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Understanding Lipid Abnormalities in Schizophrenia: A Review of Cholesterol and Triglyceride Levels Pre- and Post-Treatment

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ABSTRACT

Schizophrenia is a complicated mental condition that profoundly impairs cognitive and behavioral abilities, frequently disrupting everyday living and leading to poor health outcomes. Among the many health concerns connected with schizophrenia, lipid metabolic abnormalities, particularly in total cholesterol and serum triglyceride levels, have received attention due to their impact on cardiovascular health. This literature review examines the link between schizophrenia and lipid profiles, with an emphasis on drug-naive patients, those receiving antipsychotic medication, and first-degree relatives. This review, which synthesizes findings from several studies, highlights the impact of antipsychotic medicines on lipid levels, identifies potential biomarkers for schizophrenia, and emphasizes the importance of monitoring lipid metabolism in patients. It also looks at the historical context of lipid abnormalities in schizophrenia, including early observations and current research relating metabolic changes to the disorder's etiology. The review continues by exploring the therapeutic significance of these findings, emphasizing the need for integrated care approaches that address both mental and metabolic health in schizophrenia patients.

Keywords: Schizophrenia, Lipid Metabolism, Total Cholesterol, Serum Triglycerides, Antipsychotic Treatment

INTRODUCTION TO SCHIZOPHRENIA

Schizophrenia is a widespread mental condition that impairs a person's capacity to think, feel, and behave rationally [1]. According to the World Health Organization (WHO), this condition affects around 24 million people, or 1 in every 300 persons (0.32%) worldwide. This rate applies to 1 in every 222 adults (0.45%). In short, it affects 1% of the world's population, among that diagnosed [1]. Compared to many other mental disorders, it is less prevalent. The peak years for schizophrenia are late adolescence and early adulthood, with men often developing the disorder earlier than women [2]. This illness often causes the boundaries between reality and perception to become distorted, which is extremely upsetting for both the afflicted individual and their immediate family [3]. Although its symptoms have the potential to disrupt everyday routines, there is still hope thanks to efficacious therapies. One of the main characteristics of people with schizophrenia is cognitive and behavioral problems, which are associated with poor treatment adherence, unhealthy eating habits, and impaired independent daily functioning [4].

A person suffering from schizophrenia exhibits a range of symptoms that fall into three primary categories: cognitive, negative, and psychotic [1]. Changes in a person's thoughts, perceptions, conduct, and worldview are all part of psychotic symptoms. These symptoms include delusions, in which people firmly accept illogical beliefs, and hallucinations, in which people hear voices or sense objects that are not there. Additionally, aberrant physical motions and mental disorders may appear [5]. A lack of desire, disinterest in or enjoyment from daily activities, inability to express emotions, social disengagement, and difficulties operating regularly are all considered negative signs. Negative symptoms include talking in a dull voice, displaying limited facial expression, having trouble planning and sticking to routines like grocery shopping, as well as having trouble anticipating and being motivated by pleasure in daily life. Sometimes these symptoms progress to extreme states like catatonia [6]. Cognitive symptoms include issues with focus, memory, and attention that affect daily tasks and make decision-making difficult. Difficulties with learning, focusing, and processing information are common cognitive symptoms of schizophrenia. It is crucial to remember that these symptoms are distinct from those of other mental health issues, such as depression, and that medical professionals assess those using particular cognitive tests [7].

The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) specifies criteria for diagnosing schizophrenia that require the presence of two or more active-phase symptoms over a significant period of time, such as catatonic presentation, disorganized speech, delusions, or negative symptoms, with at least one of these being delusions, hallucinations, or disorganized speech [8]. In addition, there must be a discernible decline in functioning in job, relationships, or self-care, as well as ongoing indicators of schizophrenia for a minimum of six months, including long active-phase. In order to diagnose schizophrenia correctly, a thorough differential diagnosis must rule out substance abuse and medical conditions as the cause of presenting symptoms, as well as distinguish it from other mental disorders such as major depressive disorder with psychotic symptoms, schizoaffective disorder, schizophreniform disorder, obsessive-compulsive disorder, body dysmorphic disorder, and post-traumatic stress disorder [9]. Antipsychotic drugs, which are divided into two classes: first-generation (typical) antipsychotics and second-generation (atypical) antipsychotics, are the most often recommended treatments for schizophrenia [10]. Second-generation antipsychotics can also inhibit serotonin receptors, which are how both kinds of drugs work by blocking dopamine D2 receptors [11]. Rather than considering variations in efficacy, clinicians prescribe antipsychotics based on patient desire and side effect profiles. Olanzapine, Clozapine, Aripiprazole, Risperidone, and Ziprasidone are examples of atypical antipsychotics, whereas drugs like Haloperidol, Chlorpromazine, Trifluoperazine, and Fluphenazine are examples of typical antipsychotics [12]. Many people find that these treatments enable them to pursue employment or educational goals, become self-sufficient, and form meaningful relationships with others [13].

