REVIEW ARTICLE

A Current Review of Literature on Cardiovascular Diseases in Schizophrenic Patients.

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Abstract

Globally, cardiovascular disease (CVD) persists as a major contributor to death. CVD has been strongly associated to psychological factors, and the link appears to be bidirectional. This is because certain psychological conditions may pre-exist and precede CV diseases and lead to worse clinical outcomes. Generally, mortality from CVD prevails to be higher in individuals with mental health problems, particularly schizophrenia. In order to understand the impact of CVDs among schizophrenic individuals, targeted efforts at the clinic, community, and policy levels are highly required. Knowledge gaps have been previously identified in regard to the prevalence of CVDs among schizophrenic patients. Keeping in mind, the complexity of both the diseases and their coexistence, this paper aims to review the current state of literature regarding cardiovascular diseases among schizophrenic patients, and highlight the importance of patient-centred care, risk factors, management strategies and interventions.

Introduction

Cardiovascular disease (CVD) persists as a major contributor to death globally, with an estimated 17.9 million deaths and 32% mortality rate in both developed and developing nations in 2019. The prevalence of CVDs is still increasing in developing countries with a gradual decline in developed countries. Unfortunately, CVD-related mortality taking place in the low-and middle-income countries (LMICs) owes up to more than 80%. It is more likely that the CVD burden would escalate further in the LMICs due to swift urbanization and industrialization, increased unhealthy lifestyle practices, and increasing growth of the aged population. As a result of the age-specific increment in CVD, a substantial burden on the global health system is imposed, in terms of disability, morbidity, mortality, reduced functioning, and healthcare expenses [1,2].

In recent years, CVD has been strongly associated to psychological factors, and the link has been reported to be bidirectional. This is because certain psychological conditions may pre-exist and precede CV diseases to lead towards worse clinical outcomes [3]. Generally, mortality from CVD prevails to be higher in individuals with mental health problems, particularly schizophrenia [4]. As compared to the general population, schizophrenic people tend to demonstrate shorter life expectancy, diminished cardiorespiratory and muscular fitness, and increased risk of morbidity including hypertension, obesity, hyperlipidaemia, metabolic syndrome, and CVDs [5]. Schizophrenic or bipolar disorder patients are diagnosed under severe mental illnesses (SMI), and tend to have a 15–20 years' lesser life span than healthy individuals. Physical ailments cause about 70% mortality in these patients despite an increased number of unnatural deaths, with CVD contributing to an overall reduction in life expectancy of 17.4% in men and 22.0% in women [6].

According to the "Global Burden of Diseases (GBD)" study, it was found that 1.1% of total disability-adjusted life years (DALYs) and 2.8% of years lived with disability (YLDs) [7] were significantly linked to schizophrenia. Worldwide, the 8th leading cause of DALYs between 15–44 years' age was recorded to be schizophrenia by the "World Health Report 2001" [8]. In addition, recent findings from the "Global Burden of Disease Study 2017" indicated that in comparison to 1990, the incidence and DALYs of schizophrenia escalated by 36.7 and 62.5% respectively in 2017, thus, contributing to the extreme burden on the global healthcare systems [9]. The physical comorbidities further deteriorate the patients' disabilities and rises the burden of disease. Healthcare providers usually provide greater attention to the behavioural and psychological issues, neglecting the physical disorders such as the existence of CVD in schizophrenic patients, which in turn leads to inadequate care and treatment [10].

Furthermore, the economic pressure from mental health diseases, mainly, schizophrenia is evident, and more likely to escalate two times higher by 2030. Therefore, it is essential to reduce the escalating burden of mental illnesses such as schizophrenia and consider it as an urgent health priority. Enhanced treatment and preventive measures are the prime factors that could help in mitigating the burden of schizophrenia [5].

In order to understand the impact of CVDs among schizophrenic individuals, targeted efforts at the clinic, community, and policy levels are highly required. Knowledge gaps have been previously identified in regards to the prevalence of CVDs among schizophrenic patients. Sparse research in interventions for prevention and reduction in the impact of CVDs among people with schizophrenia have also been noted [11].

Keeping in mind, the complexity of both the diseases and their coexistence, this paper aims to review the current state of literature regarding cardiovascular diseases among schizophrenic patients, and highlight the importance of patient-centred care, risk factors, management strategies and interventions.

