Review article

The Correlation between Iron Level and Schizophrenia: A Literature Review

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Abstract

Schizophrenia is a complex psychiatric condition that, if not adequately treated, can affect functional limitations. The exact etiopathogenesis of schizophrenia remains unknown. Research suggests an interaction between many factors, including genetic susceptibility, environment and psychological processes. Specific authors describe the association of a valuable mineral in the human body, iron, with pathophysiological mechanisms and related etiological factors in the development of the severe mental illness of schizophrenia.

Iron has important roles in the human body and affects various physiological processes. Some studies have shown a connection between the dysregulation of iron levels and the development of different mental disorders, including schizophrenia. Abnormal levels of iron in a specific region of the brain have been observed in people with schizophrenia. Iron levels may contribute to the pathogenesis of schizophrenia in combination with other genetic, environmental and dietary factors. Iron can also contribute to the better cognitive functioning of a patient with schizophrenia, and due to frequent malnutrition and undernourishment in this group of patients, it is crucial to take into account the need for routine hematological examinations and the determination of essential nutritional deficiencies.

Finally, our goals were to systematically review the literature published in the last two decades using PubMed, Web of Science, Scopus and Google Scholar. We described the clinical aspects and etiological factors of schizophrenia. We determined whether schizophrenia can be associated with iron concentration disorders to recognize and identify potential patients with iron deficiency and treat them promptly in daily clinical practice.

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Introduction

Schizophrenia is a highly intricate and demanding psychiatric condition that affects a substantial proportion of individuals on a global level, about 1% of the worldwide population (1). The categorization of this condition entails the classification of different subtypes, which are based on the predominant symptoms. According to the current 10th revision of the International Classification of Diseases (ICD-10), we can differentiate paranoid, hebephrenic, catatonic and simplex forms of schizophrenia. If we are unable to categorize it into these subtypes, we are left with the possibility of other types of schizophrenia, as well as undifferentiated and unspecified types of schizophrenia (2, 3).

The etiology of schizophrenia is unknown, although empirical research suggests that there may be interactions among multiple factors, such as genetic susceptibility, environmental factors and psychological factors (4). Many considerable studies regard the involvement of iron in the pathophysiological mechanisms and etiological factors associated with schizophrenia, but some of them are inconsistent (5).

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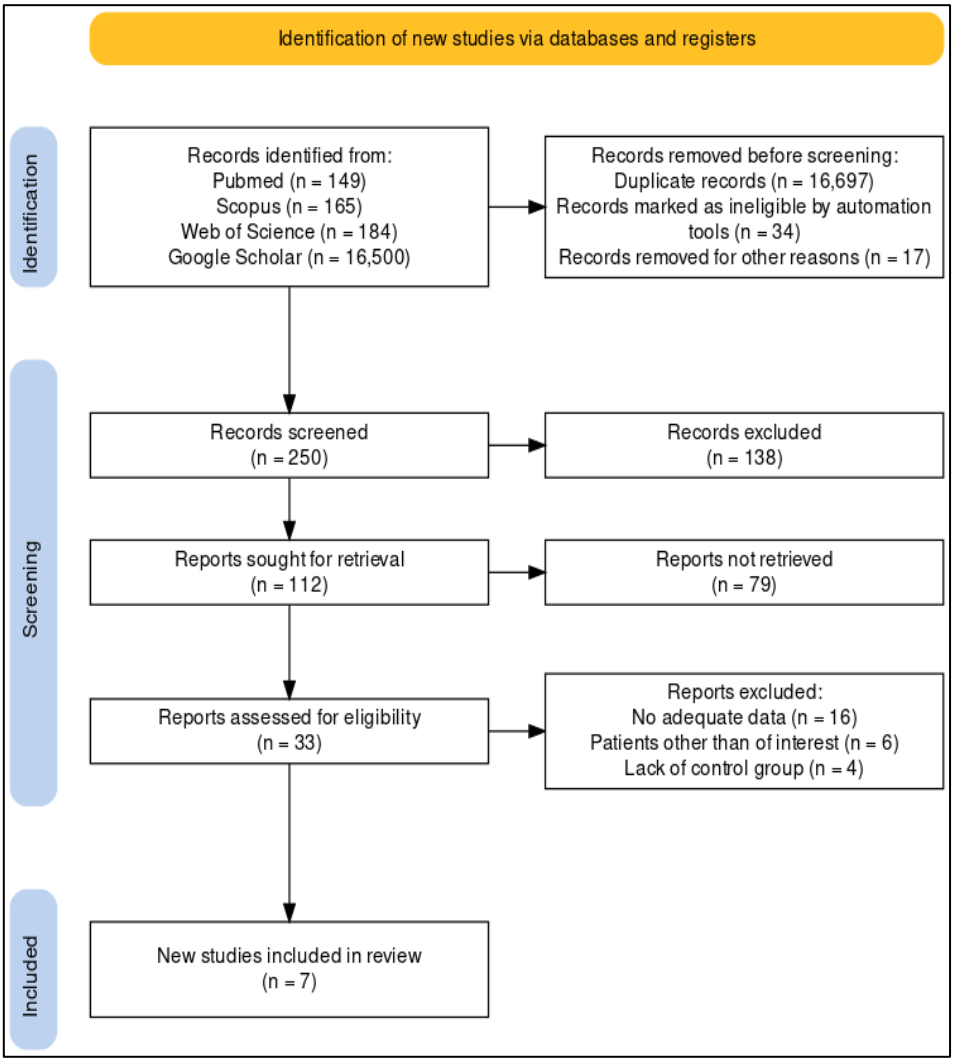

