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REVIEW

Biomarkers and schizophrenia: a qualitative review

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Abstract

Schizophrenia (SCZ) is a psychiatric disorder with a broad spectrum of biological and clinical manifestations of yet not completely clear pathophysiological mechanisms. Several lines of evidence have been supporting the idea that immunoinflammatory, oxidative, hormonal and cellular dysfunctions are implicated on the biomolecular basis of SCZ. However, accurate diagnosis and selection of appropriate treatments remains challenging as a result of the scarcity of objective tests. Furthermore, there is a compelling need to find biomarkers that could predict drug response and tailor pharmacological treatment, particularly in drug-naïve first episode psychosis (FEP). Hence, numerous technologies have been employed in order to search for SCZ biological markers, but evidence relating them to treatment efficacy is lacking. In this regard, some preliminary data suggest promising results. The current review provides information on: (1) potential biomarkers associated with biological disturbances and (2) biological markers associated with treatment response.

Keywords: Schizophrenia, Biomarkers, Treatment.

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Introduction

Schizophrenia (SCZ) is a heterogeneous psychiatric disorder of still unclear pathophysiological mechanisms, resulting from a complex interplay between genetic variants and environmental factors [1, 2]. It affects more than 21 million people worldwide [3], being characterised by heterogeneous clinical symptomatology such as delusions, hallucinations, thought disorders and behavioural and emotional changes, with progressive cognitive decline and deterioration of personality [4].

The current diagnostic criteria for psychotic disorders are based on self-report, behavioural observation and illness course (e.g. first episode vs. multiple episodes, state of remission), lacking biological validation [5-7]. Hence, as there are no reliable medical diagnostic tests available [4, 7], the identification of biological markers for SCZ has become a relevant issue.

Biomarkers are objective, quantifiable characteristics of biological processes, disease states, or responses to treatment [8, 9]. Lack of objective tools to identify common patient characteristics, makes the development of biomarkers critical in psychiatry for the application of a more directed and individualised treatment [8, 10]. A biomarker of therapeutic response will be clinically useful if it is accurate, reproducible, easy to interpret, has an adequate sensitivity and specificity, and is acceptable to the patient [11]. Multiple factors have been assigned potentially responsible for the discrepancy verified among studies, particularly when evaluating biomarkers (for example cytokines) in chronic SCZ patients on long-term antipsychotics. Patients' gender, age, body mass index (BMI), smoking and dietary habits, differences in measurement techniques, in tested material or in the stored period of the sample, sampling at different illness' stages (acute vs. chronic or active phase vs. remission), exposure to different type and dosage of antipsychotics, the length of treatment, the duration of hospitalisation, different clinical presentations, or the biological heterogeneity, were implicated in the aforementioned discrepancies [12, 13]. Accordingly, an important characteristic that should be taken into account when investigating biomarkers in SCZ is the stage of the disease. Research at illness' onset is especially significant, since it avoids the effect of confounding variables [14], such as prior psycho-pharmacological treatment [10]. For example, few studies have investigated the molecular signatures in drug-naïve first episode psychosis (FEP) patients, given the difficulty of collecting biological samples before any antipsychotic drug administration [15]. FEP might be the most critical period of SCZ and possibly the most opportune time for studying key mechanisms that influence treatment response and outcome [10]. In addition, when treated early, FEP patients might have a better response rate to antipsychotics compared to those with longer duration of untreated illness [16, 17].

This qualitative review, by no means exhaustive, based on online database search on key terms as schizophrenia, biomarkers and treatment, discusses recent and contrasting findings in the fields of immune system and inflammation, oxidative stress (OS), endocrine system, serum metabolomics, genetic and central nervous system (CNS) signatures, which have produced data of interest in identifying biological mediators that may function as potential biomarkers in SCZ.

