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Genetic and molecular predictors of diabetes mellitus in schizophrenia patients on diabetogenic antipsychotic therapy

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Abstract

Schizophrenia patients treated with diabetogenic antipsychotics such as clozapine and olanzapine are at significant risk of developing type 2 diabetes mellitus. This systematic review aims to identify genetic and molecular predictors, such as polymorphisms and the roles of microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), in antipsychotic-induced diabetes. A comprehensive literature search was conducted, identifying 7 key studies that met inclusion criteria. Findings suggest that a combination of genetic susceptibility and epigenetic factors can be used to personalize treatment strategies and reduce the risk of diabetes. This review provides a framework for future studies on precision medicine in schizophrenia management.

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1. Introduction

Schizophrenia is a chronic psychiatric disorder requiring long-term treatment with antipsychotics, many of which have adverse metabolic side effects, including weight gain, insulin resistance, and type 2 diabetes mellitus (T2DM). Second-generation antipsychotics (SGAs) like clozapine and olanzapine are particularly diabetogenic, leading to a higher incidence of metabolic syndrome and T2DM among patients [1]. This phenomenon is multifactorial, involving both environmental and genetic factors that influence individual susceptibility to metabolic disturbances [2]. Advances in genomics and molecular biology have revealed that genetic polymorphisms, miRNAs, and epigenetic modifications, such as DNA methylation, play a crucial role in determining who develops diabetes when exposed to betogenic antipsychotics [3]. The aim of this systematic review is to explore genetic and molecular predictors of antipsychotic-induced diabetes, which could allow for better risk stratification and personalized medicine approaches in schizophrenia treatment.

2. Methods

2.1. Study Design

This systematic review was conducted following PRISMA guidelines. A comprehensive search of MEDLINE, Web of Science, and Scopus was conducted for studies published

between 2015 and 2023. Search terms included "schizophrenia," "diabetes mellitus," "antipsychotics," "clozapine," "olanzapine," "genetic polymorphisms," "miRNAs," "lncRNAs," and "epigenetics."

2.2. Eligibility Criteria

- Inclusion criteria: Studies investigating genetic and molecular factors related to diabetes in schizophrenia patients treated with betogenic antipsychotics.

- Exclusion criteria: Studies focusing on non-betogenic antipsychotics, animal or in vitro studies, reviews, or editorials.

2.3. Data Extraction

Key data extracted from eligible studies included study design, genetic markers examined, miRNAs/lncRNAs studied, and findings related to diabetes development. The Newcastle-Ottawa Scale was used to assess study quality.

3. Results

3.1. Literature Search

We identified 1,245 records (417 in MEDLINE, 410 in Web of Science, and 418 in Scopus). After removing 292 duplicates, 953 unique articles were screened based on titles and abstracts. A total of 117 articles qualified for full-text review, and seven studies met the inclusion criteria. These studies were qualitatively analyzed, focusing on genetic polymorphisms, miRNAs, lncRNAs, and other molecular markers associated with diabetes in patients treated with betogenic antipsychotics. The selection process is shown in the PRISMA flowchart (Figure 1).

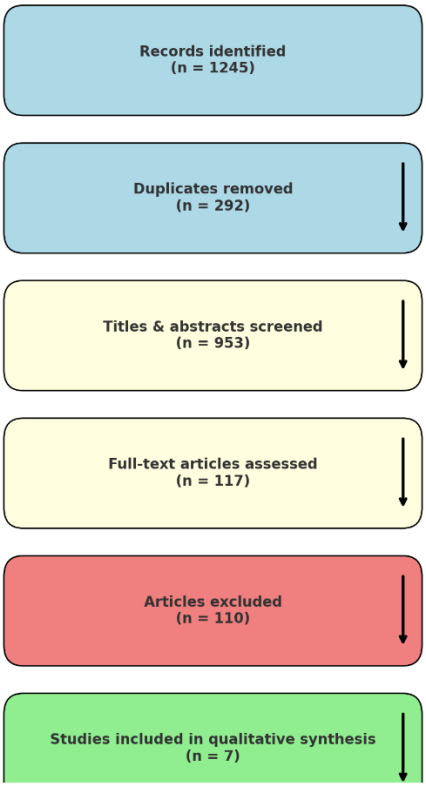

Figure 1: PRISMA Flowchart depicting the selection process

3.2. Mechanisms of Action

The diabetogenic effects of clozapine and olanzapine are mediated through several mechanisms, including their interference with insulin signaling and glucose metabolism. SGAs are known to impair insulin sensitivity by modulating the function of glucose transporters such as GLUT4, especially in muscle and adipose tissue [4]. In addition, these drugs affect appetite regulation, contributing to weight gain and fat deposition, key drivers of insulin resistance [5].