Figure 1 Flow diagram of the literature search process

Iron is an essential mineral in the human body; it is essential in many physiological processes, such as digestion, the production of enzymes, the growth of various human cells and the modulation of immunity. Iron is involved in synthesizing neurotransmitters and improves brain function by maintaining neuroplasticity (6). The existing study evidence reveals that people with schizophrenia have aberrant iron levels in specific brain regions when compared to people who do not have this disorder. This finding points to a possible link between iron dysregulation and the development of schizophrenia (7). Moreover, several studies have provided evidence suggesting that the provision of iron supplements may have the potential to improve cognitive functioning in individuals who have been diagnosed with schizophrenia (5)..

Table 1. Comparison of different studies about iron level, ferritin, hemoglobin and anemia in patients with schizophrenia

Author, year and country of study		Number of subjects				Serum iron level (µg/dl)		Ferritin (ng/ml)		Hemoglobin (g/dl)		Anemia (N)		Conclusion
		N	M	W	ALL	M	W	M	W	M	W	M	W	
Cao et al. 2019. China	S	105	44	61	211	131		X	X	X	X	X	X	There was a higher concentration of iron in the schizophrenia group.
	C	106	38	68		116		X	X	X	X	X	X	
Santa Cruz et al. 2020. Brazil	S	11	8	3	22	63.2		X	X	X	X	X	X	There was a higher concentration of iron in the schizophrenia group than in the healthy control group, but a small sample.
	C	11	8	3		42.1		X	X	X	X	X	X	
Liu et al. 2015. China	S	114	76	38	228	low(≤86)=21		X	X	X	X	21		Lower concentrations of iron and anemia are associated with an increased risk of schizophrenia.
	C	114	76	38		low(≤86)=7		X	X	X	X	7		
Chen et al. 2017. China	S	165	66	99	779	86.5		X	X	X	X	X	X	There was a lower concentration of iron in the schizophrenia group, but there were more men in the control group than women.
	C	614	518	96		108.3		X	X	X	X	X	X	
Memić-Serdarevic et all. 2020. Bosnia and Herzegovina	S	58	X	X	89	X	X	X	X	140.2		X	X	There is a lower concentration of hemoglobin in the schizophrenia group, and the control group made patients with bipolar disorder.
	C	31	X	X		X	X	X	X	146.8		X	X	
Ayyildiz et all. Turkey 2017.	S	518	384	134	609	X	X	X	X	142		X	X	Lower concentration of hemoglobin in the schizophrenia group.
	C	91	59	32		X	X	X	X	149		X	X	
Orum et al. 2018. Turkey	S	67	51	16	286	X	X	49.7		X	X	X	X	Lower ferritin in the schizophrenia group.
	C	219	127	92		X	X	50.3		X	X	X	X	

C = control group, S = schizophrenia, N = number, M = men, W = women, x = no data.