Immunoinflammatory biomarkers

The inflammatory response works both as an innate and an adaptive mechanism that allows the organism to deal with a diverse threats. However, under pathological and chronic conditions, the maintenance of this response might become deleterious [14]. Several data support the inflammatory hypothesis in SCZ's pathophysiology. It is characterised by enhanced innate immune response with overproduction and/or imbalance of cytokines, namely an increase in pro-inflammatory and a decrease in anti-inflammatory cytokines [14, 18-20]. Cytokines, key signaling molecules of the immune system, exert their effects by binding specific receptors on a variety of peripheral and brain target cells [21]. Immune changes in the CNS may originate from peripheral immune activation of cytokines that cross the disrupted blood brain barrier (BBB) or that are synthesised by invading immune cells, both of which originate from extraneuronal sources and disturb brain function [18, 22, 23]. Nevertheless, most neuropathologies are most probably due to dysfunction of resident microglia and astrocytes [24].

Although contrasting results can be found, most studies focus on plasma levels of cytokines or T-helper-1 (Th-1) and T-helper-2 (Th-2) imbalance [25-27]. Meta-analyses on serum cytokine differences between acutely relapsed (AR) and drug-naïve FEP patients found significant increases in macrophage-derived cytokines—interleukin (IL)-1β, IL-6, IL-12 and tumor necrosis factor-alpha (TNF-α)—as well as the Th-1-derived cytokines, interferon-gamma (IFN-γ) and IL-2 receptor (sIL-2R) in both groups [21, 28].

The IL-17 signalling pathway was also found to be dysregulated when compared to healthy controls and correlated with symptoms in veterans with SCZ [18]. IL-17 induces the production of factors implicated in the recruitment of monocytes and neutrophils [29]. The levels of very few of those factors were found to be positively or negatively correlated with positive, general and total scores on the Positive and Negative Syndrome Scale (PANSS) in most studies conducted so far [18, 21, 31]. Moreover, a previous study found increased activation of T-helper-17 cells in patients with recent onset SCZ [30]. Therefore, an existing imbalance of the IL-17 pathway, may be implicated in the etiology of SCZ [18, 31].

As changes in cytokine profile come with the onset of the disorder, studying inflammatory biomarkers in

untreated FEP is relevant, since antipsychotic drugs are known to influence their levels [8]. However, few studies have so far assessed the association between cytokine levels and treatment response in FEP [8].

The aforementioned meta-analyses concluded that in AR and FEP patients, increased plasma concentrations of IL-1β, IL-6 and tumor growth factor-beta (TGF-β) normalised with antipsychotic treatment, independently of its direct effects [21]. It was previously found that IL-6 decreased significantly after antipsychotic therapy in FEP and that this change was positively correlated with clinical improvement [32]. Therefore, it was suggested that IL-1β, IL-6 and TGF-β might represent disease state markers [21]. In contrast, a more recent longitudinal study demonstrated lack of changes in IL-6 over 12 weeks of antipsychotic treatment in FEP, indicating that it could be a more trait-like marker [33]. As IL-12, IFN-γ, TNF-α and sIL-2R increased levels did not normalise with treatment, these were suggested to be disease trait markers [21, 25, 34]. However, a later study did not find any cytokine to fuction as a trait marker, as all the studied cytokines—IL-6, IL-10, TNF-α and IL-4—initially increased in FEP and normalised after risperidone treatment [35].

A meta-analysis demonstrated in a quantitative manner that a 4 to 8 week-treatment with antipsychotics (typical, atypical or mixed) led to increases in sIL-2R and decreases in IL-1β and IFN-γ blood levels [20]. The latter was considered consistent with the anti-inflammatory role associated with antipsychotics [20]. In contrast, in a more recent study, an increase in INF-γ levels was observed over 12 weeks of treatment with atypical antipsychotics in FEP patients [33]. Thus, it was suggested that slightly longer treatment induces cytokines' production through the potential of atypical antipsychotics to generate metabolic syndrome [36].

In vitro studies concluded that haloperidol and clozapine decrease cytokine secretion from lymphocytes in both SCZ patients and healthy controls [37]. Increases in the soluble receptors of TNF-α, which attenuate the molecule's pro-inflammatory activity [38], were observed with clozapine, suggesting an anti-inflammatory effect of this agent [39].

