significantly higher levels of ICAM-1 ($p < 0.001$) and VCAM-1 ($p < 0.001$) compared to controls. Previously medicated patients showed higher ICAM-1 levels compared to drug-naïve patients ($p = 0.042$) and controls ($p < 0.001$), and elevated VCAM-1 levels compared to controls ($p < 0.001$). Drug-naive patients had elevated levels of VCAM-1 ($p = 0.031$) compared to controls.

Conclusions: In our study, patients with schizophrenia – including the drug-naïve – have higher levels of soluble CAMs compared to healthy controls. These findings suggest activation of the endothelial system as in inflammation.

1. Introduction

Schizophrenia is a severe and debilitating neuropsychiatric disorder with a lifetime prevalence of approximately 0.7 % (Jauhar et al., 2022; Tandon et al., 2008). The disorder is characterized by psychotic symptoms comprising positive symptoms including delusions and hallucinations (Howes and Kapur, 2009; Tandon et al., 2009), and negative symptoms such as apathy and anhedonia, as well as cognitive dysfunction (Tandon et al., 2009). Patients with schizophrenia have an up to 5-fold increase in age-adjusted mortality risk compared to the general

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https://doi.org/10.1016/j.schres.2024.03.029
Received 22 August 2023; Received in revised form 8 February 2024; Accepted 18 March 2024
Available online 3 April 2024

population, with cardiovascular risk as a major contributor (Heiberg et al., 2018; Momen et al., 2020; Tandon et al., 2009). Epidemiological studies have reported that schizophrenia patients die on average 10 to 15 years earlier from cardiovascular disease compared to the general population (Crump et al., 2013; Westman et al., 2018). Genome wide association studies (GWAS) suggest shared genetic risk factors for schizophrenia and cardiovascular disease (Andreassen et al., 2013) including type 2 diabetes mellitus (Hackinger et al., 2018).

The pathogenesis of schizophrenia is incompletely understood, but GWAS studies indicate that genes coding for proteins of the immune system (like CD19 and CD20) are related to this disorder (Khandaker and Dantzer, 2016; Ripke et al., 2013). Moreover, a strong association is observed in the major histocompatibility complex (MHC) region on chromosome 6p22.1 for schizophrenia (Muller et al., 2015; Schizophrenia Working Group of the Psychiatric Genomics, C, 2014). Also, numerous studies report modestly upregulated levels of inflammatory proteins in peripheral blood in schizophrenia patients (Rodrigues-Amorim et al., 2017). A prevailing hypothesis is that the inflammatory process starts in the peripheral tissues, and spreads to the brain causing a chronic low-grade brain inflammation (Khandaker and Dantzer, 2016; Najjar et al., 2017). Thus, the processes of flux and transport of inflammatory cells and molecules over the blood-brain barrier (BBB) may be of importance in the understanding of the pathophysiology of schizophrenia. The integrity of the BBB is crucial for brain homeostasis and immunity by regulating influx and efflux of essential nutrients and toxic substances and restricting entrance of peripheral inflammatory mediators (Najjar et al., 2017). Systemic immune activation and inflammation could enhance integrins on immune cells or chemokine production and contribute to recruitment of immune cells to the BBB (Khandaker and Dantzer, 2016). Activated endothelial cells may trigger upregulation of pro-inflammatory cytokines. This can via induced expression of cellular adhesion molecules (CAMs) cause increased permeability of the BBB facilitating cerebral transendothelial migration of inflammatory factors (Najjar et al., 2017), further promoting neuroinflammation. Indeed, BBB function may be compromised leading to increased permeability in schizophrenia, and similar problems have also been noted for affective disorders and autism spectrum disorders (Kealy et al., 2020). A possible link between BBB dysfunction and schizophrenia could be a tight junction protein, claudin-5, known to have a key function in the tight junctions between brain capillaries and endothelial cells (Jia et al., 2014). A genetic association is found between claudin-5, a single nucleotide polymorphism (allele rs10314), and schizophrenia development (Kealy et al., 2020). Claudin-5 is also implicated in affective disorders (Hochman et al., 2023), but not in other psychiatric conditions including autism spectrum disorders (Bilgic et al., 2023). In schizophrenia patients, there is found a discrepancy between expression of claudin-5 mRNA and protein in the prefrontal cortex, where mRNA expression is significantly increased followed by a reduction of protein expression and breakdown of claudin-5. This could possibly be due to abnormal signalling of cAMP and protein kinase A (Nishiura et al., 2017). In CSF, levels of tight junction proteins, including claudin-5, have been shown to correlate with BBB permeability and damage (Kealy et al., 2020).