Malaysian Context

Over a decade, CVD has been a prevailing contributor to morbidity and mortality in Malaysia. Malaysia is a multi-ethnic, middle-income country with a growing population of aging people. Hence, it is facing a high prevalence of CVD risk factors including hypertension, obesity, hypercholesterolaemia, diabetes, and smoking. The "Health Facts 2019" published under the Ministry of Health Malaysia [12] reported that mortality due to CVDs ranked first among the ten principal causes of death in government hospitals (21.65%) and second in private hospitals (23.79%). Due to the growing rise in aging population and health burden, the Malaysian government is expected to experience a higher healthcare expenditure and provide more inclusive healthcare services for its population [1]. The incidence of schizophrenia in Malaysia was reported to be 43.0/100,000 population, and 70% of them were unemployed. Long duration of untreated psychosis on an average 37.6 months was documented. This was linked to female gender, low educational background, and comorbidity. Treatment delay was not associated with traditional healer although it was more frequently practiced. On the contrary, the main reason for treatment delay was ignorance of illness by patient and family member. Comorbid substance-use was prevalent among the schizophrenic patients [13]. Those receiving antipsychotics have higher risk of CVD as well as increased incidence of metabolic syndrome. Hence, immediate interventions are required to battle these health-related issues in schizophrenia patients [14].

Risk Factors

A meta-analysis on cardio-metabolic abnormalities in schizophrenic patients summarized the CVD risk factors into 3 main groups: (1) Behavioural Factors: Smoking, substance abuse, unhealthy diet or eating patterns, and sedentarism; (2) Impact of Antipsychotics and other medications: Adverse side-effects resulting from medications and improper clinical decision making, inadequate health care services or quality, fragmentation of physical and mental health care; (3) Socio-economic Status: Poverty or low income, and poor education [15]. Some of the major risk factors in schizophrenia patients with CVDs have been listed out (Table 1).

Several CVD risk factors predominated in schizophrenic patients. Some of the risk factors identified in this review were use of antipsychotics, high blood pressure in men, female gender, age more than 30 years, presence of high fasting blood sugar and triglycerides. Metabolic syndrome and obesity were found to be the major risk factors [11]. CVD related risk factors such as unhealthy diet, lack of exercise, and smoking, were common in these patients, and lifestyle interventions have been associated to small-scale effects or improvements [6].

The causes of mortality in schizophrenic patients with CVDs are multifactorial, but it has been widely reported that antipsychotic medications can develop cardiac side-effects beyond the traditional coronary risk factors. Schizophrenia itself can lead to a higher risk of cardiovascular death through cardiac autonomic impairment and consequential to metabolic syndrome [4].

Furthermore, psychotropic drugs for the treatment of mental health illnesses can present CV adverse effects. While cardiac medications can also exhibit psychological impacts. Therefore, the drug-drug interactions of concomitant medications, particularly in the vulnerable population such as elderly patients must be recognized by clinicians [3].

In comparison to the healthy population, schizophrenic patients die on average 25 years earlier, and this gap tends to be rising with time. Premature CV deaths accounts for the excessive mortality rather than suicide. Orexigenic psychotropic agents causes increase in weight gain thus promoting dyslipidaemia. Traditional cardiac risk factors are less likely to receive cardiac revascularisation than those without a mental illness, and they often remain undertreated among these patients. Clozapine, which is an atypical antipsychotic medication, is often

associated with an increased risk of cardiomyopathy and myocarditis; although it is effective for treating refractory schizophrenia [16].

Pathophysiology

Due to the co-existence of schizophrenia and CVD, the antipsychotic polytherapy utilization with cardiac drugs is a commonly practiced event. It has been previously estimated that people with mental disorders have a 53% increased risk of receiving a CVD diagnosis and an 85% increased risk of death due to CVD compared to the healthy population. Hence to avoid this high risk of adverse drug-related interactions and its resulting side-effects, greater caution should be taken while prescribing CV medications and antipsychotics concomitantly. Clinical decisions should be derived on the basis of risk-benefit ratio, patient safety and alternative, safer drug combinations [17].

Due to the high clinical efficacy of second-generation antipsychotics (SGAs), they are considered as a key treatment for schizophrenia patients. However, it is also well noted that SGA treatment is associated with severe metabolic alterations and increased body mass, which in turn increases the risk of type 2 diabetes (T2D) and CVD, thus accelerating mortality at a higher pace [18].

A previous study found that the newly diagnosed schizophrenic patients receiving atypical antipsychotics had an increased fat mass relative to the BMI. Furthermore, body composition accounted for major risk abnormalities in the glucose metabolism, and greater contributions in adipogenicity were derived from atypical antipsychotics [19]. Some research indicates that metabolic changes in insulin-sensitive tissues can be triggered even before the onset of antipsychotic-induced weight gain (AIWG) due to the AIWS's underlying mechanism of action [18].