A 10-week risperidone treatment in drug-naïve FEP patients had a significant suppressant effect on several serum cytokine levels [35]. A specific cytokine profile indicated that risperidone may normalise monocytic and T-regulatory cell responses [35] and decrease Th-2 functions [31, 35]. The latter contradicts both in vitro studies and the idea of an aggravated inflammatory profile as a consequence of atypical antipsychotics therapy. However, the aforementioned cytokine levels normalisation was not associated with a good clinical response—defined by a 50% reduction in the PANSS total scale—to risperidone [35]. This was suggested to be due to risperidone's specific effects, not secondary to symptomatic improvement [35].

When evaluating the influence of adjunctive therapies in two groups of SCZ patients in remission, the group on both antipsychotics (typical or atypical) and mood stabilizers showed increased TNF-α levels compared to the group on treated only with antipsychotics (typical or atypical) [40]. However, since in the first group of patients the total PANSS scores reduced by 50%, it was suggested that augmentation with mood stabilizers might exert favourable effects in SCZ [40].

Another field of study includes the cyclooxygenase (COX), an enzyme involved in the fatty acid (FA) metabolism pathway, which produces prostaglandins and mediates inflammation [22]. It was demonstrated that the modulation of COX activity with anti-inflammatory agents such as aspirin [41] and celecoxib [42, 43] as adjunctive therapy to antipsychotics, may improve symptoms in SCZ. 15-Deoxy-Delta-12,14-prostaglandin J2 (15d-PGJ2) is a COX-derived product that exerts its anti-inflammatory effect by targeting peroxisome proliferator-activated receptor-gamma (PPAR-γ) [44]. In FEP patients, 15d-PGJ2 was found to be decreased in peripheral blood mononuclear cells (PBMCs), compared to healthy controls [14]. Due to its soluble nature 15d-PGJ2 was set as a potential plasmatic biomarker for FEP [14]. As 15d-PGJ2/PPAR-γ pathway can be stimulated pharmacologically, it was also suggested as a potential therapeutic target candidate [14].

Oxidative Stress—a field for new tailored therapies?

The neuroprogression theory of SCZ postulates that changes in the immune system are accompanied by increased inflammatory markers such as tryptophan catabolites and reactive oxygen species (ROS), that affect the growth and function of neuronal circuits since the intra-utero period [45]. Converging evidence indicates that the OS plays a role in SCZ pathophysiology [46-49]. A study on the disturbances in antioxidative defense systems indicated an increase in free radical generation and antioxidant defense impairment in SCZ patients [46]. Therefore, several markers have been employed to assess OS and anti-oxidative status in different diseases, including SCZ [50].

OS converts glucose and lipids to reactive carbonyl compounds, and excess of these are converted into advanced glycation end products (AGEs) and advanced lipoxidation end products [51, 52]. Accumulation of these products is called carbonyl stress, and has been suggested as an environmental factor in the pathophysiology of SCZ [47, 49, 53]. AGEs interact with AGE receptors (RAGE) on the cell membrane, which induces deleterious effects by increasing oxidative and carbonyl stress [49, 54]. A recent cross-sectional and longitudinal study showed altered carbonyl stress markers levels in SCZ [49]. Significantly increased glyceraldehyde-derived AGEs (Glycer-AGEs) levels and decreased soluble form of the RAGE (sRAGE) levels were found in acute SCZ [49]. Although controversial in humans, a counter-regulatory mechanism that abolishes the AGEs-RAGE axis effects was associated with

sRAGE [55]. Therefore, the combination of decreased sRAGE levels with increased Glycer-AGE levels might be a pattern characteristic of SCZ [49]. Glycer-AGEs and Glycer-AGEs/sRAGE ratios were set as significant diagnostic markers for SCZ that distinguished between patients and healthy controls in 70.0% of cases [49].

Sulfhydryl (SH) groups are important antioxidants, responsible for scavenging free radicals and suppress peroxidation [56]. Significant decreases in the levels of total-SH was found in SCZ patients when compared with healthy controls [46], which was explained by possibly increased turnover of these antioxidant defences, in an attempt to prevent oxidative damage in SCZ [46].

