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Review

Cardiovascular diseases among patients with schizophrenia

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ABSTRACT

The presence of comorbid physical illnesses especially, cardiovascular diseases (CVD) in schizophrenia is a growing area of concern in recent years. In order to reduce disease burden, to improve quality of life and to provide holistic care, it is important to know about the relationship between schizophrenia and CVD. The objective of this review is to explore the extent of CVD problems, relevant risk factors and potential measures for early diagnosis and prevention of CVD among patients with schizophrenia. Worldwide studies show that patients with schizophrenia have a higher mortality and lower life expectancy than the general population. CVD is the leading cause of increased mortality in schizophrenia. Common CVD risk factors in schizophrenia include metabolic syndrome, sedentary behaviour, tobacco smoking, effects of antipsychotics, long chain omega-3 fatty acid deficiency and shared genetics between CVD and schizophrenia. The potential methods for early detection and prevention of CVD in schizophrenia are also discussed. Though the patients with schizophrenia form a high risk group for CVD, consensus guidelines for early detection and prevention of CVD in schizophrenia are lacking. Comorbidity of CVD in schizophrenia needs more serious attention by clinicians and researchers.

Contents

Abbreviations: ABI, ankle brachial index; BP, blood pressure; BMI, body mass index; CATIE, clinical antipsychotic trials of intervention effectiveness; CIMT, carotid intima media thickness; CRF, cardio-respiratory fitness; CVD, cardiovascular diseases; DALY, disability-adjusted life year; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; FGA, first generation antipsychotics; GBD, global burden of disease; GP, general population; GWAS, genome-wide association studies; HDL, high density lipoprotein; JBS, joint british societies score; LCn-3, long-chain omega-3; LDL, low density lipoprotein; MetS, metabolic syndrome; NCEP, national cholesterol education program; PCBs, polychlorinated biphenyls; PF, physical fitness; PGC, psychiatric GWAS consortium; RCT, randomized controlled trial; SGA, second generation antipsychotics; SMR, standardised mortality ratio; SZ, schizophrenia; YLD, years lived with disability; WHO, World Health, Organization.

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1. Introduction

Schizophrenia is a chronic and debilitating mental illness which causes substantial degree of disability. About one out of 100 individuals will experience this mental illness in his lifetime, and this figure is similar around the world (Jablensky, 1995). The burden caused by schizophrenia is huge and multifaceted (Rössler et al., 2005). The Global Burden of Diseases (GBD) study showed that schizophrenia contributes significantly to the GBD, with 1.1% of total disability-adjusted life years (DALYs) and 2.8% of years lived with disability (YLDs) attributed to this (Murray and Lopez, 1997). In the World Health Report 2001, the 8th leading cause of DALYs worldwide in the age group 15–44 was schizophrenia (World Health Organization, 2001). Furthermore, people with schizophrenia are vulnerable to developing physical illnesses such as diabetes, metabolic syndrome, cardiovascular diseases (CVD), respiratory diseases and cancer (Brown et al., 2000). The physical comorbidities complicate their disabilities and increase the disease burden. Health care providers frequently pay more attention to the psychological and behavioural problems and ignore physical diseases such as CVD in schizophrenia and the patients have been shown to receive a lower standard of care after CVD is diagnosed (Druss et al., 2000). A cross-sectional study by Smith et al. reported a systematic under-recognition and under-treatment of CVD of patients with schizophrenia within primary care (Smith et al., 2013). The present overview has been planned to shed light on the issue of comorbidity of CVD among the patients with schizophrenia. The aim of this review is to point out the causes of mortality in schizophrenia, to discuss about the important risk factors of CVD in schizophrenia and to recommend the potential early diagnostic and preventive measures for CVD in schizophrenia. In this narrative review, we conducted PubMed, Scopus and Google search using the following combinations of keywords: 'Schizophrenia', Schizophrenic disorder', 'Cardiovascular diseases', 'Coronary disease', 'vascular disease', 'Risk factors', 'mortality', 'death', and 'prevention'.

2. Mortality and life expectancy in schizophrenia

Schizophrenia has been associated with increased risk of several adverse outcomes which lead to a reduced life expectancy. A meta-analysis which extracted data from 37 studies in 25 countries, showed that the risk of death of people with schizophrenia was 2.5 times the general population (Saha et al., 2007). An earlier meta-analysis also reported significantly increased mortality rate in people with schizophrenia (Brown, 1997). A retrospective study of mortality among 3623 patients with schizophrenia in Alberta, Canada found that the risk of mortality in schizophrenia patient was approximately double that of the Alberta population (Newman and Bland, 1991). Another life expectancy study on large samples in Nordic countries (Denmark, Sweden and Finland) reported that the overall mortality was 2 to 3 times higher than the general population (Laursen et al., 2013).

It was observed that life expectancy of people with schizophrenia is shorter than that of the general population and standardised mortality ratio (SMR) is high. Among persons with bipolar disorder or schizophrenia in Nordic countries, life expectancy has been shown to be 12 to 20 years shorter in men and 11 to 17 years shorter in women, compared to the general population (Laursen et al., 2013). In Alberta, Canada, schizophrenia patient have approximately 20% shorter life expectancy than that of the general population (Newman and Bland, 1991). A 11-year follow-up study in Finland (FIN11 study) showed that the gap in life expectancy between patients with schizophrenia and the general population had not significantly changed over time, for example, the gap was 25 years in 1996 and in 2006, it was 22·5 years (Tiihonen et al., 2009). We can summarize that people with schizophrenia have a higher mortality rate and about 2 to 3 times greater risk of death than the general population. Also, their life expectancy is around 15–20 years shorter than the general population.