Biomarkers in Schizophrenia

A biomarker, sometimes referred to as a biological marker, is a clinical sign that gauges an organism's or cell's current state. Biomarkers have the potential to serve as early health warning systems [14]. For instance, elevated bloodstream levels of lead, especially in youngsters, may suggest that neurological system and cognitive abnormalities need to be tested for [15]. Elevated cholesterol is a prevalent biomarker associated with cardiovascular disorders [16]. Since there are currently no approved laboratory tests, prognoses, or biomarkers for schizophrenia diagnosis,

treatment response prediction, schizophrenia is generally diagnosed based on clinical symptoms.

Potential biomarkers for schizophrenia, such as those found in neuroimaging, genetic, neurochemical, inflammatory, oxidative stress, metabolic, and epigenetic processes, have been the subject of some investigation [17].

i. **Neuroimaging Markers:** Schizophrenia is usually linked to abnormalities in the structure and function of the brain. Disparities in brain structure and activity, such as decreased gray matter volume in specific brain regions like the prefrontal cortex and hippocampus, can be seen with magnetic resonance imaging (MRI) and functional magnetic resonance imaging (fMRI) [18].
ii. **Genetic Markers:** Genetic studies estimate that 60-80% of schizophrenia cases are attributed to genetics [19]. A higher chance of contracting the illness has been linked to a number of genetic variants. Although few genetic markers have been found by genome-wide association studies (GWAS), their prediction ability is still quite low [20].
iii. **Neurochemical Markers:** In schizophrenia, there is a dysregulation of neurotransmitters such glutamate, serotonin, and dopamine. These neurotransmitter systems' biomarkers, such as dopamine metabolite levels in CSF fluid or receptor density determined by positron emission tomography (PET), have been studied [21].
iv. **Inflammatory Markers:** Numerous theories propose that inflammation could be a primary factor in schizophrenia. Schizophrenia patients have been shown to have elevated levels of several inflammatory indicators, such as cytokines, in their cerebrospinal fluid or blood [22,23].
v. **Oxidative Stress Markers:** One possible explanation for schizophrenia has been suggested to be increased oxidative stress, which arises from an imbalance between reactive oxygen species (ROS) and antioxidant mechanism. Oxidative stress biomarkers, such as antioxidant enzyme activity or lipid peroxidation markers, have been researched [24].
vi. **Metabolic Markers:** In individuals with schizophrenia, metabolic disorders such as dyslipidemia, insulin resistance, and obesity are more prevalent. Metabolic biomarkers, such as insulin, blood glucose, and lipid profiles, can shed light on the mechanisms underlying disease and its risk factors [25].
vii. **Epigenetic Markers:** Without altering the underlying DNA sequence, epigenetic modifications like DNA methylation and histone acetylation can affect the patterns of gene expression. Schizophrenia-related epigenetic biomarkers may serve as predictors of illness risk or responsiveness to therapy [26].

The subject of schizophrenia biomarkers is currently developing, with continued study aimed at deepening our knowledge of the illness and enhancing the precision of diagnosis. New biomarkers will transform schizophrenia diagnosis and treatment standards as soon as they are proven.

Cholesterol and Triglyceride

Triglycerides and cholesterol are significant components of the lipid section in our human body [27]. All animal cells depend on cholesterol, an unsaturated alcohol that is a member of the steroid family of chemicals, for proper operation. Cholesterol also serves as a structural element of cell membranes. Moreover, it serves as a precursor for the synthesis of bile acids, vitamin D, and all other steroids [28].

Triacylglycerols, or neutral fats, are other names for triglycerides. They are the primary lipid component present in animal fat depots and feed fat; they are esters of the trihydric alcohol, glycerol, with fatty acids. Natural oils and fats are composed of triglycerides. A straightforward triacylglycerol, such as tripalmitin, triolein, etc., is created when all three groups of

glycerol are esterified to the same fatty acid [29].