A decrease in superoxide dismutase (SOD) enzyme activity, which has antioxidative effects against superoxide anion, was detected in SCZ patients selected from an outpatient clinic [46]. Although the this confirms some studies [57, 58], it also contradicts others that found no difference in SOD activity between chronic SCZ patients and healthy controls [59] or found increased SOD activity in FEP and chronic SCZ patients compared to normal controls [60]. As in the latter study, the levels of SOD were greater in FEP than in chronic patients, the authors suggested that OS might occur in the initial phase of SCZ, getting worse with the chronicity of the disorder. This could either be explained by aging or by antipsychotic treatment [60].

Regarding gluthatione peroxidase—an OS-inducible enzyme with significant role in the peroxyl scavenging mechanism [61]—and catalase—the enzyme that protects the cells from H_2O_2 accumulation [46]—contrasting results were found. When compared to healthy controls, gluthatione peroxidase was found to be decreased and catalase increased in SCZ [46]. Nevertheless, some previous studies reported the opposite [57, 58].

Gluthatione reductase activity, essential to maintain the reducing capability of the cell, was found to be significantly increased in SCZ patients compared to normal controls [46], contradicting previous studies [57, 58]. Hence, these results are in line with an existing dysregulation of the oxidant-antioxidant balance in the pathophisiology of SCZ.

In drug-naïve FEP patients, paraoxonase 1 (PON1)—an antioxidant and anti-inflammatory enzyme that protects high-density lipoprotein particles against OS damage [62, 63]—was decreased when compared to healthy controls [48, 62]. Decreased levels of PON1 activity in FEP indicate lowered protection against lipid peroxidation and lowered anti-inflammatory potential [64]. Impaired antioxidant defence and increased levels of the lipid peroxidation product—malondialdehyde—were also detected in the serum of chronic SCZ patients [58, 59]. It was shown that increasing lipid peroxidation accompanies SCZ [65] and further suggested that lowered PON1 activity in the early phase of illness might be associated with increased lipid peroxidation during the course of SCZ [48]. Moreover, the decreased PON1 activity levels in drug-naïve FEP patients was indicated as a key component of the disease rather than a consequence of antipsychotic treatment [62].

Increased total radical-trapping antioxidant parameter (TRAP)—a marker of total non-enzymatic antioxidant defenses [66]—was also detected in drug-naïve FEP patients [48]. Increased TRAP can possibly be an early compensatory mechanism, which may counterbalance the increase in ROS production [48]. Hence, it was suggested that in an early phase, SCZ may be characterised by lowered PON1 activity and compensatory elevations in non-enzymatic antioxidants [48]. Nonetheless, with disease progression, lipid peroxidation, accumulation of protein damage and decreases in antioxidant levels due to chronic inflammation, lead to OS damage [48, 50].

After treating drug-naïve FEP patients with risperidone, an increase in PON1 activity and a reduction in the marker of lipid peroxidation—lipid hydroperoxide—occurred, indicating an antioxidant effect of risperidone [48]. The latter might be explained by risperidone's specific effects, as those alterations were not significantly associated with clinical response to treatment and nor were they dosage-sensitive [48].

A recent meta-analysis reviewed relevant randomised controlled trials that compared the effects of add-on treatment (to standard antipsychotics) of several antioxidants —allopurinol, Ginkgo biloba, N-acetyl cysteine, selegiline, vitamins C and E—with placebo in SCZ [67]. Although most results shown no differences, there was moderate evidence that Ginkgo biloba had a positive effect on psychotic symptoms [67].

The need to evaluate adjunctive antioxidant therapies in SCZ with parallel assessment of oxidative changes before and after treatment is therefore being reinforced.

Hormones, possible biological markers?