The CAMs are a group of transmembrane proteins (Elangbam et al., 1997). The intercellular adhesion molecule (ICAM)-1, the vascular adhesion molecule (VCAM)-1, the mucosal addressin cell adhesion molecule (MADCAM) and the junctional adhesion molecule (JAM)-A are all soluble glycoproteins belonging to the immunoglobulin superfamily (Elangbam et al., 1997; Kronig et al., 2005). They are expressed on blood cells and connective tissue after activation by signals from pro-inflammatory cytokines. ICAM-1 and VCAM-1 are involved in the adhesion and migration of immune cells from the blood through endothelium in inflammation (Najjar et al., 2017; Schwarz et al., 2000), including the BBB. Upon production CAMs are released in circulation, and levels of ICAM-1 and VCAM-1 in peripheral blood may therefore reflect inflammatory BBB permeability (Schwarz et al., 2000; Stefanovic et al., 2016). Also, loss of claudin-5 can induce expression of CAMs, including ICAM-1 and VCAM-1, and possibly promote an immune response (Greene et al., 2022). MADCAM expression is mainly by endothelial cells in mucosa (Elangbam et al., 1997) and elevated levels could contribute to increased traffic of leukocytes into the intestine (Jensen et al., 2023). JAM-A is expressed by thrombocytes, neutrophils and mononuclear cells in endothelial and epithelial cell tight junctions (Haarmann et al., 2010; Stamatovic et al., 2012). JAM-A is involved in endothelial cell adhesion and migration of leukocytes (Yeung et al., 2008). Neural cadherin (N-CAD) take part in intracellular signalling pathways and modulates morphogenesis by mediation of cell adhesion (Redies et al., 2012). A schematic overview of the levels of CAMs in schizophrenia is given in table S6 in the supplementary material, which is built upon current knowledge including findings in a recent article (Sheikh et al., 2022) and a recent systematic review and meta-analysis (Zinellu and Mangoni, 2023), showing the sparsity of studies in the field. One current hypothesis is that altered levels of CAMs may link systemic inflammation and neuroinflammation in schizophrenia (Najjar et al., 2017; Rodrigues-Amorim et al., 2017). However, the sparse literature reports conflicting results on levels of CAMs in patients with schizophrenia (Cai et al., 2020a; Kronig et al., 2005; Nguyen et al., 2017; Radu et al., 2020; Schwarz et al., 2000; Stefanovic et al., 2016). There have been reports of lower (Kronig et al., 2005; Radu et al., 2020; Schwarz et al., 2000), higher (Cai et al., 2020a; Nguyen et al., 2017; Sheikh et al., 2022; Stefanovic et al., 2016) and normal (Stefanovic et al., 2016) levels of ICAM-1, and lower (Stefanovic et al., 2016), higher (Radu et al., 2020) and normal (Nguyen et al., 2017; Sheikh et al., 2022) levels of VCAM-1. There have also been reports of higher levels of MADCAM (Jensen et al., 2023) and JAM-A (Sheikh et al., 2022) and normal levels of N-CAD (Sheikh et al., 2022) in schizophrenia patients. Our hypothesis of the function of CAMs in schizophrenia pathology can also build on findings in the nervous system. In a study of patients with neuromyelitis optica, an immune-mediated neuroinflammatory disease, ICAM-1 and VCAM-1 levels were higher in patients compared to controls, which could emphasize CAMs as possible biomarkers in BBB breakdown signalling (Chang et al., 2020). In a study of patients with acute spontaneous intracerebral haemorrhage, ICAM-1 and VCAM-1 levels were elevated in patients compared to controls, concluding that elevated ICAM-1 could suggest worse treatment outcomes, but also offer a potential target for therapy (Wang et al., 2011).

