METABOLIC, CARDIOVASCULAR AND NEUROPSYCHOLOGICAL COMORBIDITIES IN SCHIZOPHRENIA

RITHIKA SHATRASHI, KEERTHIJA REDDY KOMMIDI, REYNAA MARY NEEREDU, PRIYANKA TATIKONDA, AKHIL AKKENAPALLY, BANDI NANDEESHWAR, NARENDER BOGGULA*

Omega College of Pharmacy, Edulabad, Ghatkesar, Hyderabad, Telangana, India.

Corresponding author:
Dr. NARENDER BOGGULA
Associate Professor,
Department of Pharmaceutical Chemistry,
Omega College of Pharmacy,
Edulabad, Ghatkesar, Hyderabad, Telangana, India - 501 301.
E-Mail: drnarenderboggula@gmail.com
Mobile: +91 9666 55 2211

ABSTRACT

A chronic mental condition, schizophrenia can alter brain action resulting in dopamine breakdown, which can result in both positive and negative side effects, as well as changes to the white and grey matter and ventricular dilation. Schizophrenia is a disabling psychiatric condition impacting around 1% of people worldwide and ranking among the top 10 global disability causes. Schizophrenia is characterized by positive psychotic symptoms such as hallucinations, delusions, disorganized speech, and disorganized or catatonic behaviour; negative symptoms such as reduced motivation and expressiveness; and cognitive impairments affecting executive function, memory, and mental processing speed. It may result in reduced working memory and attention within the individual. Comorbid conditions such obesity, metabolic syndrome, type 2 diabetes mellitus, chronic obstructive pulmonary disease, and cardiovascular disease are more likely to occur. Furthermore, antipsychotics, mood stabilizers, and antidepressants are utilized as treatments for schizophrenia. This article discusses schizophrenia, its comorbidities, and the variables that impact it.

Key words: *Schizophrenia, metabolic disorder, diabetes mellitus, metabolic syndrome.*

INTRODUCTION

Schizophrenia may be a chronic mental illness characterized by symptoms such as delusions and hallucinations, which lead to irregular mental functioning. Emotional working and cognitive recognition are moreover affected. Negative indications include less emotional expression, low inspiration, and social withdrawal are also included. Multiple factors contribute to the development of schizophrenia, including genetics, natural factors like family history, and hereditary transformations that occur when genes connected to dopamine and glutamate systems, as well as genes like DISC1 and COMPT, change. Environmental Components: These include social isolation, childhood trauma, or being criticized by others when one isn't in a typical state. Additionally, schizophrenia patients have an excess of dopamine, particularly in D_2 receptors [1,2].

Schizophrenia, a serious mental illness, affects 1% of the global population and is marked by hallucinations, delusions, disorganized speech, grossly disorganized behaviour, and negative signs and symptoms such as reduced emotional expression, avolition, and cognitive impairment. Symptoms generally emerge in late adolescence or early adulthood, and the disorder may be more common in men. Causes include genetic, environmental, and neurobiological factors. No single gene is responsible; there is an interplay of multiple genetic factors. Environmental influences include prenatal and obstetrical risks, psychosocial stressors, and cannabis use. Neurobiologically, schizophrenia is associated with neurotransmitter dysfunction in dopamine and glutamate

systems, as well as brain structural changes. Individualized comprehensive management plans, including antipsychotic medications for positive symptoms and evidence-based psychosocial interventions, are essential for improving patient quality of life [2-4].

Pathophysiology

There's an increased ventricular size, decreased brain size and brain asymmetry are seen within the patients who are suffering from schizophrenic disorder.

Dopaminergic and glutamate hypothesis: It leads to subcortical dopamine dysfunction and it also produces positive and negative side effects. The hyperactivity within the dopamine in mesolimbic pathway leads to positive side effects such as (hallucinations, delusions). And the hypo activity within the dopamine in neocortical pathway leads to negative side effects such as (reduced emotional expression, social withdrawal, lack of motivation). Glutamate is the excitatory neurotransmitter and it leads to the decreased function within the N-methyl-D-aspartate (NMDA) receptor antagonists such as ketamine and phencyclidine (PCP) can disrupt the thalamus functioning and lead to cognitive dysfunction and psychotic symptoms and also negative side effects.

Serotonin and GABA (gamma amino butyric corrosive): This neurotransmitter is included in Mood, sleep. Antipsychotics mainly blocks the 5HT2A receptor which maintains psychological and neurological forms in CNS & PNS. Can also leads to schizophrenia and interacts with dopamine system and leads to its dysfunction. GABA regulates the brain activity. brain derived neuro trophic factor it improves the glutamatergic transmission and reduces GABAergic transmissions. And it leads to the dye's regulation of brain action additionally considering and sensory abnormalities [5-7].

