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Zinc in schizophrenia: A meta-analysis

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ABSTRACT

Objective: The role of zinc homeostasis in various psychopathologies is an emerging area of interest. Zinc is strongly implicated in depressive disorders but is inadequately studied in schizophrenia, despite growing evidence of abnormal zinc transporters associated with schizophrenia. A meta-analysis of serum zinc concentrations in persons with schizophrenia was conducted to address this gap.

Method: PubMed and Embase were searched for all articles published through February 2018 that reported serum zinc concentrations in individuals with schizophrenia and in comparison subjects. A random-effects meta-analysis was carried out to compare mean serum zinc concentrations between the groups in terms of the weighted mean difference.

Results: The current meta-analysis combined 10 studies, including a total of 658 schizophrenia patients and 1008 controls. Serum zinc concentration was significantly lower in individuals with schizophrenia than controls (12.81 μg/dl (1.96 μmol/l), $t = -2.59$, 95% CI: −22.50 to −3.12, $p < 0.05$). The reduction in zinc levels was more pronounced among inpatients and newly diagnosed, drug-naïve patients.

Conclusions: The current meta-analysis supports a disturbance of zinc homeostasis in individuals with schizophrenia compared to healthy controls, although the relationship between reduced serum zinc levels and psychotic symptoms remains unknown. Altered serum zinc might be linked to defective transporters and/or inflammation that impact the brain's glutamatergic system.

1. Introduction

Zinc is essential for the function of up to 10% of human proteins and modulates many others, playing a critical role in almost every cellular process, including signal transduction, gene expression and apoptosis. Zinc is most concentrated in the limbic system of the brain, where it is released in vesicles within a network of glutamatergic zinc-enriched neurons (ZENs) located in hippocampal mossy fiber synapses. Reaching concentrations of up to 300 μM, zinc modulates NMDA receptor activity [8,36]. Its additional interactions with GABA, AMPA, 5-HT1A, and GPR39 receptors are implicated for its antidepressant effect [24,35].

Zinc concentrations are tightly controlled across cell membranes and vesicular compartments by numerous zinc transporters, regulatory molecules, and concentration gradients. Alterations in zinc homeostasis leading to deficiency or excessive concentrations have pathogenic consequences. Specific transporter molecules may have hypofunctional genetic variants that are directly related to the etiopathophysiology of certain domains of psychopathology. Serum zinc levels can provide one indicator of zinc sufficiency, but they are not routinely assessed in psychiatric practice.

The evidence for zinc dyshomeostasis in psychiatric disorders is growing. Several meta-analyses describe reduced serum zinc concentrations in patients with depression and Alzheimer's Disease [19,34,38,41]. However, a review of serum zinc concentration in schizophrenia, for which NMDA receptor physiology is widely implicated [42], is lacking in the literature.

Schizophrenia has recently been linked to variants in several zinc transporters [16,18,26,28,31]. Intriguingly, the zinc transporter SLC39A8 also influences the risk of inflammatory bowel disease, hypothesized to act through effects on the gut microbiome [18,28]. The transporter's pleiotropic effects also include changes in T cell immunity, lipid levels, blood pressure, and obesity, therefore highlighting the relationship between schizophrenia, inflammation, and metabolic dysregulation that is commonly observed [18].

Zinc functions as an NMDA antagonist. It is well known that other NMDA antagonists such as PCP and ketamine are able to induce psychotic symptoms in otherwise healthy individuals [12,17], through a mechanism of blocking the activity of NMDA-dependent GABAergic