Furthermore, experimental and clinical studies suggest that treatment with antipsychotics may influence levels of CAMs, thereby confounding comparisons (Barcones et al., 2017; Graham et al., 2008; Meyer et al., 2009). Thus, it is of importance to investigate drug-naïve patients.

The aim of the present study was to explore levels of circulating CAMs, in patients with schizophrenia-spectrum disorders, including drug-naïve patients and previously medicated patients, compared to healthy controls.

2. Materials and methods

2.1. Design

The study was a cross sectional observational study with participants from a multi-site randomized rater-blinded antipsychotic drug trial with four collaborating centres; Bergen, Stavanger and Trondheim in Norway and Innsbruck in Austria (BeSt InTro study). Inclusion started in 2012. There were included 138 patients with blood tests available for measurements of CAMs. All patients were assessed at baseline before initiating antipsychotic treatment. Of the 138 included patients, 54 patients were first episode and drug-naïve with respect to antipsychotic medication, meaning no previous exposure to antipsychotic drugs before the study. There were recruited 41 of the 317 healthy controls from the Bergen inclusion centre of the BeSt InTro study. Healthy controls were also included from the ongoing Thematically Organized Psychosis (TOP)

Study at the Norwegian Center for Mental Disorders Research (NORMENT) in Oslo for extended analyses. The BeSt InTro study was approved in Norway by the Regional Committee for Medical and Health Research Ethics, and by the Norwegian Medicines Agency, and in Austria by the Etikkommission der Medizinische Universität Innsbruck, and the Austrian Federal Office for Safety in Health Care (BASG). The TOP Study was approved by the Regional Committees for Medical and Health Research Ethics.

2.2. Patients

Patients recruited were ≥ 18 years with an ICD-10 (World Health Organization (WHO), 1993) diagnosis in the schizophrenia spectrum (F20-F29). Patients were eligible if they had a score of ≥4 on ≥1 of the items Delusions, Hallucinatory behaviour, Grandiosity, Suspiciousness/persecution, or Unusual thought content in the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). Patients with the following characteristics were excluded: Inability to understand the native language, organic psychosis, pregnant or breastfeeding women or individuals with concomitant prolactin-dependent tumours (e.g. pituitary gland prolactinomas, breast cancer or phaeochromocytoma), or a known risk of narrow-angle glaucoma. Patients were recruited from the Haukeland University Hospital, the Stavanger University Hospital, St. Olavs University Hospital of Trondheim and the Medizinische Universität, Innsbruck, consecutively on the basis of written informed consent.

2.3. Controls

Healthy controls from the Bergen inclusion center of the BeSt InTro study were recruited among employees and colleagues, and their relatives, on the basis of written informed consent. These participants were screened for psychiatric disorders, brain-related somatic illnesses including neurological conditions, and drug abuse/dependency.

Healthy control data were also obtained from the Thematically Organized Psychosis (TOP) study at the Norwegian Centre for Mental Disorders Research (NORMENT) Centre of Excellence. These participants were randomly drawn from the Oslo area from Statistics Norway and screened for severe psychiatric disorders, severe psychiatric disorders in close relatives, brain-related somatic illnesses including neurological conditions, mental retardation and drug abuse/dependency. The control group was created by matching 1:2 the 138 patients for age, gender, smoking and BMI with 138 × 2 healthy controls selected from the 901 available controls of the TOP sample. Finally, the 276 matched controls from the TOP study were merged with the 41 controls form the BeSt InTro study to create the control group consisting of 317 healthy controls. Healthy control data, included from the TOP study, overlapping with the current study have been previously published (Elkjaer Greenwood Ormerod et al., 2022; Jensen et al., 2023; Saether et al., 2023; Sheikh et al., 2022). The TOP study was approved by the Regional Committees for Medical and Health Research Ethics in Norway and the Norwegian Data Protection Agency, and all participants gave written consent.