Brain structural changes

Nerve strands covered in myelin, which facilitates communication between distinctive brain regions then the schizophrenia gets to be chronic. And the ventricular size will be larger within the schizophrenic patient as compared to the typical patient which is seen in CT imaging. It may lead to reduced brain tissue volume. And the pathophysiology of schizophrenia is unknown till date.

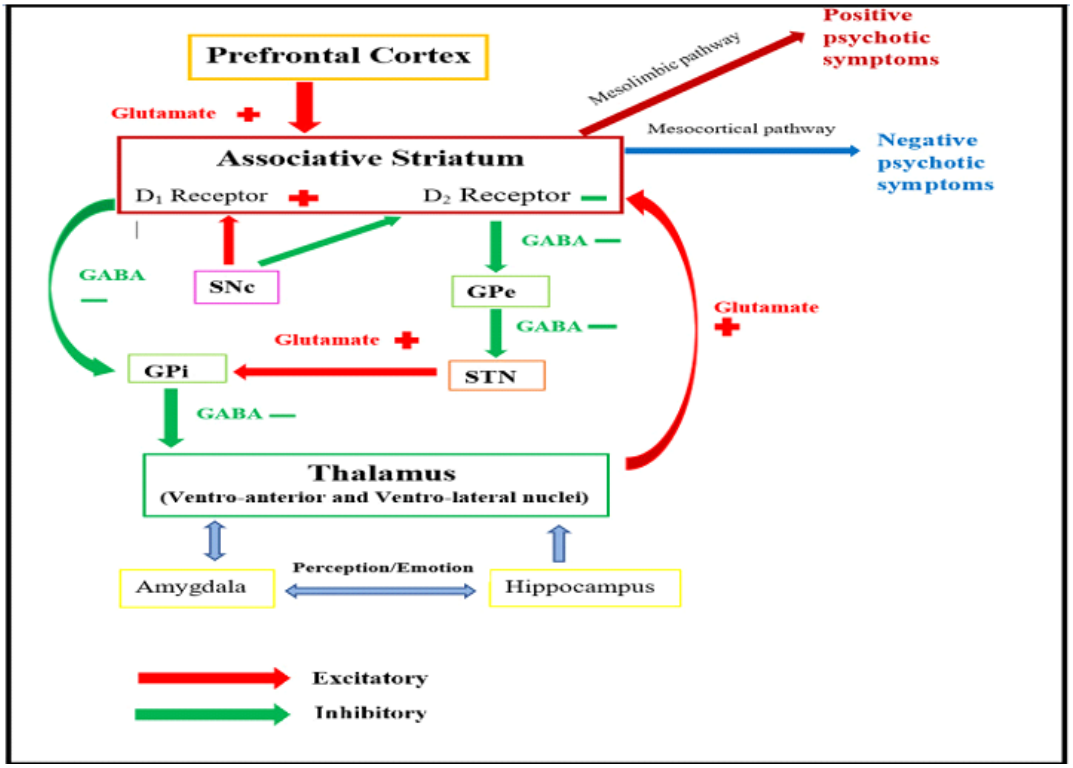

Figure 1: Network of direct and indirect pathways of basal ganglia involved in motor activity and psychotic symptoms; stimulation and increased activity of excessive D_2 receptors in the associative striatum causing schizophrenia.

Comorbidities in schizophrenia

Schizophrenia causes mental illness which is able to prone other health related conditions such as type 2 diabetes mellitus, cardiovascular diseases, chronic obstructive pulmonary disorder and metabolic syndrome.

Schizophrenia with type 2 diabetes mellitus

Patients with schizophrenia face a significantly reduced life expectancy, with mortality rates 2–3 times higher than the general population and a lifespan shortened by 10–20 years. While suicide and accidents contribute to this disparity, metabolic disorders particularly type 2 diabetes mellitus (T2DM) play a major role. The prevalence of T2DM in schizophrenia is alarmingly high, driven by a complex interplay of antipsychotic side effects (e.g., weight gain), poor lifestyle habits (e.g., sedentary behaviour, unhealthy diet), and socioeconomic disadvantages that limit access to healthcare. Beyond these well-known risk factors, emerging evidence suggests a shared genetic susceptibility between schizophrenia and T2DM. Several genes implicated in both disorders regulate neuronal development in the brain and insulin function in the pancreas, pointing to common biological pathways. This review explores these overlapping genetic risks, their functional consequences, and the mechanistic links between schizophrenia and T2DM.Shared Susceptibility Genes and Common Pathways Genome-wide association studies (GWAS) and candidate gene analyses have identified multiple loci associated with both schizophrenia and T2DM, Including:

TCF7L2; A key regulator of glucose metabolism that also influences synaptic plasticity.