The hypothalamic-pituitary-adrenal (HPA) axis is the main biological system involved in stress response [70]. In FEP patients hyperactivity of the HPA axis was demonstrated [68-70], leading to increased cortisol levels throughout the day, blunted cortisol awakening response (CAR) and decreased cortisol response to psychosocial stressors [71-73]. A reduction in cortisol levels after antipsychotic treatment was associated with an improvement in psychotic symptoms after 12 weeks of follow-up, in both chronic and FEP patients [36, 74]. A longitudinal study conducted in FEP patients showed that those who did not respond to 12-week antipsychotic treatment already had at illness onset a significant lower CAR (measured in the saliva) compared with patients who responded [72]. It was observed that at psychosis onset CAR predicts subsequent treatment response, as blunted CAR shown a tendency to remain unchanged with antipsychotic treatment [75]. On the whole, it is possible that more blunted CAR can possibly be a trait marker, reflecting a more severe illness not modifiable by treatment [33, 72, 75]. It was suggested that future studies should investigate the impact of antiglucocorticoid treat-

ments in psychotic symptoms [33]. Therefore, this would be particularly important in patients with a blunted CAR, thus less likely to respond to antipsychotic treatment [33].

Arginine-Vasopressin (AVP) is classically known for its role as a potent antidiuretic hormone, being also released centrally during stressful experiences [8]. Increased AVP levels were associated with greater positive symptoms and worse verbal learning in female drug-naïve FEP patients, but not in male [76]. In contrast, a further study found AVP levels to be decreased in SCZ patients and their first-degree relatives compared with healthy controls [77]. Therefore, because alterations were observed in patients and relatives, AVP was suggested as a marker of biological vulnerability for SCZ [77].

Apart from its classically known role as a hormone involved in parturition and lactation, oxytocin (OT), also influences behaviours that are typically impaired in SCZ [78]. The risk factors associated with psychotic disorders were related to some extent to a disruption in the ability of physiological levels of OT to modulate social cognition and neuropsychological function [77].

As OT decreases anxiety and neuroendocrine response, while AVP plays an anxiogenic role, interactions between these two hormones, may lead to a shift in positive social behaviour and defensive states observed in SCZ [8].

Accordingly, the above mentioned suggests that it is important to consider neuroendocrine and gender-specific alterations in early FEP.

Metabolomics—signatures implicated in disease process

Metabolomics refers to the study of metabolism at the global level, involving the complete repertoire of small molecules present in cells, tissues and organisms [79].

Proteomic techniques are becoming increasingly popular for biomarker identification [80]. For example, a recent investigation found higher expression of N-terminal fragments of fibrinogen in serum of first onset, drug-naïve SCZ patients [81]. It was further concluded that these proteins may be useful as biomarkers for SCZ molecular diagnosis.

Cryoglobulins (Cgs) are considered a marker of immune system chronic activation, inflammation, and autoimmune sensitisation [82, 83]. Detectable blood levels of type III (a mixture of polyclonal immunoglobulins) Cgs along with the presence of complement activation split products were found in SCZ patients [84]. The complement cascade hyperactivation in SCZ was demonstrated in a previous study [85] and a complement-dependent mechanism may be implicated in Cgs-induced effects both in vivo and in vitro [86]. An in vitro study shown that type III Cgs, isolated from PBMCs of SCZ patients, may induce the expression of pro-inflammatory and chemotactic cytokines [86]. Thus, type III Cgs contribute to increase blood levels of cytokines in SCZ, being involved in disease-associated peripheral inflammatory responses [19, 86-88].

A number of authors agree that antipsychotics have varying effects on the immune system [89], liver [90] and whole body metabolism [91], which might be manifested by proteomic changes in the circulation. Most proteomic studies attempted to identify changes in protein levels, not considering the effects of post-translational modifications (PTMs). Nevertheless, characteristic changes in PTMs, such as phosphorylation, can be biologically informative [92]. Phosphorylation abnormalities in proteins involved in acute phase response and coagulation pathways were observed in serum from drug-naïve FEP patients compared to healthy controls [93]. More recently, another study was performed in order to investigate the effects of olanzapine on the serum phosphoproteome profile in FEP after 6-weeks treatment [92]. The main effects of olanzapine treatment were changes in the state of protein phosphorylation rather than in protein abundance [92]. Despite no information provided regarding the clinical response, it was suggested that antipsychotic drugs lead to downstream effects, which can be detected in the peripheral circulation, having utility as response biomarkers [92].