2.4. Assessments

Patients were assessed at baseline before randomization and initiation of the antipsychotic drug treatment. The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) (Spitzer et al., 1992) was used for psychiatric diagnostics and DSM IV diagnosis was converted into corresponding ICD-10 diagnosis. General assessments included demographics, mental and physical illness, and use of drugs/alcohol/nicotine. Psychometric assessments included the Positive and Negative Syndrome Scale (PANSS). Controls were assessed with screening interview about severe mental illness and controls from the TOP study were also assessed with Primary Care Evaluation of Mental Disorders (PRIME-MD) (Simonsen et al., 2011). Physical examinations included body mass index (BMI). All laboratory blood tests for the patients were performed the same day as the PANSS rating and included general biochemical and inflammatory markers. For analyses of CAMs, serum (for patients and controls from the BeSt InTro study) were collected, after fasting overnight, in the morning between 8 AM and 10 AM and plasma (for controls from the TOP study) were collected between 8 AM and 5 PM, drawn in serum tubes and plasma tubes respectively, centrifugated at 3300 rpm and stored in a freezer at -80 Celsius until analyses.

Levels of ICAM-1, VCAM-1, MADCAM, JAM-A and N-CAD were measured in duplicate through enzymelinked immunoassays using commercially available antibodies (R&D Systems) in a 384-format using a combination of a SELMA (Jena, Germany) pipetting robot and a Bio-Tek (Winooski, VT, USA) dispenser/washer. Absorption was read at 450 nm with wavelength correction set to 540 nm using an EIA plate reader (Bio-Rad, Hercules, CA, USA). The intra-assay coefficient of variation (%), based on data from our laboratory in Oslo, was <10 %.

2.5. Statistics

Data were extracted from SPSS data files (SPSS version 26.0, IBM SPSS statistics, Armonk, NY, USA) and all analyses were performed using R 4.0 (https://www.R-project.org). In analyzing the variables, a skewness was observed in the CAMs data with a heavy tailed distribution to the right. Therefore, the CAMs values were log-transformed to make them more normally distributed. Previous studies have shown that age (Blann et al., 1996), gender (Blann et al., 1996), smoking (Scott and Palmer, 2002) and BMI (Bosanska et al., 2010) could possibly influence the levels of CAMs. Therefore, patients and plasma sample controls were matched for these potential confounders with the package "MatchIt" in R. The following comparisons were performed: 1) all patients vs. controls; 2) antipsychotic-naive patients vs. controls; 3) previously medicated patients vs. controls; 4) antipsychotic-naive patients vs. previously medicated patients. In the analysis, unadjusted comparisons of groups were done using *t*-tests, adjusted comparisons using a model adjusting for the aforementioned confounders. Missing data were handled with multiple imputation with the package "mice" in R.

3. Results

3.1. Demographics of the study population

In the patient group, mean age was 31.7 years, 36 % were female and mean BMI was 25.5.

In the control group, mean age was 31.5 years, 36 % were female and mean BMI was 25.2. Years of education differed between the groups, with significant more years of education in the control group ($p < 0.001$). Smoking were similar between the groups, see Table 1.

Drug-naïve patients and previously medicated patients were overall similar, except for years of education and living situation were the drug-naïve patient group had significant less years of education ($p = 0.032$) and the previously medicated patient group had significantly more participants that lived alone ($p = 0.034$), see Table 2.

Table 1
Demographic and clinical data in patients versus controls.