Triglycerides and cholesterol are nonpolar lipids that are insoluble in water and must be carried in the plasma along with other lipoprotein particles. Chylomicrons, very-low-density lipoproteins (VLDL), intermediate-density lipoproteins (IDL), low-density lipoproteins (LDL), and high-density lipoproteins (HDL) are the five main classes of plasma lipoproteins based on size, hydrated density, electrophoretic mobility, and the relative amounts of protein, triglycerides, and cholesterol [30].

Maintaining blood cholesterol levels within a safe range is essential for preventing cardiovascular illnesses [31].

Total Cholesterol

- Desirable: Less than 200 mg/dL
- Borderline High: 200-239 mg/dL
- High: 240 mg/dL and above [32]

An increased risk of atherosclerosis, which can result in peripheral arterial disease, coronary artery disease, and stroke, is linked to abnormal cholesterol levels [33].

The risk of cardiovascular illnesses can also be increased by elevated triglyceride levels. Additionally, it can result in pancreatitis, and is frequently linked to other illnesses like hypothyroidism, obesity, metabolic syndrome, and type 2 diabetes mellitus [34].

- **Serum Triglyceride**

- Normal: Less than 150 mg/dL
- Borderline High: 150-199 mg/dL
- High: 200-499 mg/dL
- Very High: 500 mg/dL and above [35]

Reducing these health risks requires maintaining cholesterol and triglyceride levels within the prescribed ranges via medication and lifestyle modifications [36].

History of Total Cholesterol and Serum Triglyceride in relation to Schizophrenia

Researchers first started looking at the metabolic anomalies connected to schizophrenia in the middle of the 19th century. They noticed that lipid metabolism abnormalities were common in people with schizophrenia, which led to the theory that these abnormalities could be related to the pathophysiology of the illness [37].

A review of the literature was conducted on the history of total cholesterol and serum triglyceride in relation to schizophrenia by consulting a number of articles, scientific journals, and pertinent textbooks on biochemistry and schizophrenia. It was found that there were not many published works on this subject; a few of these are listed below.

In an 8-week study, Garyfallos et al. (2003) investigated the relationship between changes in PANSS scores and changes in blood lipid levels in 50 individuals with schizophrenia spectrum disorders receiving olanzapine or risperidone treatment [38]. Increased blood TG levels were significantly correlated with improved symptoms (i.e., lower PANSS total scores) in the olanzapine group ($r = 0.71$, $p < 0.001$), but not in the risperidone group, according to the investigators' findings. Using 64 patients with schizophrenia treated with clozapine, olanzapine, or risperidone over a 12-month period, Atmaca et al. (2003) investigated this association [39]. Increased blood TG levels were shown to be significantly correlated with symptom improvement (i.e., reductions in PANSS total scores) in the groups receiving clozapine ($r = 0.60$, $p < 0.05$) and olanzapine ($r = 0.58$, $p < 0.05$), but not in the groups receiving quetiapine or risperidone.

Responders (defined as a 50% decrease in PANSS total scores at 3-week follow-up) were compared to nonresponders in a study by Huang and Chen (2005) [40]. They discovered that serum TG (+23.6 mg/dL, $p = 0.003$) and TC (+7.0 mg/dL, $p = 0.040$) significantly increased in responders to any treatment (FGA or SGA) compared to baseline. Procyshyn et al. (2007) conducted a Mann-Whitney U analysis on the rankings of changes in serum lipid concentrations for the responders versus the nonresponders treated with clozapine monotherapy or clozapine-risperidone polypharmacy, in

addition to a hierarchical multiple regression analysis [41]. The authors determined that respondents had significantly higher serum TG (+21% vs. -10%, U = 126.0, p = 0.004) and TC (+7% vs. -4%, U = 139.5, p = 0.008) concentrations compared to non-responders. Response was defined as a 20% reduction in PANSS total scores at the 8-week follow-up.

In a different investigation, Chen et al. (2014) examined The Positive and Negative Syndrome Scale was used to evaluate 372 chronic schizophrenia patients who had been taking antipsychotics for more than two years. A set of metabolic features was also examined. Body mass index (BMI) and the total score and all subscales had negative correlations, according to multiple regressions adjusted for sex; TG and the whole score and negative syndrome had negative correlations, but HDLC and negative syndrome had positive connections [42].