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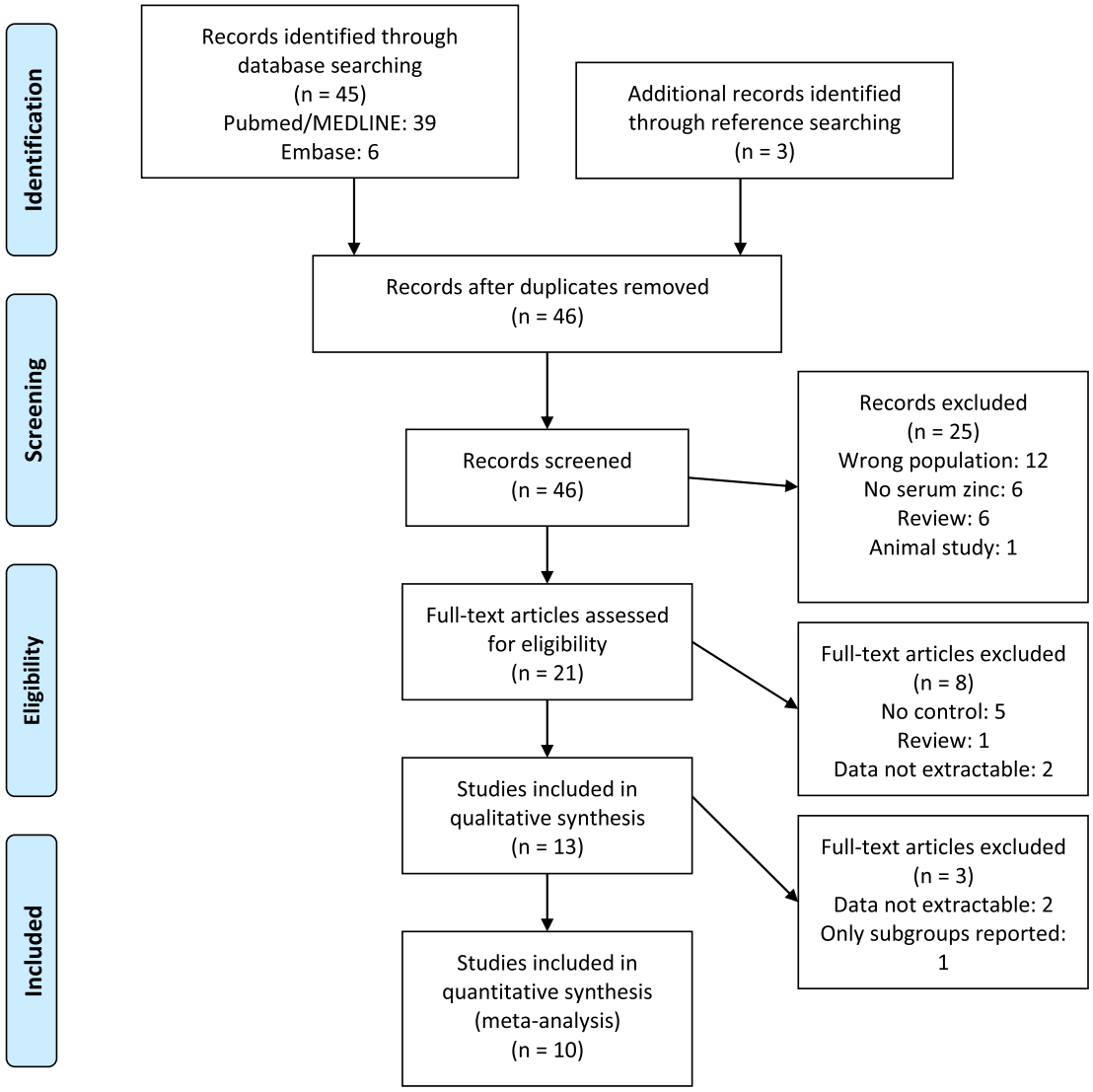

Fig. 1. PRISMA flow diagram of search results.

interneurons that project to the prefrontal cortex (PFC), thereby increasing excitability in this region of the brain [42]. It is this glutamatergic hyperactivity in the PFC that is proposed to be the link between hypofunctioning NMDA receptors and psychotomimetic symptoms.

Given this growing body of evidence of zinc's involvement in schizophrenia and its comorbid metabolic conditions, the present meta-analysis was conducted to examine whether serum zinc, the most readily available assessment of zinc status, is altered in patients with schizophrenia versus healthy comparison subjects.

2. Methods

2.1. Data sources

The current review was carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. PubMed and Embase were searched up to February 2018 using the following search terms: “zinc AND (serum OR plasma OR blood) AND human AND (schizophrenia OR psychosis)”. PubMed filters were applied to include only English articles and studies of human subjects. Search of the Embase database was restricted to articles not indexed in MEDLINE.

2.2. Study selection

Inclusion criteria were: 1) studies measuring serum or plasma zinc concentration at the time of clinical assessment; 2) studies of patients with schizophrenia without other mental health disorders, as diagnosed by standard criteria; 3) inclusion of a medically healthy control group. Non-human studies, studies without a control population, or studies that did not report mean serum zinc concentrations were excluded.

2.3. Data extraction

Two independent reviewers assessed the articles for eligibility. Articles clearly not relevant based on the title and abstract were excluded. The remaining full-length articles were reviewed, with special attention given to the methods and results sections. Mean serum zinc concentrations and standard deviations in patients and controls were extracted and converted to units of μg/dl if necessary. Corresponding authors were contacted for missing data. The information that was extracted included population characteristics (sample size, mean age, gender distribution, and medication status), clinical setting (inpatient vs. outpatient), and country in which the study was conducted. Results from each study were also summarized descriptively.

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