	Patients (N = 138)	Controls (N = 317)	p-Values
Age, mean (SD)	31.7 (12.7)	31.5 (11.2)	0.726
Gender, males	88/138 (64 %)	204/317 (64 %)	0.989
Years of education	12.2 (2.8)	14.4 (2.3)	**<0.001**
Smoking	82/138 (59 %)	192/317 (61 %)	0.900
BMI	25.5 (5.9)	25.2 (4.2)	0.773

BMI, body mass index. SD, standard deviation. Numbers in the table are mean (SD) for continuous variables, and portion (%) for categorical variables. Continuous variables are compared using *t*-tests, categorical variables using chi-squared tests. Statistical significance in bold font.

Table 2
Demographic and clinical data in drug-naive versus previously medicated.

	Drug-naive (N = 54)	Previously medicated (N = 84)	p-Values
Age, mean (SD)	31.3 (12.5)	32.0 (12.9)	0.861
Gender, males	34/54 (63 %)	54/84 (64 %)	1.000
Years of education	11.6 (2.6)	12.6 (2.9)	**0.032**
Living alone	18/54 (33 %)	42/84 (50 %)	**0.034**
Employed	13/54 (24 %)	21/84 (25 %)	1.000
Smoking	33/54 (61 %)	49/84 (58 %)	0.699
BMI	24.4 (6.7)	26.3 (5.2)	0.087
Duration of illness (years), mean (SD)	4.3 (7.0)	6.9 (8.0)	0.099
Diagnosis: Schizophrenia	30/54 (56 %)	51/84 (61 %)	0.672
Diagnosis: Delusional disorder	10/54 (19 %)	9/84 (11 %)	0.214
Diagnosis: Brief psychotic disorder	4/54 (7 %)	14/84 (17 %)	0.129
Diagnosis: Schizoaffective	2/54 (4 %)	7/84 (8 %)	0.482
PANSS total	76.3 (13.0)	80.1 (17.5)	0.144
PANSS positive	20.8 (4.5)	21.5 (5.0)	0.361
PANSS negative	17.6 (5.5)	18.1 (6.4)	0.604
PANSS general	37.9 (6.9)	40.5 (9.4)	0.071

PANSS, positive and negative syndrome scale. BMI, body mass index. Statistical significance in bold font.

3.2. Comparisons of CAMs in patients and healthy controls

The total patient group had significantly higher levels of ICAM-1 ($p < 0.001$) and VCAM-1 ($p < 0.001$) compared to the control group. MADCAM, JAM-A and N-CAD showed similar levels between patients and controls, see Table 3.

Drug-naïve patients had significantly higher levels of VCAM-1 ($p = 0.031$) compared to controls. The other CAMs showed similar levels between the groups, see Table 3.

The previously medicated patient group had significantly elevated levels of ICAM-1 ($p < 0.001$) and VCAM-1 ($p < 0.001$) compared to the control group. MADCAM, JAM-A and N-CAD showed similar levels in previously medicated patients, see Table 3.

The previously medicated patient group had significantly elevated levels of ICAM-1 compared to the drug-naïve patient group ($p = 0.042$). Furthermore, the drug-naïve patients showed non-significant lower levels of all measured CAMs compared to the previously medicated patients, see Table 3.

3.3. Comparison between serum CAMs and plasma CAMs

We also did an in-house validation of our method in form of a small scale intra-individual comparison trial between serum CAMs and plasma CAMs samples in 12 healthy subjects. Of the measured parameters, differences in serum and plasma were noted for ICAM-1 and VCAM-1 with median 15 % ($p = 0.024$) and 13 % ($p = 0.018$) lower levels in serum compared to plasma, respectively, and MADCAM with median 20 % higher levels in serum ($p = 0.01$).

4. Discussion

The main finding in our study is that patients with schizophrenia had higher levels of ICAM-1 and VCAM-1 compared to controls. Previously medicated patients had significantly higher levels of ICAM-1 compared to both drug-naïve patients and controls. Furthermore, the levels of VCAM-1 in both drug-naïve patients and previously medicated patients were significantly elevated compared to controls. These findings of elevated CAMs support the hypothesis that inflammatory processes are involved in schizophrenia development independent of antipsychotic drug treatment (Najjar et al., 2017; Rodrigues-Amorim et al., 2017).