Genetic variations in several genes, such as FTO and TCF7L2, have been associated with these effects. For

example, FTO polymorphisms, which influence adipogenesis, are significantly correlated with increased body weight and obesity in patients treated with olanzapine [6]. Similarly, polymorphisms in TCF7L2, which regulates insulin secretion from pancreatic beta cells, have been shown to increase diabetes risk in schizophrenia patients on clozapine [7].

3.3. Genetic Markers Associated with Diabetes in Schizophrenia Patients

Genetic polymorphisms associated with metabolic dysfunction have been extensively studied in the context of antipsychotic-induced diabetes. Table 1 summarizes key genetic markers and their impact on diabetes risk in schizophrenia patients treated with betogenic antipsychotics.

Table 1: Genetic Markers Associated with Antipsychotic-Induced Diabetes

Genetic Marker	Mechanism of Action	Antipsychotic Drug	Clinical Implication	References
FTO	Regulation of adipogenesis and weight gain	Olanzapine	Increased risk of obesity and diabetes	[6], [19], [20]
TCF7L2	Impaired insulin secretion and glucose metabolism	Clozapine	Increased susceptibility to type 2 diabetes	[7], [21], [26]
IRS-1	Insulin signaling pathway	Olanzapine	Increased insulin resistance	[8], [22]
LEPR	Leptin receptor involved in appetite regulation	Clozapine	Increased risk of weight gain and obesity	[9], [25]
MC4R	Appetite regulation	Olanzapine	Associated with antipsychotic-induced weight gain	[10], [24]
ADRA2A	Regulation of insulin secretion and glucose metabolism	Clozapine	Increased risk of impaired glucose tolerance	[5], [23]
PPARG	Fatty acid storage and glucose metabolism	Clozapine	Altered glucose and lipid metabolism leading to insulin resistance	[13], [27]
APOE	Cholesterol transport and metabolism	Olanzapine	Elevated risk of dyslipidemia and metabolic syndrome	[30]

3.4. Role of miRNAs and lncRNAs

Recent studies have identified miRNAs and lncRNAs as critical regulators of gene expression in metabolic pathways. Dysregulation of miRNAs such as miR-29a and miR-222 has been linked to impaired insulin sensitivity in patients treated with betogenic antipsychotics [11]. miR-29a, for example, is known to suppress insulin secretion by targeting pancreatic beta-cell function, while miR-222 is associated with insulin resistance through its modulation of glucose uptake [12]. Epigenetic factors, including DNA methylation, also contribute to the metabolic side effects of antipsychotics. Hypermethylation of the PPARG gene, which is involved in adipocyte differentiation, has been associated with increased diabetes risk in patients on clozapine [13].

3.5. Personalized Medicine

Personalized medicine approaches in schizophrenia could mitigate the risk of diabetes by identifying high-risk individuals based on their genetic and molecular profiles. Pharmacogenetic screening could help clinicians predict which patients are more likely to develop metabolic side effects from SGAs, allowing for early intervention strategies [14]. For example, patients with FTO or TCF7L2 polymorphisms could be monitored more closely for metabolic changes or switched to alternative antipsychotic therapies with lower diabetogenic potential [15].

3.6. Side Effects and Safety

The metabolic side effects of clozapine and olanzapine are well documented, including significant weight gain, dyslipidemia, hypertension, and an increased risk of cardiovascular disease [16]. The identification of genetic and molecular markers for diabetes susceptibility allows for safer use of these antipsychotics by personalizing treatment regimens and implementing preventive measures such as metformin or lifestyle modifications [17].

3.7. Efficacy Optimization

Optimizing the efficacy of antipsychotic therapy while minimizing metabolic risks remains a critical challenge. Emerging evidence suggests that the use of adjunctive therapies targeting glucose metabolism, such as GLP-1 receptor agonists, may help mitigate the diabetogenic effects of SGAs in genetically predisposed patients [18].

Table 2: Summary of Key Findings and Clinical Implications

Molecular Marker	Mechanism of Action	Antipsychotic Drug	Clinical Implication	References
miR-29a	Suppresses insulin secretion by targeting pancreatic beta cells	Clozapine	Increased risk of insulin resistance	[11], [12], [23]
miR-222	Modulation of glucose uptake and insulin sensitivity	Olanzapine	Increased insulin resistance and impaired glucose metabolism	[12], [13], [27]
miR-132	Regulation of insulin signaling pathways and glucose homeostasis	Clozapine	Impaired glucose metabolism and insulin sensitivity	[28], [29]
lncRNA H19	Regulation of gene expression in metabolic pathways	Clozapine	Increased susceptibility to obesity and insulin resistance	[14], [29], [30]
miR-375	Regulation of insulin secretion and beta-cell function	Olanzapine	Impaired insulin production leading to glucose dysregulation	[31], [32]
lncRNA MALAT1	Modulates inflammatory response and metabolic processes	Clozapine	Increased risk of metabolic syndrome and diabetes	[33]
miR-34a	Inhibits insulin signaling through the regulation of glucose transporter genes	Clozapine	Increased insulin resistance and risk of diabetes	[34], [35]