This review was conducted with the intention of not only providing a comprehensive analysis of the clinical symptoms and etiology of schizophrenia but also studying the probable relationship between schizophrenia and disruptions in iron levels. The primary goal of this review is to identify disorders in iron concentration and their association with schizophrenia. It could help to find disturbances in iron metabolism in schizophrenia patients in routine clinical practice with the possibility of more successful treatment

Methods of literature search

We exhaustively examined the literature published earlier using PubMed, Web of Science, Scopus and Google Scholar to identify articles published within the last two decades, from 2000 to the present. We oriented our search efforts towards meta-analyses, systematic reviews, randomized controlled trials and landmark studies that have previously addressed comparable subjects connected with iron levels and schizophrenia; see the flow diagram of the literature search process in Figure 1.

The first identification included the search strategy: (schizophrenia OR psychosis) AND (iron), and we got 16,814 results. Before screening, we removed duplicate records (n=16,697). Most of them were citations, illegible (n=34), and some of them were not in English or Croatian (n=17). We screened 250 records and excluded 138. We sought 112 records for retrieval but did not successfully retrieve 79 of them. For eligibility, we assessed 33 records, but some of them were excluded because some of them did not have adequate data (n=16), patients with other diagnoses but not schizophrenia (n=6), and a control group (n=4). We summarized our results in Table 1.

Classification of schizophrenia

The currently valid classifications that define and classify the differences in this clinical entity are the Fifth Edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), the tenth revision of the International Classification of Diseases (ICD-10) and the upcoming eleventh revision of the International Classification of Diseases (ICD-11) (8, 9) (Table 2).

There are specific differences between these classifications in terms of schizophrenia.

According to the DSM-5, the patient must have exhibited a minimum of two (or more) of the symptoms to satisfy the diagnostic criteria for schizophrenia. These symptoms include delusions, hallucinations, negative symptoms, disorganized speech and catatonic postures. The presence of delusions, hallucinations or disorganized speech is a minimum requirement. The presence of ongoing symptoms of the disorder must endure for a minimum of six months. During this time, the patient must manifest active symptoms for at least one month (or shorter if effectively treated), resulting in significant functional limitations in social, occupational and other domains. There must not be other psychiatric, medical or substance abuse disorders that could explain the symptoms. When a child has a history of autism spectrum disorder or a childhood-onset communication disorder, the diagnosis of schizophrenia is only made if prominent delusions or hallucinations have been present for at least one month and only if they are effectively treated (10). Paranoid, disorganized, catatonic, undifferentiated and residual type are the five sub-classifications of schizophrenia that were included in the past DSM classifications, but they are not in the DSM-5. This sub-classification has been eliminated in DSM-5 due to its inadequate diagnostic stability, low reliability and poor validity (2, 11).

Schizophrenia is defined in ICD-10 in the block of disorders F20–F29, together with schizotypal and delusional disorders. This block includes schizophrenia (F20), schizotypal disorder (F21), persistent delusional disorders (F22), acute and transient psychotic disorders (F23) and induced delusional disorder (F24). Despite their controversial nature between delusional and affective disorders, schizoaffective disorders (F25) have been retained here..