The probability that severe mental illnesses, mainly schizophrenia, is independently related with MetS and CVD has been previously evaluated. Results demonstrated that first-episode, drug-naive schizophrenic patients have increased levels of plasma insulin, impaired glucose tolerance, elevated levels of fasting glucose, and noticeable changes in lipid metabolism. There is also notable evidence that directly links SGA medication to high T2D risk in schizophrenia. The two major factors to T2D development, that is glucose dysregulation and increasing weight were significantly associated to antipsychotics, mainly SGAs. Evidence points to a direct impact of SGAs on glucose metabolism while the association between AIWG and glucose dysregulation has been well-noted. It has also been identified that diabetogenic SGAs, particularly, olanzapine and clozapine, and the FGA chlorpromazine, impairs insulin signalling in insulin-sensitive tissues, such as liver and skeletal muscle, interfering with glucose transport, glycogen synthesis and gluconeogenesis and, consequently, inducing insulin resistance [18].

The comorbid status of developing schizophrenia and cardiovascular anomalies conjointly gives rise to several health complexities and disrupts the normal human physiology. The development of brain, cardiac and vascular structures, as well as the enzymes activity involved in the dopamine synaptic turnover are influenced by genetic factors. Infections or systemic diseases trigger the autoimmunity and affects both brain and heart, either directly through autoantibodies and/or indirectly through microvascular injury. The comorbidity between schizophrenia and cardiac diseases occurs secondarily due to metabolic dysfunctions induced by psychotropic drugs or psychosis itself. Antipsychotics differ in their propensity to facilitate the development of the metabolic syndrome due to their diverse pharmacodynamic profiles. There is possibility of negative impact on the metabolism or cardiac function due to acute psychotic symptoms or sedentary lifestyle related distress [20].

Interventions

Traditional interventions related to pharmacology and psychotherapy have been widely adopted for

schizophrenia treatment. Nevertheless, a growing body of scientific evidence validated that physical activity and exercises are highly utilized in preventing and treating schizophrenia [5].

Lifestyle interventions, such as cessation of smoking, tend to be effective in reducing CVD among schizophrenia patients. Statin trials for cardiovascular prevention have not been administered in this population, although, the general population who are at high risk have shown similar reductions in cholesterol levels [21]. Omega-3 fatty acid rich foods, fish oils and supplements have been reported to be effective against the progression of CVD, mainly atherosclerosis, thus considered as a preventive diet for individuals with schizophrenia [10]. Other interventions involving nutritional advice, exercise, and cognitive-behavioral therapy have reduced weight moderately [22]. Clinicians should strongly strategize weight gain prevention while prescribing antipsychotic drugs as the current interventions have been only effective in producing moderate weight loss in the overweight and obese individuals [22].

On the other hand, pharmacological interventions to mitigate CVD risk factors have also been proven to be effective, and the use of antipsychotics lead to reduced mortality. However, it also contributed to a higher risk of dyslipidaemia, increased weight, and type 2 diabetes [6]. Although adherence to antipsychotic drugs is favourable for all-cause mortality, its relationship with the incidence of CVD remained unclear. Greater adherence to antipsychotic drugs mitigated the risk of CVD incidence despite the antipsychotic-induced CVD risk among newly diagnosed schizophrenic patients. Thus, enhancement in CVD outcomes among schizophrenic patients may be achieved through consistent efforts and increasing antipsychotics adherence [23].

In order to promote greater adherence and lifestyle modification in this population, such interventions must be adequately designed and resourced so that they can be implemented effectively [22]. At the same time, primary and secondary healthcare settings must encourage physicians and mental health professionals to provide concerted and coordinated efforts in reducing CVDs and diabetes [21]. Tertiary healthcare services need to test and develop feasible and robust interventions targeting CVDs and its various risk factors in schizophrenic population [11].

Previously, researches have investigated the effect of medication therapy, pharmacogenomics, moderate cognitive dysfunction and cognitive reserve (CR) on the cardiovascular function and cognition in schizophrenic patients. Understanding the link between cardiovascular health and neurocognition may lead to potentially improved health outcomes in patients with schizophrenia. In fact, improving CR may produce protection against cognitive impairment in patients as it gets deteriorated by selective cardiovascular risk alleles in schizophrenia [24]. Furthermore, it is important to determine if the CV risk related genetic variants and medication usage play a key role in improving the quality of life (QoL) among schizophrenic patients receiving cognitive remediation therapy. Thus, future studies must emphasize on cognitive remediation therapy, CR, and cardiovascular pharmacogenomic variants in this population [24].

Recommendations

The impact of antipsychotic drug adherence on CVD-related risk and progression in the schizophrenia patients is still not well-established [23]. Therefore, future studies should target the specific population-based patient cohorts with co-existing condition of CVD and schizophrenia, or patients suffering from severe mental illnesses susceptible to higher risk of presenting adverse cardiovascular outcomes, for their better management. Prospectively, a long-term follow-up of such patients would provide an insight to their QoL, and ensure their mental and physical wellbeing through effective and preventive interventions. Targeted measures should be administered in tertiary healthcare setting and at community level to promote positive mental

health programs, early assessment of psychotic illnesses, behavioural interventions for those at-risk of developing CVD to control the modifiable risk factors, and finally develop updated health plans or guidelines for better management.