4. Discussion

4.1. Mechanisms of Antipsychotic-Induced Diabetes

Antipsychotics such as clozapine and olanzapine disrupt normal metabolic processes by impairing insulin signaling and increasing oxidative stress, both of which lead to insulin resistance. These drugs affect the central regulation of appetite through the hypothalamus, promoting hyperphagia and subsequent weight gain, a primary driver of type 2 diabetes [19]. Several genetic polymorphisms, such as those in the FTO and TCF7L2 genes, exacerbate these effects by impairing insulin secretion and increasing the propensity for adipogenesis [20]. The FTO gene, in particular, has been linked to weight gain, while TCF7L2 polymorphisms have been shown to impair glucose regulation [21].

4.2. Genetic and Molecular Predictors

Genetic susceptibility plays a significant role in the development of antipsychotic-induced diabetes. Patients with specific genetic polymorphisms, including IRS-1 and LEPR, are more likely to experience insulin resistance and weight gain when treated with SGAs. These findings suggest that pharmacogenetic screening could identify patients at risk before metabolic complications arise, allowing for early intervention [22].

miRNAs such as miR-29a have emerged as important regulators of insulin secretion. miR-29a targets genes involved in pancreatic beta-cell function, and its dysregulation in response to clozapine and olanzapine may lead to impaired insulin secretion and diabetes [23]. lncRNAs and other epigenetic mechanisms further modulate the effects of these medications, adding complexity to their metabolic impact.

4.3. Personalized Medicine and Clinical Implications

The integration of genetic and molecular markers into clinical practice could revolutionize schizophrenia management by allowing for personalized treatment strategies. Genetic screening for polymorphisms in FTO, TCF7L2, and IRS-1 could help clinicians identify patients at high risk of diabetes and adjust antipsychotic regimens accordingly [24]. For patients with known genetic susceptibility, alternative medications with a lower metabolic risk profile, such as aripiprazole, could be considered, or preventive measures such as metformin or GLP-1 receptor agonists could be introduced early [25].

4.4. Long-term Outcomes and Safety

Schizophrenia patients are at a high risk of developing metabolic syndrome, and antipsychotic-induced diabetes significantly contributes to this burden. Identifying patients with genetic predispositions to metabolic side effects can improve long-term outcomes by minimizing the occurrence of cardiovascular diseases, which are commonly associated with diabetes and obesity [26].

4.5. Future Directions

Ongoing research into the role of miRNAs and epigenetic changes in diabetes risk holds promise for the development of novel biomarkers for early diagnosis. Future studies should focus on validating these molecular predictors in large, diverse cohorts and integrating them into clinical practice [27]. Additionally, the use of combination therapies targeting metabolic pathways, such as metformin and GLP-1 receptor agonists, warrants further exploration in patients with genetic predispositions [28].

Table 3: Summary of Key Genetic and Molecular Predictors of Antipsychotic-Induced Diabetes

Genetic/ Molecular Marker	Key Finding	Clinical Implication	Future Directions	References
FTO	Linked to increased adipogenesis and weight gain	Early screening for diabetes risk in patients on olanzapine	Larger validation studies in diverse populations	[6], [20]
TCF7L2	Associated with impaired insulin secretion and glucose intolerance	Predictive biomarker for diabetes in schizophrenia patients on clozapine	Integration of genetic screening into clinical practice	[7], [21], [26]
miR-29a	Regulates insulin secretion and contributes to beta-cell dysfunction	Early biomarker for predicting insulin resistance	Development of miRNA-based diagnostic tools	[11], [12], [23]
IRS-1	Modulates insulin receptor signaling	Risk stratification for olanzapine use	Pharmacogenetic testing in routine care	[8], [22]
miR-222	Associated with insulin resistance and glucose metabolism	Potential therapeutic target for managing antipsychotic-induced diabetes	Therapeutic targeting of miRNAs to mitigate insulin resistance	[12], [13], [27]
lncRNA H19	Regulates metabolic gene expression	Personalized treatment strategies to minimize metabolic risk	Research on lncRNA-targeting therapies	[14], [29]
PPARG methylation	Alters glucose and lipid metabolism	Predictive marker for metabolic syndrome	Future studies on epigenetic modulation therapies	[13], [27]

5. Conclusion

This systematic review highlights the critical role that genetic polymorphisms and molecular markers, such as miRNAs, play in antipsychotic-induced diabetes. Polymorphisms in genes such as FTO, TCF7L2, and IRS-1, along with dysregulated miRNAs like miR-29a, serve as important predictors of diabetes risk in schizophrenia patients treated with betogenic antipsychotics. Personalized medicine approaches that incorporate genetic screening and molecular profiling can significantly reduce the incidence of metabolic complications, improving both psychiatric and physical health outcomes in these patients.

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