Table 2. Comparison between current classification systems of schizophrenia

Difference	DSM-5	ICD-10	ICD-11
Chapter in...	Schizophrenia is within the schizophrenia spectrum and other psychotic disorders.	Schizophrenia is together with schizotypal and delusional disorders.	Schizophrenia is with other primary psychiatric disorders.
DFi	Not highlighted	Highlighted	Not highlighted
Du	At least six months	At least one month	At least one month
Function...	Work, relationships and self-care are below premorbid levels	Not included	Not included
Subtypes	Without	Paranoid, hebephrenic, catatonic, simplex, undifferentiated post-schizophrenic depression residual, other, non-specific	Without
Specific symptoms	Delusions, hallucinations Disorganised speech Psychomotor impairment Affective, negative, cognitive	Without	Positive, negative, affective, psychomotor, cognitive, aggressive
Cognit...	Specific symptom	Not included	Specific symptom
Course	The first episode or multiple episodes, continuous or unspecified. Currently in acute episode, partial remission, complete remission.	Continuous or episodic with a progressive deficit or with a stable deficit. Remittent, with incomplete or with complete remission. Other, with uncertain course or with a very short observation period.	First episode, multiple episodes, continuous, other, or unspecific. Currently symptomatic, in partial, in complete remission or unspecified.

Other nonorganic psychotic disorders (F28) and unspecified nonorganic psychosis (F29) are included in this category (12). According to the ICD-10, schizophrenia is defined by specific abnormalities in perception and thinking, as well as improper or reduced emotional responses. While clear thinking and intellectual capacity are typically preserved, specific cognitive impairments may manifest as time passes. Possible manifestations of schizophrenia include a continuous course, an episodic course with a growing or persistent deficiency, or one or more episodes with remission (13). It is advised not to get the diagnosis of schizophrenia when there are noticeable manic or depressed symptoms unless it becomes clear that the signs of schizophrenia precede the emotional disturbance. Schizophrenia should not be diagnosed in cases of evident brain illness, intoxication or drug withdrawal. When comparable symptoms occur alongside epilepsy or another neurological disorder, they should be classified as F06.2. However, if psychoactive substances induce these disorders, they should be categorized as F10-F19 (14). The ICD-10 classification of schizophrenia includes the following subtypes: paranoid schizophrenia (F20.0), hebephrenic schizophrenia (F20.1), catatonic schizophrenia (F20.2), undifferentiated schizophrenia (F20.3), post-schizophrenic depression (F20.4), residual schizophrenia (F20.5), simple schizophrenia (F20.6), other schizophrenia (F20.8) and unspecified schizophrenia (F20.9) (15).

Stable delusions, auditory hallucinations and perceptual disturbances characterize paranoid schizophrenia. Affect, volition, speech and catatonia disturbances are absent or mild (16).

Affective changes, fleeting delusions and hallucinations, irresponsible behavior and mannerisms characterize hebephrenic schizophrenia: poor disposition, disorganized thought and incoherent speech. People tend to isolate themselves. Rapid "negative" symptoms, such as affect flattening and loss of volition, typically worsen the prognosis. It is generally diagnosed in adolescents or young adults (17).

Hyperkinesis, stupor or automatic obedience are psychomotor disturbances that distinguish catatonic schizophrenia and negativism predominates. Extended periods can be spent in limited postures. Violent excitement may characterize the condition. Catatonia may be present along with oneiroid dreams and vivid scenic hallucinations (18).

Undifferentiated schizophrenia can be defined as psychotic conditions that meet the general diagnostic criteria for schizophrenia but do not fit any of the subtypes in F20.0-F20.2 or exhibit symptoms of multiple subtypes with no clear predominance (2).

Long-lasting post-schizophrenic depression is possible following schizophrenic episodes. While some "positive" or "negative" symptoms of schizophrenia may continue, they do not predominate in the clinical presentation. The state of post-schizophrenic depression increases the risk of suicide (14, 19).

Residual schizophrenia is a chronic stage of schizophrenia that is characterized by progressive "negative" symptoms. These symptoms include psychomotor slowdown, decreased activity, dulled affect, inactivity, lack of initiative, impaired speech and poor nonverbal communication (such as facial expression, eye contact and voice modulation) (20).