DISC1: Disrupted in schizophrenia, this gene affects neurodevelopment and β-cell function.

FTO: Linked to obesity and insulin resistance, it may also influence cognitive function.

BDNF: Critical for neuronal survival and synaptic plasticity, but also modulates insulin sensitivity.

These genes converge on pathways such as: Insulin signalling (impaired in T2DM, but also crucial for neuronal survival), Inflammation and oxidative stress (elevated in both disorders).

metabolic dysfunction (affecting energy metabolism in neurons and pancreatic cells) [8-10].

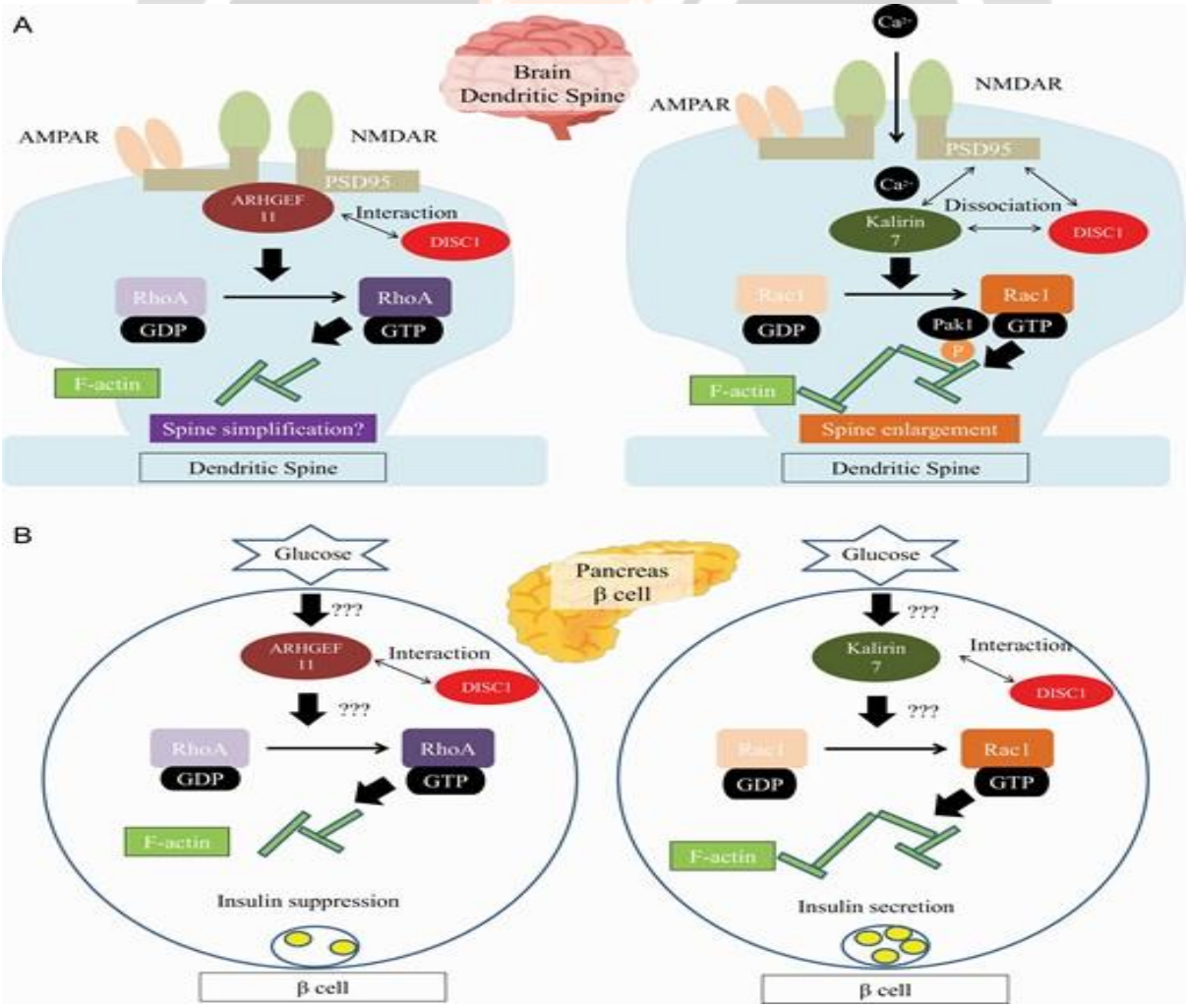

Figure 2: Brain functioning and synaptic plasticity and pancreatic beta cell functioning and insulin secretion

Schizophrenia with metabolic syndrome

Isn't just one condition it's a cluster of health problems that often occur together. These include high blood pressure, excess body weight (especially around the belly), abnormal cholesterol levels, and high blood sugar. When these conditions come together, they greatly increase the risk of heart disease, stroke, and type 2 diabetes.