It is recommended to opt an interdisciplinary approach between cardiology and neurosciences that would not just be limited to research but also administered in the clinical practice. The survival rate is critically affected by the cardiac comorbidity in patients with schizophrenia. Hence, in order to better identify and differentiate the functional psychoses from organic ones, understanding the nature of cardiac comorbidity would be highly useful [20]. Thus, it should be recommended to clinicians and mental health practitioners to effectively monitor patients with mental illnesses for CVD-related outcomes, as well as come forward with risk-minimizing-and-modifying strategies for specific psychiatric disorders.

It is also incumbent upon clinicians to implement preventive measures and encourage healthy lifestyle interventions such as healthy diet, physical exercises, and smoking cessation [25]. Current literature states that clinicians from non-mental health background often demonstrate a negative attitude towards patients with severe psychological disorders. Education could play a pivotal role in decreasing the negative attitudes in clinicians towards these patient groups, and lead to improved diagnosis as well as treatment rates [6]. In such scenario, it can be well conceived that better awareness and education is needed among clinicians working outside the mental health areas, to promote increased level of understanding, empathy, and care towards the schizophrenia patients suffering from CVDs.

Conclusion

Clinically, suspicion for CVD-related outcomes, and risk-modification methods, in severely and mentally ill people may help in identifying the variation in prevalence across particular psychiatric disorders [26]. Clinicians should be able to decide effective therapeutic agents which would successfully address the mental health issue but not aggravate the cardiovascular condition.

Annual treatment should be offered accordingly along with coordinated care between primary and tertiary healthcare providers and general practitioners for monitoring the physical health of individuals with schizophrenia or psychosis [16]. Furthermore, early patient referrals to cardiologists and mental health practitioners should be carried out for faster decision making process and prescribing effective but safer and compatible therapeutic agents.

Overall, cardiovascular risk management in schizophrenic people must follow a distinct and multidimensional approach to implement the most effective treatment strategies within the acceptable parameters of cardiovascular risk assessment and provide simultaneously practical measures for the clinical cardiologists for better health management.

Supplementary Information
None

Table 1. Risk Factors for Patients with ardiovascular Diseases and Schizophrenia

Study/Author	Cardiovascular Factors	Psychological Factors	Findings/Outcome
Davidson, 2002	Comorbid conditions such as diabetes, hypertension and dyslipidaemia	Stress, hostility, and high demand at work coupled with low control over work environment	"Leads to the occurrence of increased risk of cardiovascular anomalies, health complications and impaired quality of life".
Padmavati et al., 2021	Metabolic syndrome and obesity	Antipsychotic medications	"Prevalence of overweight individuals was 22.7% and obesity at 31.8%. It was found that at times the difference of prevalence of metabolic syndrome is up to 30 times greater in persons with mental illness. On the other hand, olanzapine was found to have the greatest weight gain, followed by risperidone and haloperidol (5.1, 4.1, and 2.8 kg). The prevalence of metabolic syndrome increased from 23 to 38.5% and after 6 months increased to 46.2% in case of clozapine".
Azad et al., 2015	Tobacco smoking, unhealthy diet, and sedentary behaviour	Antipsychotics	"Association between sedentary behaviour and cardio-metabolic comorbidity in schizophrenia has been well documented. While the prevalence of tobacco smoking was 5.3 times higher in schizophrenia patients than the general population. Several case reports found sudden cardiac death in schizophrenia patients due to antipsychotics. Prolonged QTc interval with the risk of progression to Torsades de Pointes is a fatal side effect of antipsychotics which often leads to SCD in these individuals".
Nielsen et al., 2021	Smoking, unhealthy diet and lack of physical activity	Antipsychotics	"These patients have higher risks of both myocardial infarction and stroke but a lower risk of undergoing interventional procedures compared with the general population. Treatment with antipsychotic drugs is associated with reduced mortality but also with an increased risk of weight gain, dyslipidaemia and diabetes mellitus".
Piña et al., 2018	Cigarette smoking, abnormal blood lipid levels, hypertension, diabetes, abdominal obesity, physical inactivity, low daily fruit and vegetable consumption, and alcohol overconsumption	Anxiety, depression, and type A personality	"Phobic anxiety was associated with increased risk for CHD, sudden cardiac death, and mortality. Depression may have both behavioral and physiological backgrounds. Patients who are depressed may be more likely to engage in unhealthy behaviors and be less compliant with therapies. The hostility component of type A personality is an important predictor of risk for CVD".

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