Heart-type fatty acid binding protein (H-FABP), is a lipid carrier protein expressed primarily in brain, cardiac and skeletal muscles and the mammary gland [94, 95]. In early stage drug-naïve SCZ patients, it was found that H-FABP serum levels were baseline predictors of response to olanzapine [22]. It was also shown that H-FABP levels and monocyte expression of H-FABP molecular partner—cluster of differentiation 36 (CD36)—were inversely correlated [22]. Patients with low concentrations of H-FABP and high expression of CD36 on monocytes were less likely to respond to olanzapine [22].

MicroRNAs (miRNAs) are 20–25 nucleotide long, single-stranded, nonprotein-coding RNA molecules that regulate protein expression levels [2, 96]. There is evidence of a key role for miRNAs in neurogenesis, neural maturation and brain development [96, 97]. Thus, dysfunction in miRNA signaling contributes to neurodegenerative and psychiatric disorders [2]. A number of circulating miRNAs was quantified in the serum of first-onset SCZ patients and that of healthy individuals [2, 98]. In a recent study aiming to identify miRNAs that are clinically practicable biomarkers, it was observed a significant decrease in miR-132 in the PBMCs of SCZ patients compared with controls [2]. Moreover, miR-132 was previously found to be significantly downregulated in prefrontal cortical tissue in SCZ patients [99]. Taking into account the latter findings, miR-132 might be a superior marker in SCZ. Therefore, serum miRNAs changes can reflect SCZ status and may be used as biomarkers for diagnosing SCZ [98].

Hence, the identified markers might have utility in diagnosing and in critical decision-making regarding antipsychotic treatment.

Biomarkers and genetics

The most studied risk gene in SCZ is the Disrupted-in-Schizophrenia 1 (DISC1) gene whose function depends on binding to cytoskeleton proteins, such as the Nuclear-distribution gene E homolog like-1 (NDEL1) [100]. Myelin basic protein (MBP) is the only structural myelin protein known to be absolutely required for generating compact myelin sheaths [101]. While longitudinally assessing gene expression in the blood of very early stage drug-naïve FEP patients, NDEL1 and MBP were found to be upregulated [15]. This effect appeared to be attenuated by risperidone treatment [15]. Hence, the authors suggested that both genes NDEL1 and MBP, which are involved in important neuronal processes (neurodevelopment and myelination, respectively), may be putative biomarkers for psychotic disorders [15].

The possibility of cell cycle-related genes to function as biomarkers was tested by measuring and comparing messenger RNA (mRNA) levels in the peripheral blood of SCZ patients and healthy controls [102]. It was found that the combination of cyclin-dependent kinase 4 (CDK4), minichromosome maintenance complex component 7 (MCM7) and DNA polymerase delta 4 accessory subunit (POLD4) mRNA expression might be a potential useful biomarker for SCZ [102]. The latter three genes were significantly decreased in acute SCZ [102]. However, CDK4 expression levels recovered significantly in the remission state [102]. Therefore, it was suggested that the combination of CDK4, MCM7 and POLD4 might be a trait biomarker for SCZ and that CDK4 may be a state biomarker for SCZ [102].

Other genes associated with SCZ are identified in several genome-wide association studies including L-type calcium channel α subunit type 1 c (CACNA1C), dopamine D2 receptor (DRD2), AMPA receptor subunit 1 (GRIA1), NMDA receptor 2A (GRIN2A), metabotropic glutamate receptor 3 (GRM3), neuregulin 1 (NRG1) and miRNA137 (MIR137), among others [103, 104].

CNS biomarkers candidates in SCZ

Microglia—the resident macrophages of the brain—are the primary reservoirs of pro-inflammatory cytokines, such as IL-1β, IL-6, TNF-α and INF-γ [24, 105]. These macrophages act as antigen presenting cells in the CNS, responding rapidly to even minor pathological changes in the brain [24, 105]. It was hypothesised that subsets of microglia are maintained permanently in an activated or primed state into adulthood as a consequence of a perinatal infection [106]. A subsequent immune challenge in adulthood can cause exaggerated levels of cytokines from primed glia [106]. The microgial hypothesis predicts an increase in pro-inflammatory cytokines by the activated microglia, leading directly to neuronal degeneration, white matter abnormalities and decreased neurogenesis [21, 24]. Thus, this can possibly cause impaired brain function and SCZ symptoms [18, 89]. Recently, it has become possible to quantify microglial activation in vivo using a positron emission tomography ligand that recognizes the translocator protein, a receptor found on activated microglial cells [107, 108]. Binding of one such agent, (R)-[11C]PK11195, was found to be increased, suggesting differential microglial activation, in gray matter [107] and in hippocampus [108] of SCZ patients.