Simplex schizophrenia is a subtype of schizophrenia characterized by a gradual development of unusual behavior, an inability to meet social expectations and diminished performance with residual symptoms, such as affective blunting and loss of motivation, occurring without the presence of psychotic symptoms (21).

If the symptoms do not fit into one of the specified subtypes of schizophrenia, we can diagnose it as other schizophrenia or unspecified schizophrenia (14).

In ICD-11, schizophrenia is classified as a primary psychotic disorder that is characterized by persistent or recurring hallucinations, delusions or disordered thinking or behavior. First-rank symptoms are not prioritized, and the duration of psychotic disorders is a minimum of one month. There are no functionality criteria or specified subtypes. Symptom specifiers include positive symptoms, negative symptoms, affective symptoms, aggressive symptoms and cognitive impairments (2). Schizophrenia is diagnosed when specific symptoms accompany a noticeable deterioration in social, academic or occupational functioning. In addition, a severity specifier was added to ICD-11 to denote the degree of severity associated with the disorder. The degree of functional impairment and the quantity and severity of symptoms determine the severity specifier. The specifier comprises three severity levels: mild, moderate and severe. The specifier provides a more thorough and meaningful representation of the condition's severity degree and guides treatment decisions (8).

Etiology and pathophysiology of schizophrenia

Schizophrenia covers a wide range of mental disorders characterized by distortions in reality perception, affect and behavior. Although the precise etiology of this disease remains unclear, empirical research shows that it is a multifactor phenomenon that occurs under several psychological, biological and environmental factors. Several psychological factors, such as stress, trauma and addiction, are associated with initiating schizophrenia or exacerbating its symptoms (22).

Numerous studies of genetic factors have provided evidence to suggest that people with a family background associated with schizophrenia are more likely to develop psychotic disorders. Nevertheless, the etiology of schizophrenia is not only ascribed to genetic

and psychological causes. The effects of the environment can also exert a substantial impact (16). There have been several environmental factors found to include prenatal exposure to viruses, bacterial or parasitic infections, complications during pregnancy or childbirth, exposure to stress or trauma and abuse of various psychoactive substances (4).

The pathophysiological mechanisms underlying schizophrenia involve alterations in neuronal connectivity within the brain, resulting in disturbances in perception, cognition and behavior (23). The onset of schizophrenia is shaped by a complex interaction of multiple factors that ultimately affect the structure and function of the brain, as well as other clinical symptoms. Previously, different clinical presentations of schizophrenia were categorized into subtypes according to earlier classifications like ICD-10. Nevertheless, this classification has been discarded in the present DSM-5 and forthcoming ICD-11 (8).

Scientific research has investigated the impact of malnutrition as a possible causative element in the onset of schizophrenia. Several studies have provided evidence suggesting a higher prevalence of insufficient levels of some essential nutrients, such as vitamin D, B6, B8 and B12, omega-3 fatty acids, zinc, magnesium, calcium and iron, among individuals diagnosed with schizophrenia (5, 24). They are associated with the weight of the clinical presentation and the quality of life of the sick. Ensuring adequate consumption of vital nutrients is an integral part of treating individuals with schizophrenia (25).

Various studies have provided evidence of the important role of iron in brain functions and its potential impact on the onset of mental disorders such as schizophrenia. While specific studies characterize iron deficiency as a contributing factor to the development of schizophrenia, others propose that iron contributes to oxidative stress, resulting in harm to neurons and the progression of the disease (6). Further investigations are required to fully understand the role of iron in the onset and development of schizophrenia, given the difficult interplay among genetic factors and environmental effects. This will facilitate the development of extra efficacious preventive and healing tactics for this complicated mental disease (5).