In a five-year follow-up research, 55 individuals with schizophrenia who were brought to psychiatric emergency rooms during an acute phase of the illness (T1) had their clinical and lipid data collected. At a stable phase (T2), the patients were reexamined five years later. Among the clinical evaluations were the Global Assessment of Functioning (GAF) and the Positive and Negative Syndrome Scale (PANSS total, positive, negative). Hospital staff members were chosen as healthy controls, and serum lipids (triglycerides and cholesterol) and membrane polyunsaturated fatty acids (PUFA, LCPUFA) were examined. They discovered that serum cholesterol did not differ significantly from serum triglyceride, which was shown to be considerably higher in patients with schizophrenia at both T1 and T2 ($p < 0.001$) [43].

B Ramakrishna et al. (2017) compared first-degree relatives of those who were untreated, those who were treated, and themselves. The whole study sample has 90 triglyceride levels; of them, 30 are treated patients with schizophrenia, 30 are untreated patients with schizophrenia, and 30 are randomly selected first-degree relatives of either group. In comparison to patients with schizophrenia and FDR who were not receiving treatment, they discovered that the mean triglycerides of treated patients with schizophrenia were considerably higher. Compared to first-degree relatives and drug-naive patients, patients receiving anti-psychotics had a noticeably increased risk of hypertriglyceridemia. The rate of hypertriglyceridemia did not significantly differ between individuals who were drug naive and those who were FDR [44].

However, 35 male subjects treated with clozapine or olanzapine-of whom 18 received orlistat and 17 received a placebo-did not show a significant association, according to Chukhin et al. (2016) [45]. The influence of orlistat and a methodological issue could have contributed to the lack of a significant link. For example, the authors' study did not utilize the entire dataset because they only included the male participants who benefited from orlistat, leaving out the 24 female individuals who did not. Additionally, Hermes et al. (2011) assessed the association between alterations in BMI and serum TC or TG levels and alterations in symptoms in patients receiving ziprasidone, olanzapine, quetiapine, risperidone, or perphenazine for schizophrenia [46]. However, they were unable to discover any meaningful correlations between alterations in serum lipid levels (TC & TG) and modifications in schizophrenia symptoms.

Cholesterol Metabolism

The liver is the primary site of cholesterol synthesis; the colon, the adrenal cortex, and the gonads are secondary sites. Almost every human cell has the ability to produce cholesterol. Significant amounts of energy from ATP, a source of carbon atoms, and reducing power are needed for the production of cholesterol. Acetyl-CoA offers a high-energy foundation. 18 moles of acetyl-CoA, 36 moles of ATP, and 16

moles of NADPH are needed to synthesize 1 mole of cholesterol. The cytoplasm is the site of all cholesterol production processes [47].

There are five stages in the production of cholesterol from acetyl-CoA:

①Condensation of three acetate units to form a six-carbon intermediate, Mevalonate

②Conversion of Mevalonate to Farnesyl pyrophosphate

③Condensation of Farnesyl pyrophosphate to Squalene

④Cyclization of Squalene to Lanosterol

⑤Final stage by a carrier protein [47]

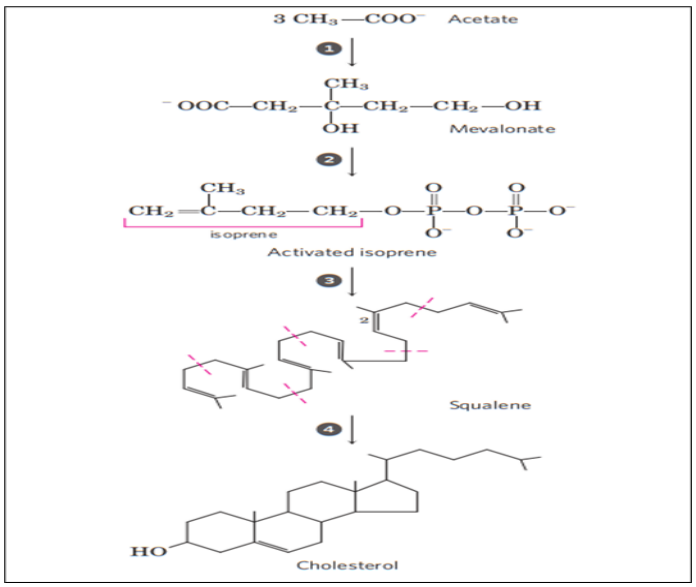

Fig. 1: Summary of Cholesterol Biosynthesis

Stage ❶ Synthesis of Mevalonate from Acetate:

- 3 molecules of acetyl-CoA are converted into mevalonate
- First 2-steps occur in cytoplasm & condensation reactions leading to the formation of 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA)
- These reactions, catalyzed by acetoacetyl-CoA thiolase/ACAT & HMG-CoA synthase
- Rate-limiting reaction is catalyzed by HMGR that leads to formation of Mevalonate [48]

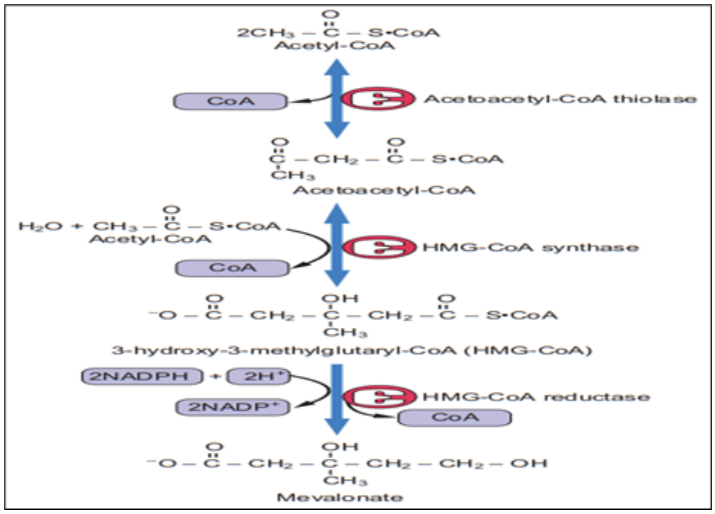

Fig. 2(Stage 1): Pathway of cholesterol synthesis: Synthesis of mevalonate

Stage ❷ Conversion of Mevalonate to Farnesyl pyrophosphate:

- Two reactions that require ATP are needed to phosphorylate three molecules of mevalonate.
- Isoprene units, isopentenyl pyrophosphate, and dimethylallyl pyrophosphate are produced by further decarboxylation and condense to generate geranyl pyrophosphate.
- Farnesyl pyrophosphate is produced by further condensation with isopentenyl pyrophosphate.
- Farnesyl pyrophosphate is the starting point for the ubiquinone and dolichol production [49].