So far, research of CAMs in schizophrenia is scarce, particularly in drug-naïve patients, where to the best of our knowledge, there is only one previous report. This study of first episode schizophrenia patients, later treated with olanzapine or risperidone, found higher levels of VCAM-1 compared to matched controls. However, they found levels of ICAM-1 to be lower in the patient group (Radu et al., 2020). In contrast to our results, decreased levels of ICAM-1 in a mixed patient sample compared to controls have also been found by others (Kronig et al., 2005; Schwarz et al., 2000). However, in the aforementioned studies the patient samples were smaller compared to our study. Our results in the whole schizophrenia sample are in line with three other recent studies reporting significantly elevated ICAM-1 levels in schizophrenia (Cai et al., 2020a; Nguyen et al., 2017; Sheikh et al., 2022). Furthermore, we also found significantly elevated levels of VCAM-1 in comparison between patients and controls. However, three recent studies did not find elevated levels of VCAM-1 (Cai et al., 2020a; Nguyen et al., 2017; Sheikh et al., 2022), which could be due to lack of control for confounders and a poorly matched control sample. Another study reported decreased levels of VCAM-1 in patients both in early and late stage of psychotic disorders, while patients in the later stages had elevated levels of ICAM-1 compared to matched controls (Stefanovic et al., 2016).

Our finding of elevated levels of ICAM-1 in patients with schizophrenia could represent an activation of a Th1 response in the immune system (Nguyen et al., 2017; Stefanovic et al., 2016). Comparing levels of inflammation in first episode schizophrenia and multi-episode patients, one study suggested that a decreased ICAM-1 level could be characteristic of first episode patients, supporting the hypothesis about activation of Th2 response in the immune system, and furthermore that an elevated ICAM-1 level could indicate a Th1 response in multi-episode patients with schizophrenia (Stefanovic et al., 2016). However, other findings do not support that inflammation in schizophrenia follows a strict schematic Th1/Th2 separation (Kim et al., 2004). Elevated ICAM-1 in patients compared to controls could reflect endothelial inflammation in patients with schizophrenia spectrum disorders, which has been suggested in the literature (Najjar et al., 2017).

Higher ICAM-1 levels have been related to BBB leakiness in schizophrenia (Schwarz et al., 2000). The immune system and the brain interact actively at the level of the BBB, where the endothelial lining of

Table 3
CAMs in all patients, previously medicated patients, drug-naïve patients and controls.

					All patients (N = 138) versus controls (N = 317)		Drug-naïve patients (N = 54) versus controls (N = 149)		Previously medicated patients (N = 84) versus controls (N = 209)		Drug-naïve patients (N = 54) versus previously medicated patients (N = 84)	
	All patients	Previously medicated	Drug-naive	Controls	p-Values unadjusted	p-Values adjusted	p-Values unadjusted	p-Values adjusted	p-Values unadjusted	p-Values adjusted	p-Values unadjusted	p-Values adjusted
ICAM-1	325.6	339.2	304.5	275.3	**<0.001**	**<0.001**	0.081	0.065	**<0.001**	**<0.001**	**0.032**	**0.042**
VCAM-1	578.9	583.8	571.3	516.4	**<0.001**	**<0.001**	**0.035**	**0.031**	**<0.001**	**<0.001**	0.661	0.536
MADCAM	8.00	8.05	7.91	7.76	0.277	0.335	0.370	0.492	0.355	0.454	0.646	0.596
JAM-A	1.48	1.54	1.35	1.50	0.182	0.241	0.564	0.638	0.224	0.272	0.083	0.261
N-CAD	20.84	24.8	13.4	18.1	0.175	0.155	0.612	0.570	0.155	0.108	0.657	0.540