Fat stored deep in the abdomen around the internal organs is particularly harmful and strongly linked to metabolic complications. A major driver of metabolic syndrome is long-term inflammation caused by obesity and something called insulin resistance. Normally, insulin helps the body control blood sugar levels and use fat for energy. But when cells stop responding properly to insulin, fat metabolism gets disrupted. Fatty acids build up in the blood and interfere with insulin's actions in muscles and the liver, making blood sugar levels harder to control. Over time, the pancreas struggles to keep up with the increased demand for insulin, and this can eventually lead to diabetes.

Fat tissue isn't just passive storage: It's active and produces hormones and chemicals that affect how the body works. In obesity, this balance gets thrown off. The body makes more pro-inflammatory substances like Leptin, TNF-alpha, and Interleukin-6, which promote inflammation. At the same time, levels of protective, anti-inflammatory signals-like adiponectin and Interleukin-10 go down. This creates a state of chronic low-grade inflammation that worsens metabolic health [11,12].

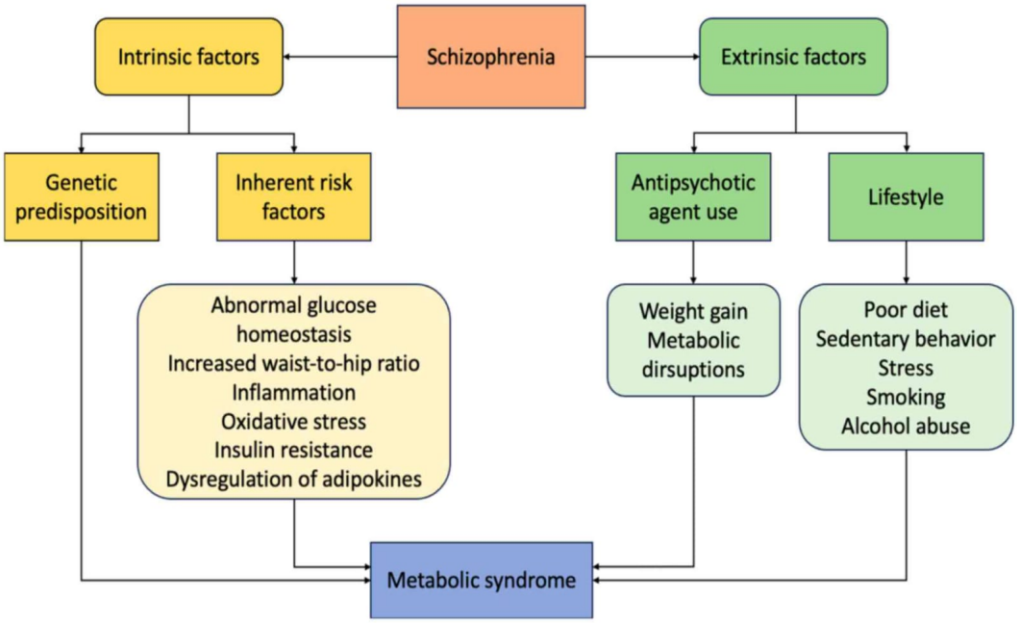

Figure 3: Factors leading to the schizophrenic metabolic syndrome

Schizophrenia with cardiovascular diseases

People living with schizophrenia often face a greater risk of developing coronary heart disease (CHD) due to the higher prevalence of contributing factors like smoking, high cholesterol, high blood pressure, obesity, and diabetes. In the general population, people often prefer taking medication over making difficult lifestyle changes. But for those with schizophrenia, even consistently taking prescribed medications such as antipsychotics can be a real challenge. This makes it all the more important that when we prescribe antipsychotic medications, we do so thoughtfully, taking into account not just the illness, but the person behind it their struggles, routines, and support system [13,14].