The role of iron in the etiopathogenesis of schizophrenia

Iron is essential for many biological processes in the human body. Most iron in the human body is bound to proteins such as hemoglobin, myoglobin and various enzymes. In the body, iron is stored in the liver with ferritin and hemosiderin. Protein transferrin permits the transport of plasma iron. When it reaches the tissue, the transferrin forms a complex with a specific receptor (26). Iron is crucial in many intracellular processes, such as DNA replication, enzyme activity, mitochondrial function and neurotransmitter regulation. When the quantity of iron consumed fails to satisfy physiological requirements, the body will mobilize its iron reserves (27). The iron required to mature red and white blood cells is diminished under such conditions. As a result, inadequate cytokine synthesis, hypochromatic microcytic anemia and insufficient lymphocyte maturation may ensue. These conditions also deteriorate immune systems or processes implicated in inflammatory diseases that could harm brain functioning (28).

Iron is essential for developing and operating the central nervous system, particularly in synthesizing mood-regulating, behavior-improving and cognition-enhancing neurotransmitters (e.g. serotonin and dopamine). Iron facilitates myelin formation and maintenance, improving neural communication's effectiveness. Iron is also crucial for energy production in brain cells and for regulating oxidative stress (6). Oxidative stress arises from a discrepancy between the organism's capacity to eliminate reactive oxygen species (ROS) and its production capacity (29). Iron can cause oxidative stress by making more reactive oxygen species (ROS). This is done through the Fenton reaction, which creates highly reactive hydroxyl radicals that can induce pathological conditions and harm cellular

constituents such as proteins, lipids and DNA. Iron can be distributed throughout many human body compartments, such as intracellularly or within the extracellular space. Insufficient iron in the brain can lead to notable alterations in both structure and function, potentially giving rise to various neurological and psychiatric disorders (30). Figure 2 shows the pathophysiological mechanism of iron accumulation and its influence on the development of schizophrenia.