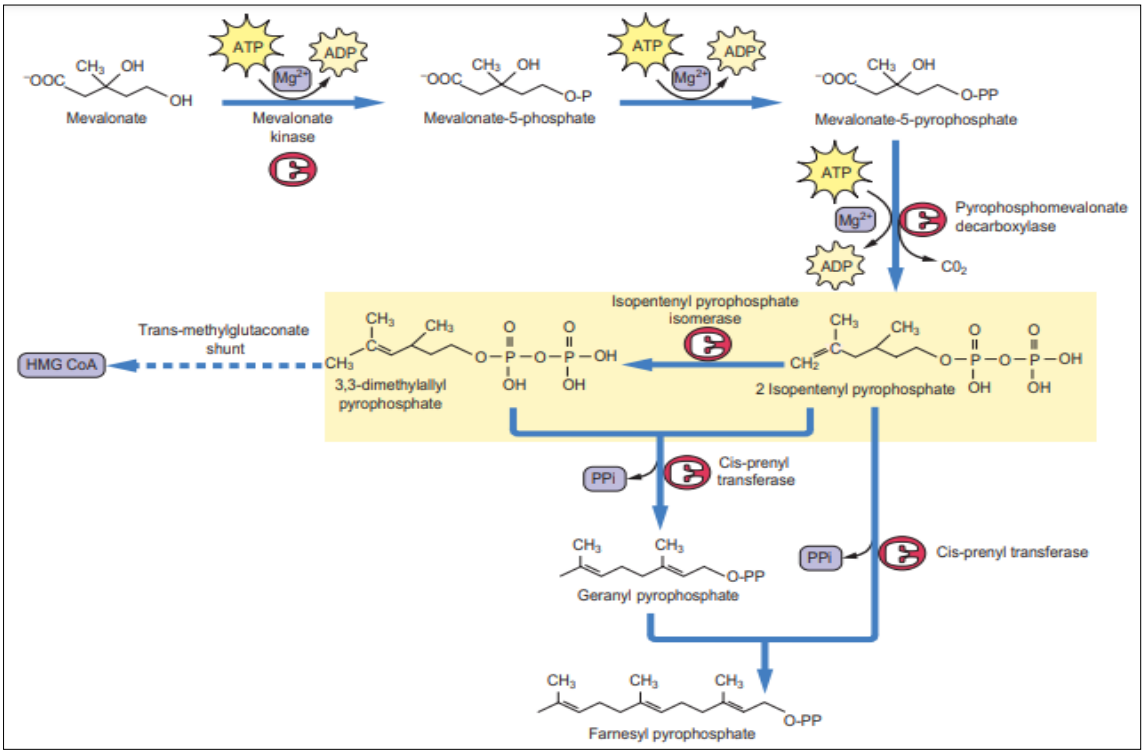

Fig. 3(Stage 2): Pathway of cholesterol synthesis: Mevalonate to farnesyl pyrophosphate

Stage ❸ Condensation of Farnesyl pyrophosphate to Squalene:

- Squalene synthase creates squalene, a hydrocarbon with six double bonds that allows it to eventually fold into a ring, by condensing two molecules of farnesyl pyrophosphate.
- At this point, many intermediates are created [50].

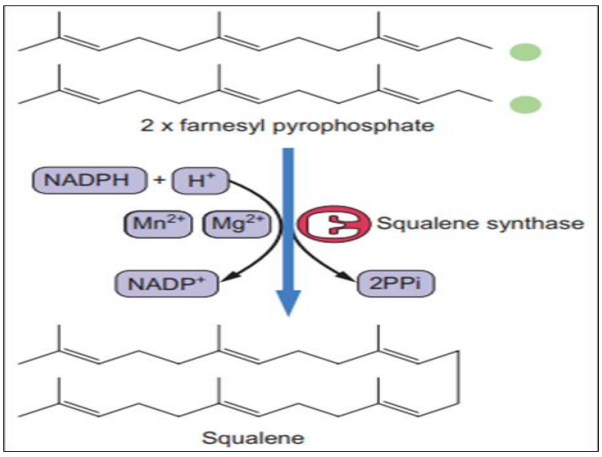

Fig. 4(Stage 3): Pathway of cholesterol synthesis: Farnesyl pyrophosphate to squalene

Stage ❹ Cyclization of Squalene to Lanosterol:

- Squalene mono-oxygenase transforms squalene into squalene 2,3-oxide prior to the ring closing.
- The oxygen molecule is inserted into the structure by this NADPH-dependent enzyme.
- Oxidosqualene cyclase catalyzes cyclization, which results in lanosterol [51].

Stage ❺ Final stage by a carrier protein:

- All following stages in the synthesis of cholesterol, including squalene and lanosterol, are hydrophobic.
- While bound to a squalene- and sterol-binding protein, these intermediates react to cause the pathway's final stages to occur in an aqueous medium.
- Three methyl groups are eliminated during the decarboxylation, isomerization, and reduction processes that convert lanosterol to cholesterol [47].