Depression in schizophrenia

Depression in schizophrenia is more than just feeling sad and it's a deep, often silent burden that can make already complex illness even harder to bear. Many people think of schizophrenia only in terms of hallucinations or delusions, but depression is a quiet shadow that often follows behind, deeply affecting daily life, relationships and even hope for recovery. It's not simply a side effect of the illness it's part of it. People may struggle to get out of

bed, lose interest in things they once loved, or feel disconnected from others. It can lead to social withdrawal, worsening of other symptoms, and even thoughts of self-harm for some, the depression feels heavier than the hallucinations [15,16].

CONCLUSION

People with schizophrenia have a decreased life expectancy of 13 to 15 years. While this population experiences higher rates of deaths from unnatural causes compared to the general population, most premature deaths are attributable to natural causes. Living with schizophrenia is already a deeply challenging journey, marked by disruptions in thought, emotion, and perception. When comorbid physical conditions like diabetes, cardiovascular disease, obesity, and respiratory disorders enter the picture, they not only complicate medical care but also intensify the burden on individuals physically, emotionally, and socially. These comorbidities they represent real struggles shortness of breath during a walk, the sting of daily insulin injections, the anxiety of monitoring blood pressure, or the fatigue from carrying excess weight. All these silently erode quality of life, especially in those who may already feel misunderstood or isolated due to the stigma surrounding mental illness. Understanding and addressing these interconnected health issues is not merely a medical responsibility it is a moral one. In essence, tackling comorbidities in schizophrenia isn't just about improving outcomes it's about acknowledging the whole person behind the diagnosis and giving them a fighting chance at wellness and humanity.

Conflicts of interest

None declared.

REFERENCES

1. Marder SR, Cannon TD. Schizophrenia. N Engl J Med. 2019; 381(18):1753-1761.
2. Jauhar S, Johnstone M, McKenna PJ. Schizophrenia. Lancet. 2022; 399(10323):473-486.
3. Kahn RS. On the Origins of Schizophrenia. Am J Psychiatry. 2020; 177(4):291-297.
4. Hjorthøj C, Stürup AE, McGrath JJ, Nordentoft M. Years of potential life lost and life expectancy in schizophrenia: a systematic review and meta-analysis. Lancet Psychiatry. 2017; 4(4):295-301.
5. Brown S, Inskip H, Barraclough B. Causes of the excess mortality of schizophrenia. Br J Psychiatry. 2000; 177:212–217.
6. Mitchell AJ, Vancampfort D, Sweers K, Van Winkel R, Yu W, De Hert M. Prevalence of metabolic syndrome and metabolic abnormalities in schizophrenia and related disorders-a systematic review and meta-analysis. Schizophrenia Bulletin. 2013; 39(2):306–318.
7. Carney CP, Jones L, Woolfson RF. Medical comorbidity in women and men with schizophrenia: a population-based controlled study. J Gen Intern Med. 2006; 21:1133–1137.
8. Goh, K. K., Chen, C. Y., Wu, T., Chen, C., & Lu, M. Crosstalk between Schizophrenia and Metabolic Syndrome: The Role of Oxytocinergic Dysfunction. International Journal of Molecular Sciences. 2022; 23(13):7092.
9. Manta A, Georganta A, Roumpou A, Zoumpourlis V, Spandidos D, Rizos E, & Peppa M. Metabolic syndrome in patients with schizophrenia: Underlying mechanisms and therapeutic approaches (Review). Molecular Medicine Reports. 2025; 31(5):1-16.
10. Hennekens CH, Hennekens AR, Hollar D. Schizophrenia and increased risks of cardiovascular disease. Am Heart J. 2005; 150:1115–1121.
11. Joukamaa M, Heliovaara M, Knekt P. Mental disorders and cause-specific mortality. Br J Psychiatry. 2001; 179:498–502.
12. Leucht S, Crippa A, Siafis S, Patel MX, Orsini N, Davis JM. Dose-Response Meta-Analysis of Antipsychotic Drugs for Acute Schizophrenia. Am J Psychiatry. 2020; 177(4):342-353.
13. DE Hert M, Schreurs V, Vancampfort D, VAN Winkel R. Metabolic syndrome in people with schizophrenia: a review. World Psychiatry. 2009 ; 8(1):15-22.
14. Messias EL, Chen CY, Eaton WW. Epidemiology of schizophrenia: review of findings and myths. Psychiatr Clin North Am. 2007; 30(3):323-38.
15. Rizvi A, Reyazuddin M, Shaan F. Low-Dose Clozapine in Early-Onset Resistant Schizophrenia: Case Report and 2-Year Follow-up. J Am Acad Child Adolesc Psychiatry. 2023; 62(8):839-841.
16. Brown S. Excess mortality of schizophrenia. A meta-analysis. Br J Psychiatry. 1997; 171:502–508.