All concentrations in ng/ml. Statistical significance in bold font.

neurovascular vessels plays an essential role to maintain brain homeostasis, which includes regulating the permeability for immune active substances and immune cells (Najjar et al., 2017). Endothelial activation can decrease function of the BBB (Najjar et al., 2017) and disruption of the BBB has been linked to cognitive dysfunction (Khandaker et al., 2017). An influence of the level of CAMs on cognition in schizophrenia is suggested (Adamowicz et al., 2022; Cai et al., 2020b; Hargreaves et al., 2014), but research is still limited. CAMs including ICAM-1 and VCAM-1 are involved in endothelial inflammation and implicated in cardiovascular disease as well as associated with an increased risk of atherosclerosis (Barcones et al., 2017; Meyer et al., 2009; Nguyen et al., 2017) and type 2 diabetes (Hadi and Suwaidi, 2007). ICAM-1 take part in atherosclerosis initiation. VCAM-1 is involved in immune reactions related to atherosclerosis including proliferation of smooth muscle and atheroma plaque formation (Radu et al., 2020). Elevated levels of ICAM-1 are predictive of increased cardiovascular risk (Meyer et al., 2009) and of developing type 2 diabetes (Qiu et al., 2019). Higher levels of soluble ICAM-1 reflect activation of endothelial cells and could be hypothesized as a common pathway of development of atherosclerosis and diabetes mellitus type 2 in patients with schizophrenia (Qiu et al., 2019; Rohde et al., 1998). GWAS studies show that this possible common pathway is partly explained by shared genetic mechanisms (Hackinger et al., 2018). However, larger longitudinal studies are needed to clarify this possibility.

A strength of our study is the large subgroup of drug-naïve patients undergoing assessments before the initiation of drug treatment. Therefore, potentially confounding effects of antipsychotic therapy related to measurements of CAMs are absent. Also, the patient and control groups are larger than in most comparable studies (Cai et al., 2020a; Kronig et al., 2005; Nguyen et al., 2017; Radu et al., 2020; Schwarz et al., 2000; Stefanovic et al., 2016). Our group difference findings were confirmed after adjusting for age, gender, smoking and BMI. Therapeutically, a possible approach for future treatment of schizophrenia could be targeting specifically ICAM-1 or VCAM-1 as adjunctive medication. In one study, including patients with hypertension and type 2 diabetes mellitus, one month of pioglitazone therapy significantly decreased ICAM-1 and VCAM-1 levels (Takase et al., 2007). In another study, including patients with vasculitis, blockade of ICAM-1 with antisense oligonucleotides (ASON) had adequate effect in treatment of inflammatory disease (Xu and Li, 2009). Intriguingly, an experimental study demonstrated that high endothelial cell surface expression of ICAM-1, rather than BBB integrity, promoted T-cell diapedesis across the BBB, indicating that reduction of ICAM-1, even in absence of BBB disruption, could attenuate neuroinflammation (Abadier et al., 2015). In a Finnish study, including patients with multiple sclerosis, methylprednisolone decreased VCAM-1 levels (Elovaara et al., 2000). However, currently it is not established whether levels of CAMs, including ICAM-1 and VCAM-1, are markers of inflammation in general or specific treatment targets in schizophrenia.