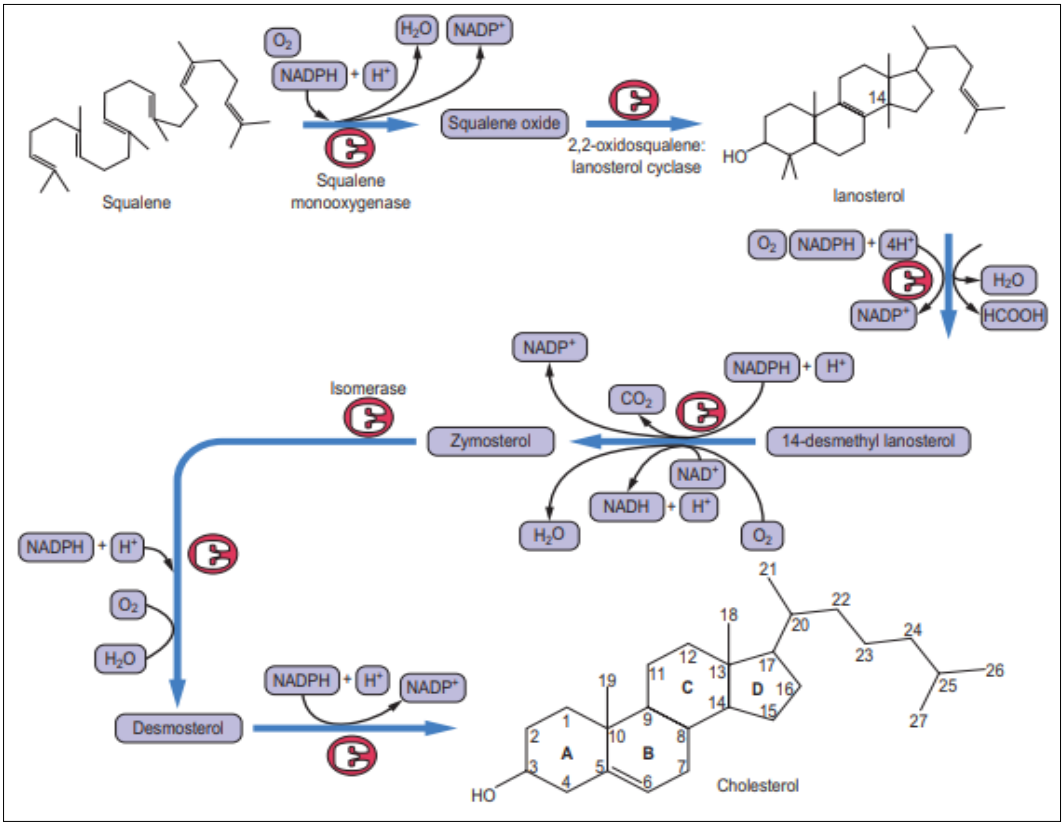

Fig. 5(Stage 4): Pathway of cholesterol synthesis: Squalene to cholesterol

The liver produces cholesterol, which is transported and eliminated from the body by the enzyme lecithin-cholesterol acyl-transferase (LCAT) and HDL. It catalyzes the transfer of fatty acids from the OH-group of cholesterol to the second position of phosphatidyl choline, or lecithin [52]. HMG-CoA reductase is the regulator of cholesterol production [53]. HMG-CoA reductase is connected to the endoplasmic reticulum and is governed by several metabolic processes:

a. Controlling Feedback
b. Regulating Hormones
c. Pharmacological Inhibition
d. Bile Acid And Fasting [54]

Triglyceride Metabolism

Triacylglycerols (TAG) are created by a mechanism that uses phosphatidic acid as an intermediary in both adipose tissue and the liver. But glycerol-3-phosphate comes from a distinct source in the two tissues [55]. In the liver, phosphatidic acid is derived from glycerol. But in adipose tissue, where

glycerol kinase is absent, glucose serves as the indirect source of glycerol, with the immediate precursor being the glycolytic metabolite dihydroxy-acetone phosphate [56].

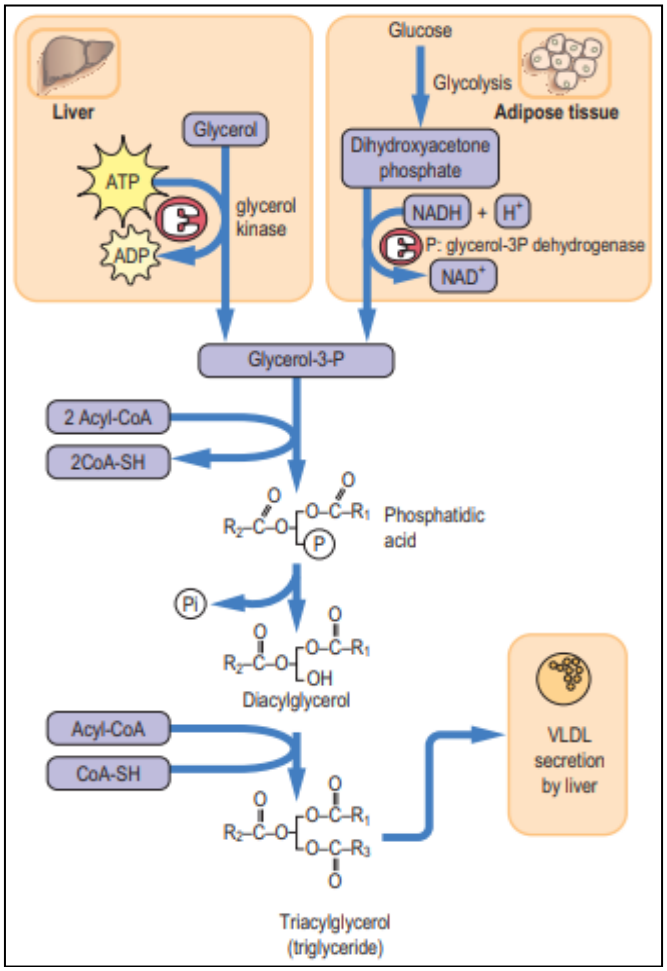

Fig. 6: Stages of Triacylglycerol synthesis.