Activated microglia also stimulates astrocytes to produce S100B—an astrocyte-specific cytokine and a marker of inflammation—that is considered to be the equivalent of C-reactive protein in the brain [109, 110]. Increased concentrations of S100B were found in cerebrospinal fluid (CSF) of SCZ patients in an acute psychotic episode compared to matched healthy controls. Serum levels concomitantly measured were also elevated, correlating closely with the CSF concentrations [109]. Another study showed elevated S100B serum levels in both drug-naïve early stage patients and medicated chronic SCZ patients [111], supporting the activation or damage of glial cells in SCZ. Moreover, lower levels of S100B were detected in medicated chronic SCZ patients compared to drug-naïve early stage patients, possibly suggesting that antipsychotic treatment may reduce neurodegeneration or at least the ongoing neuroinflammatory process [111].

The CSF has been a highly informative source of biomarkers in Alzheimer's disease and neuroinflammatory disorders [112]. However, it was less frequently studied in SCZ. CSF biomarkers may be informative by identifying invading immune cells, inflammatory cytokines, pathogens, disease-associated extracellular proteins, alterations in choroid plexus secretory patterns, and diffusion from blood, particularly if the BBB is dysrupted [113]. Of the cytokines that are reliably measured in CSF—IL-6, IL-8 and IL-1β—only IL-1β was found to be elevated in the CSF of FEP patients compared to healthy controls [114]. In contrast, in olanzapine-treated chronic SCZ patients, only IL-6 was increased in the CSF compared to normal controls, while IL-1β was undetectable [115]. Moreover, treatment with olanzapine appeared not to influence IL-6, as CSF or serum levels of olanzapine did not correlate with CSF IL-6 [115]. Although unclear, the reason for the discrepancy regarding CSF IL-6 levels in FEP versus chronic SCZ seemed to be related to the chronic progress of the disease [115].

The endogenous cannabinoid receptor agonist, anandamide, reduces inflammation by blocking microglial activation and stimulates neurogenesis [116]. Anandamide concentrations in CSF were found to be 10-fold increased in drug-naïve FEP who were non-heavy cannabis abusers (lifetime users ≤ 5 times) when compared to drug-naïve FEP high-frequency users, healthy low-frequency or high-frequency users [116]. Moreover, elevated anandamide concentrations inversely correlated with psychotic symptoms [116]. Elevated concentrations of anandamide were detected exclusively in CSF, making its central origin

more likely [116, 117]. A trend for an association of anandamide elevation in CSF with a longer time to psychosis transition was observed [117]. The latter might indicate that the patients expressing higher CSF anandamide are less likely to have psychotic symptoms [117].

Kynurenic acid (KYNA)—a metabolite of tryptophan and an antagonist of the N-methyl-D-aspartate receptor—is neuroprotective against glutamatergic excitotoxicity but may contribute to psychosis and cognitive impairment [118]. Kynurenine (KYN)—KYNA's precursor—is actively transported into the brain and metabolised by astrocytes to KYNA [118]. In SCZ, elevated levels of KYNA and KYN in the CSF or in the postmortem brain have been consistently reported [119-121]. Because KYNA does not cross the BBB, only CSF levels appear to be informative [113]. It was suggested that increased brain KYNA might constitute a major trigger for cognitive and psychotic symptoms and should encourage the development of biomarkers and novel treatment approaches based on the KYN pathway [115].

A promising new pathway to explore SCZ's molecular mechanisms, seems to be the technology of induced pluripotent stem cells (IPS), derived from peripheral somatic cells of SCZ patients. IPS cells provide a source of human CNS cell lines, including neurons, for discovering biomarkers and testing of target engagement, mechanism and response to medications [122].