A limitation of our study is the cross-sectional design. Longitudinal studies are necessary to possibly establish a potential causal relationship between the CAMs and schizophrenia. Another limitation of our study is the measurements of CAMs in blood between the patient group and the controls with a mix of serum and plasma measurements. This could possibly influence our results in our extended analyses with comparisons of patients with serum samples and controls with plasma samples. In the studies on CAMs in schizophrenia, some studies measured CAMs in serum (Kronig et al., 2005; Radu et al., 2020; Schwarz et al., 2000; Stefanovic et al., 2016) and other studies measured CAMs in plasma (Cai et al., 2020a; Cai et al., 2020b; Nguyen et al., 2017). Importantly, our small in-house study comparing serum and plasma levels within n = 12 healthy individuals, plasma levels of ICAM-1 and VCAM-1 were ~15 % higher than in serum. Thus, in the comparison between patients versus plasma sample controls, the increase of the proteins in patients compared to controls may have been underestimated. It is not clear whether any association between schizophrenia and CAMs is causative via inflammation, related to common genetic conditions, caused by another common factor (nutrition, substance use, etc.) and our cross-sectional study cannot reveal this. For differences between drug-naïve patients and those previously using drugs also factors like severity of illness, general health status and care, dental care (also influencing inflammation) may be active. Regarding the total patient group compared to the control group there are several potential differences including health and dental care, nutrition, physical exercise, family support, mental stress, use of legal and illegal drugs that are likely to differ between the two groups and affect inflammation and levels of CAMs. This could be related to the fact that those volunteering for controls in a study will often be the ones most interested in different health aspects. However, these factors should be adjusted for as far as possible in future studies. In our study, which contains analysis of 5 CAMs, we did not correct our findings for multiple testing due to the exploratory nature of the study. Thus, the findings should be interpreted accordingly.

5. Conclusion

In our study, we found that patients with schizophrenia-spectrum disorders, including the subgroup of drug-naive, had higher levels of CAMs compared to controls. Previously medicated patients had significantly elevated levels of ICAM-1 compared to both drug-naïve patients and controls after adjusting for age, gender, smoking and BMI. Furthermore, all patients, both drug-naïve and previously medicated, showed significantly elevated levels of VCAM-1 compared to controls. Our results are in line with the hypothesis of an inflammatory process involved in schizophrenia. More studies are needed to establish the underlying mechanisms.

Role of the funding source

The first author has received PhD grant from the Health West Regional Authority. The study was supported with grants from the Research Council of Norway (213727, 223273, 300309), the Western Norway Regional Health Trust (911679, 911820), and EEA-RO-NO-2018-0535.

The funding sources had no involvement in the preparation of the article, in study design, in the collection, analysis and interpretation of data, in the writing of the report or in the decision to submit the article for publication.

CRediT authorship contribution statement

Kristian Varden Gjerde: Writing – original draft, Writing – review & editing, Visualization, Formal analysis. **Christoffer Bartz-Johannessen:** Methodology, Formal analysis, Visualization, Writing – review & editing. **Vidar Martin Steen:** Conceptualization, Funding acquisition, Investigation, Project administration, Writing – review & editing. **Ole A. Andreassen:** Conceptualization, Funding acquisition, Investigation, Project administration, Writing – review & editing. **Nils Eiel Steen:** Conceptualization, Investigation, Writing – review & editing. **Thor Ueland:** Conceptualization, Investigation, Project administration, Resources, Writing – review & editing. **Tove Lekva:** Investigation, Validation, Writing – review & editing. **Maria Rettenbacher:** Conceptualization, Investigation, Project administration, Writing – review & editing. **Inge Joa:** Conceptualization, Investigation, Project administration, Writing – review & editing. **Solveig Klæbo Reitan:** Conceptualization, Investigation, Project administration, Writing – review & editing. **Erik Johnsen:** Conceptualization, Funding acquisition, Investigation, Project administration, Writing – review & editing. **Rune Andreas Kroken:** Conceptualization, Supervision, Writing – review & editing, Investigation, Project administration.

Declaration of competing interest

Kristian Varden Gjerde, Christoffer Bartz-Johannessen, Vidar M. Steen, Nils Eiel Steen, Thor Ueland, Tove Lekva, Maria Rettenbacher, Inge Joa, Solveig Klæbo Reitan, Erik Johnsen and Rune Andreas Kroken report no disclosures relevant to the manuscript. Ole A. Andreassen has received speaker's honorarium from Janssen, Lundbeck, Sunovion, and is a consultant to CorTechs.ai.

Acknowledgements

The authors thank all patients and control persons for participating in this study, and all personnel who contributed to planning and conducting this study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2024.03.029.

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