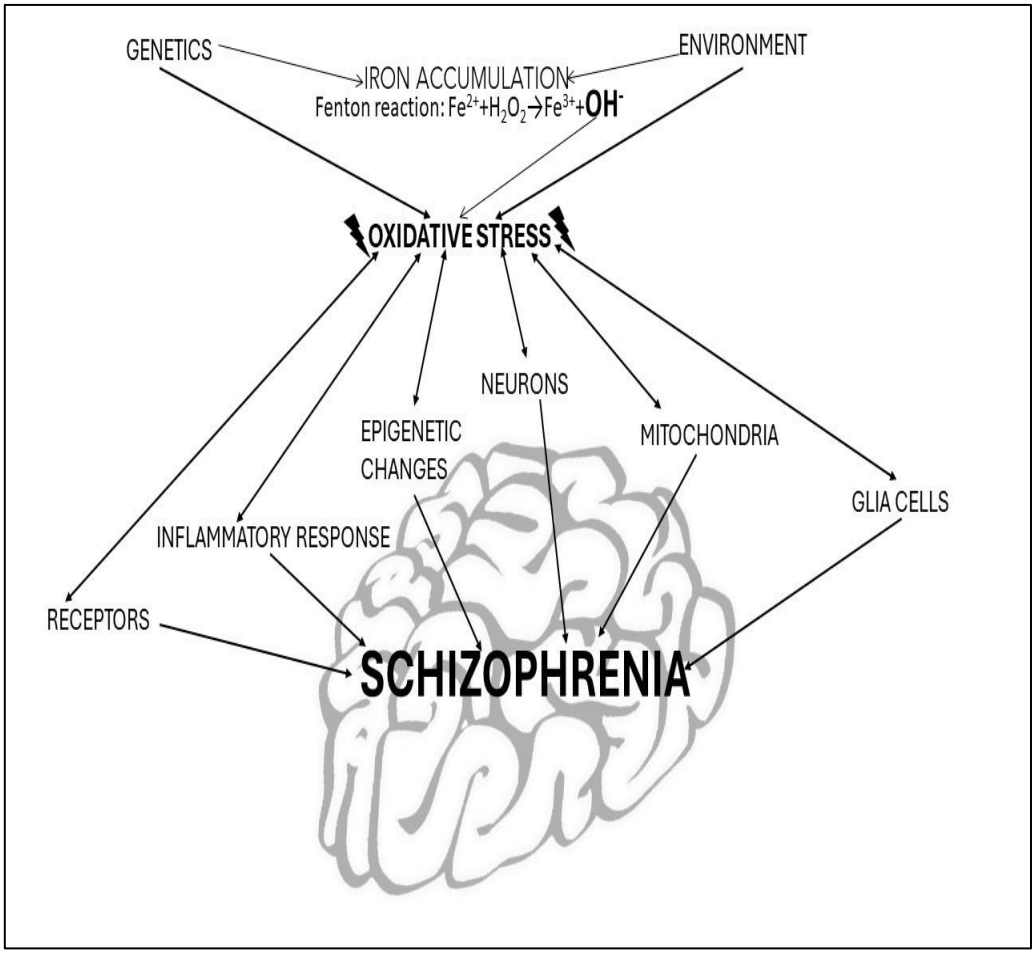

Figure 2. The influence of iron accumulation on oxidative stress and its impact on the development of schizophrenia

Studies showed a potential correlation between iron levels and the initiation and progression of schizophrenia. Insufficient iron levels throughout critical periods of brain development may be associated with incorrect synaptogenesis and, consequently, inadequate communication among neurons. Numerous studies prove the connection between disturbed iron levels in the brain or other spaces in the human body and numerous physiological processes, such as inflammation, oxidative stress and malfunctioning of mitochondria (6). As we explore the mechanisms underlying the causes of schizophrenia, it becomes clear that our understanding of this complicated mental disorder has been significantly improved. It is now evident that insufficient iron levels play a more substantial role in the development and progression of schizophrenia than we previously believed. These studies deepen our understanding of the complexities of this intricate psychiatric condition (31). Additional research is necessary to fully understand the role of iron in the development of schizophrenia. However, based on the existing research,

maintaining optimal iron levels might lower the chances of having this complex mental disease.

Discussion

The impact of iron deficiency on the development of schizophrenia has been examined by multiple researchers, giving inconclusive findings (see Table 1).

Some studies have concluded that a higher level of iron is associated with the onset of schizophrenia, indicating the possible harmful role of iron in stimulating oxidative stress. The study by Cao et al. 2019 showed lower serum iron levels in a healthy population compared to patients with schizophrenia (31). Brazilian research by Santa Cruz et al. from 2020 also observed higher serum iron levels in patients compared to a healthy control group. However, this study's small sample was noticeable, with only 22 subjects in the affected and control groups (32).

On the other hand, some studies found that low iron levels are associated with schizophrenia. In the 2015 study by Liu et al., lower serum iron levels were observed in patients with schizophrenia, leading to the conclusion of possible poorer nutrition in these patients and the role of iron deficiency in the inadequate production of neurotransmitters important for mental functions (33).

The Chen et al. study, conducted in 2017 with 779 subjects, showed lower serum iron levels in patients with schizophrenia. However, more men in the control group had higher iron levels physiologically (34).

In the study from Bosnia and Herzegovina, from 2020, Memic-Serdarevic et al. compared hemoglobin levels in patients with schizophrenia with a control group who had bipolar affective disorder and concluded that hemoglobin levels were lower in patients with schizophrenia, which may speak in favor of poorer malnutrition in patients with schizophrenia who have significantly impaired cognitive and social functions and consequently a more inferior quality of life compared to patients with bipolar affective disorder (35).

A 2017 Turkish study by Ayyildiz et al. also confirmed lower hemoglobin levels in applications with schizophrenia compared to a healthy control group (36), and the Turkish study by Orum et al. from 2018 showed lower ferritin levels in patients with schizophrenia (37).

The relationship between oxidative stress and iron levels has been identified as significantly associated with the etiology and development of schizophrenia (38). Oxidative stress is characterized by disequilibrium between generating reactive oxygen species and the organism's capacity to counteract their harmful effects, resulting in cellular and tissue damage (39). Research has revealed that individuals diagnosed with schizophrenia frequently exhibit elevated levels of oxidative stress within their cerebral regions, thereby potentially instigating neuronal impairment and detriment to other components of the brain (40).