Conclusion

Efforts in identifying and describing biomarkers for SCZ have been claimed by psychiatrists as a way to help inform early diagnosis and monitor the evolution and treatment of the disease. Stratification of SCZ patients could be based on serum molecular profiles [22]. This would allow the adoption of preventive strategies by identifying at-risk individuals, facilitating early intervention, reducing medication non-response, adverse side effects, non-compliance and thereby minimizing morbidity [14, 22]. Furthermore, it would help the development of a personalised medicine approach that is emerging in other areas, such as oncology, increasing the chances of positive therapeutic outcome for each patient [22].

This review identified multiple putative biomarkers and drug targets for SCZ. However, several limitations render it difficult to find reliable biomarkers of the disease and its actual state at each moment. First of all, many of the genetic and immune/inflammatory processes involved in SCZ are reported in other neurological and psychiatric disorders. Second, heterogeneous research methodologies concerning timing, disease phase of the sampled individuals, their gender, age, BMI and other confounders and drug regimens can prevent in-depth conclusions. Most studies do not evaluate clinical responses but only biomarker changes after treatment. Other studies evaluate the statistical association between a specific biomarker and a PANSS subscore only. In addition, different antipsychotics were used in the same study and between studies. As they have distinct affinities for receptors, they might also have different efficacy biomarkers [8]. Heterogeneous results can be found even when using the same antipsychotic agent, with discrepancies between in vitro and in vivo studies, stages of illness and SCZ different clinical presentations [35]. Moreover, many studies did not take into account patients' baseline symptoms severity. Finally, our conclusions must take into consideration the limitations of this review, particularly the lack of systematic research methods.

Targeting molecular pathways in multi-factorial diseases such as SCZ requires well designed studies, capable of correlating molecular and clinical data, which should be conducted in the future.

Abbreviations

15d-PGJ2: 15-Deoxy-Delta-12,14-prostaglandin J2; AGE: Advanced glycation end product; AR: Acutely relapsed; AVP: Arginine-Vasopressin; BBB: Blood brain barrier; BMI: Body mass index; CACNA1C: L-type calcium channel α subunit type 1 c; CAR: Cortisol awakening response; CD36: Cluster of differentiation 36; CDK4: cyclin-dependent kinase 4; Cgs: Cryoglobulins; COX: Cyclooxygenase; CNS: central nervous system; CSF: Cerebrospinal fluid; DISC1: Disrupted-in-Schizophrenia 1; DRD2: Dopamine D2 receptor; FA: Fatty acid; FEP: First episode psychosis; Glycer-AGEs: glyceraldehyde-derived AGEs; GRIA1: AMPA receptor subunit 1; GRIN2A: NMDA receptor 2A; GRM3: metabotropic glutamate receptor 3; H-FABP: Heart-type fatty acid binding protein; HPA: Hypothalamic-pituitary-adrenal; IL: Interleukin; IFN-γ: interferon-gamma; IPS: Induced pluripotent stem cells; KYN: Kynurenine; KYNA: Kynurenic acid; MBP: Myelin basic protein; MCM7: Minichromosome maintenance complex component 7; miRNAs: MicroRNAs; mRNA: messenger RNA; NDEL1: Nuclear-distribution gene E homolog like-1; NRG1: neuregulin 1; OS: Oxidative stress; OT: Oxytocin; PANSS: Positive and Negative Syndrome Scale; PBMC: Peripheral blood mononuclear cells; POLD4: DNA polymerase delta 4; PON1: Paraoxonase 1; PPAR-γ: Peroxisome proliferator-activated receptor-gamma; PTM: Post-translational modification; RAGE: AGE receptors; ROS: Reactive oxygen species; SCZ: Schizophrenia; sIL-2R: L-2 receptor; SH: Sulfhydryl; SOD: Superoxide dismutase; sRAGE: soluble RAGE; TGF-β: Tumor growth factor-beta; Th-1: T-helper-1; Th-2: T-helper-2; TNF-α: Tumor necrosis factor-alpha TRAP: total radical-trapping antioxidant parameter.

Competing interests

The author declares no conflict of interest.

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