Fatty acid acylation by glycerol-3-phosphate acyltransferase, for which the fatty acyl chain originates from a fatty acyl-CoA, is the initial step from glycerol-3-phosphate. After lysophosphatidic acid is produced, phosphatidic acid is produced by acylglycerol acyltransferase (AGPAT2) undergoing a second fatty acid acylation [57]. This stage is crucial for the synthesis of triacylglycerol in adipocytes; disruptions in AGPAT2 prevent adipose tissue from producing triacylglycerol, which results in congenital complete lipodystrophy. Phosphatidic acid phosphatase converts phosphatidic acid to diacylglycerol (DAG). This process forms DAG that is contained in the smooth endoplasmic reticulum, separating it from DAG that is created in the cytoplasm or membrane by the phospholipase C reaction of phosphatidylinositol [58]. Saturated and monounsaturated fatty acids are commonly found in DAG produced by the TAG synthesis pathway, while the cytoplasmic DAG typically consists of 1-stearoyl-2-arachidonoylglycerol, the normal fatty acid composition of phosphatidylinositol. Ultimately, diacylglycerol acyltransferase (DGAT) converts DAG into TAG [59]. The so-called monoacylglycerol process is outlined in these stages; however the Kennedy pathway, which provides an input at the phosphatidic acid phase, can also generate TAG [60].

Function of Cholesterol and Triglyceride in Central Nervous System

The human brain is also mostly composed of cholesterol; an adult brain has approximately 35 grams of cholesterol. It makes up around 20% of the total cholesterol in the body [61]. The lipids found in the brain are composed of cholesterol, sphingolipids, and glycerophospholipids in about equal amounts [62]. For healthy brain growth, cholesterol is necessary and strictly regulated between the main brain cells, known as neurons and glia, or astrocytes, microglia, and oligodendrocytes. Axonal guidance, synapse and dendritic development, and cholesterol are all dependent on one other [63]. Reduced synaptic plasticity, failure neurotransmission, and degradation of the dendritic spine and synapses are all caused by low cholesterol [64]. A vital component of steroid hormones, cell membranes, and the hedgehog protein's activity is cholesterol [65]. Diseases of the central nervous system (CNS), including Huntington's disease, Smith-Lemli-Opitz syndrome, Niemann-Pick type C (NPC) disease, and Alzheimer's disease, are caused by abnormalities in the metabolism of cholesterol. Numerous metabolic pathways, including (1) cholesterol manufacturing, (2) lipid transport and lipoprotein assembly, (3) receptors that mediate the cellular intake of lipids, and (4) signaling molecules, are impacted by these metabolic abnormalities [66].

Brain cholesterol is mostly produced by de novo synthesis, in contrast to cholesterol found in other peripheral organs. In vertebrates, the blood brain barrier (BBB) remains intact, preventing lipoproteins from entering the bloodstream [63]. The need for cholesterol is met in cells outside of the brain by both de novo synthesis and cell uptake of lipoprotein cholesterol. As early as 1834, Couerbe referred to cholesterol as "un element principal" (a crucial component of the central nervous system), highlighting the significance of this distinct pool of cholesterol in the brain.

As though In addition, triglycerides are essential for the CNS because they function as an energy source, maintain the integrity of cell membranes, and aid in the creation of the myelin sheath, which is necessary for the effective transmission of nerve signals. In addition, they take part in neuroprotection, signal transduction, and the transport and storage of fat-soluble vitamins, all of which are crucial for a number of CNS cellular functions. Triglycerides also supply important fatty acids, which are necessary for neurogenesis and neuronal repair, preserving the general health and functionality of the brain [67].

CONCLUSION

Triglycerides, cholesterol, and schizophrenia have a complicated and multidimensional interaction. Recent and historical research shows that anomalies in lipid metabolism are frequently seen in people with schizophrenia. These abnormalities may be impacted by pharmaceutical side effects, disease pathology, and genetic factors. Comprehending these correlations is essential for formulating all-encompassing therapeutic approaches that tackle the mental and metabolic well-being of individuals suffering from schizophrenia.

Declaration by Author

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