Iron is a vital mineral involved in numerous physiological processes within the human body, encompassing the synthesis of erythrocytes and facilitating cerebral oxygen transportation. Nevertheless, scholarly investigations have revealed a correlation between individuals diagnosed with schizophrenia and disordered iron levels in their bloodstream. This phenomenon has been linked to oxidative stress and subsequent impairment of cerebral cells (6).

The precise correlation between iron, oxidative stress and schizophrenia remains incompletely comprehended; however, it is evident that these variables play a significant role in the onset and advancement of the disorder (38). More research is needed to understand better how iron and oxidative stress affect schizophrenia and to come up with more effective treatments that target these essential factors.

Conclusion

Several controlled studies have been conducted to analyze the hematological status and iron levels of patients diagnosed with schizophrenia. Nevertheless, the methodologies, sample sizes, inclusion criteria, reference values, gender distribution and other variables lack standardization. Hence, the

findings remain inconclusive, as specific authors assert a robust correlation between iron levels and the onset of schizophrenia, while others hold a contrasting viewpoint.

Based on a comprehensive review of several studies and a subsequent detailed analysis of the data, we can conclude that iron has a significant impact on the pathogenesis of schizophrenia. Iron is an essential element that plays a vital role in a multitude of biological processes, and its lack is related to the emergence of various mental disorders, including schizophrenia. However, there are also dubious conclusions about the harmfulness of elevated iron levels and the development of oxidative stress. It is essential to point out that the deficiency itself or high iron levels cannot cause schizophrenia. Probably, disturbances in the amount of iron can contribute to the pathogenesis of schizophrenia as a combination of genetic, environmental and nutritional factors.

Potential benefits of including routine hematological examinations in people diagnosed with schizophrenia include the identification of essential dietary deficiencies and the mitigation of systemic manifestations associated with malnutrition, which is more common in people with schizophrenia than in the general population. Further research is needed to gain a more detailed understanding of the association between the role of iron in the pathogenesis of schizophrenia as well as its possible implications for therapeutic and prevention options.

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Povezanost razine željeza i shizofrenije: Pregled literature

Shizofrenija je složeno psihijatrijsko stanje koje, ako se ne liječi na odgovarajući način, može dovesti do funkcionalnih ograničenja. Točna etiopatogeneza shizofrenije još uvijek je nepoznata. Istraživanja upućuju na interakciju između mnogih čimbenika, uključujući genetsku osjetljivost, okoliš i psihološke procese. Pojedini autori opisuju povezanost željeza, kao vrijednoga minerala u ljudskom tijelu, s patofiziološkim mehanizmima i povezanim etiološkim čimbenicima u razvoju teške mentalne bolesti - shizofrenije.

Željezo ima važne uloge u ljudskom tijelu i utječe na različite fiziološke procese. Neke su studije pokazale povezanost između disregulacije razina željeza i razvoja različitih mentalnih poremećaja, uključujući shizofreniju. Abnormalne razine željeza u specifičnoj regiji mozga zapažene su kod osoba sa shizofrenijom. Razine željeza mogu doprinijeti patogenezi shizofrenije u kombinaciji s drugim genetskim, okolišnim i prehrambenim čimbenicima. Željezo također može doprinijeti boljoj kognitivnoj funkciji pacijenata sa shizofrenijom, te je zbog česte pothranjenosti i malnutricije kod te skupine pacijenata važno uzeti u obzir potrebu za rutinskim hematološkim pregledima i određivanjem osnovnih prehrambenih nedostataka.

Na kraju, naš je cilj bio sustavno pregledati literaturu o ovoj temi objavljenu u posljednja dva desetljeća koristeći PubMed i Google Scholar. Opisali smo kliničke aspekte i etiološke čimbenike shizofrenije. Odredili smo može li se shizofrenija povezati s poremećajima koncentracije željeza kako bismo prepoznali i identificirali potencijalne pacijente s nedostatkom željeza te ih pravovremeno liječili u svakodnevnoj kliničkoj praksi.