2.1. Causes of mortality in schizophrenia

The significantly lower life expectancy in schizophrenia can be attributed to death from both natural and unnatural causes. Causes of natural deaths in schizophrenia include cardiovascular diseases, respiratory diseases, cancer, unrecognized medical diseases, poor compliance, refusal of treatment for medical diseases, unhealthy life style, substance misuse and antipsychotic drug side effects (Brown et al., 2000; Bushe et al., 2010; von Hausswolff-Juhlin et al., 2009). Unnatural deaths are mainly caused by suicides and accidents (Brown, 1997). Natural and unnatural causes account for about 60% and 40% of all deaths in schizophrenia respectively (Ringen et al., 2014).

The contribution of cancer to mortality in schizophrenia ranges from 7 to 21% of all causes of deaths (Brown et al., 2000; Capasso et al., 2008; Chong et al., 2009; Dean and Thuras, 2009; Fors et al., 2007; Mortensen and Juel, 1993; Tran et al., 2009). The cancer mortality rate among patients with schizophrenia has been reported higher than the general population in studies in Australia and Denmark (Dalton et al., 2008; Lawrence et al., 2000). Lung and breast cancer are the two commonest malignancies in schizophrenia (Bushe et al., 2009; Catts et al., 2008; Hippisley-Cox et al., 2007). An 11-year prospective mortality study among 3470 patients with schizophrenia revealed that lung cancer contributed 50% of all cancer in males and breast cancer contributed 39% of all cancer in females (Tran et al., 2009). 80% of incident cases of breast cancer arose among patients with schizophrenia who were over 50 years old (Bushe et al., 2009). A remarkably large mortality study among 17,600 patients with schizophrenia over seven years period reported mortality rate ratio for CVD 2.07 and 1.72 and malignant neoplasms 1.24 and 1.32, for males and females, respectively (Laursen et al., 2007).

The contribution of respiratory diseases and other natural causes to mortality in schizophrenia varies across the studies. There may be different causes of excess mortality in Asian

countries, compared to Western countries with an excess of respiratory causes and infectious disease in-patient with schizophrenia. For example, a study in France reported 18% contribution from respiratory causes, whereas other study among Asian patients reported 66% contribution to mortality (Chong et al., 2009; Tran et al., 2009). However, the data from Asian countries is sparse.

2.2. Mortality due to CVD among patients with schizophrenia

Cardiovascular diseases and suicide are the leading causes of mortality in schizophrenia (Casey and Hansen, 2003; von Hausswolff-Juhlin et al., 2009). The relative risk of suicide and coronary heart diseases among people with schizophrenia are 10-fold and 2-fold higher, respectively, compared to the general population (Casey and Hansen, 2003; Meltzer, 1998). But it was observed that out of 50% of the people who attempted suicide, only 10% of them succeeded to commit suicide and thus, prevalence of CVD is higher than the suicide (Hennekens et al., 2005). A meta-analysis on mortality of mental disorders showed that death rates from CVD was 90% higher in schizophrenia than among the general population (Harris and Barraclough, 1998). Observation of a large group of patients with schizophrenia by Ösby et al. (2000) concluded that the largest single cause of death was CVD in both males and females. So, we can summarize that among the multiple causes of increased mortality, CVD is the chief cause of mortality among the patients with schizophrenia.

3. Risk factors of CVD in schizophrenia patients

There are many studies investigating different risk factors of CVD in schizophrenia. A meta-analysis on cardio-metabolic abnormalities in patients with schizophrenia divided risk factors of CVD into three groups: (a) behavioural factors such as substance abuse, smoking, unhealthy eating patterns, sedentary behaviour, (b) management factors such as side effects of antipsychotics and other medications, inequalities in quality of medical care, fragmentation of physical and mental health care and (c) low socio-economic status such as poverty, poor education (Vancampfort et al., 2013). Some important risk factors of CVD in schizophrenia are summarized in Table 1.

3.1. Metabolic syndrome (MetS)

According to the third report of the National Cholesterol Education Program (NCEP), metabolic syndrome (MetS) is a multiplex risk factor for CVD. The report identified CVD as the primary clinical outcome of MetS and defined MetS as a cluster of risk factors for CVD (American Heart Association, 2002) (see Table 2 for the list of components of MetS cluster associated with CVD).

Several studies have reported that the prevalence of MetS is significantly high among patients with schizophrenia and the risk of MetS is also higher among them compared to the general population (see Table 1). Obesity is also common in schizophrenia. The report of National Institute of Mental Health, USA indicated that obesity was one of the common problem among patients with schizophrenia (Allison et al., 2009).

There are multiple factors behind the increased prevalence of MetS in schizophrenia such as dietary habits, sedentary lifestyle, tobacco smoking and effects of second generation antipsychotics (McEvoy et al., 2005). The roles of these factors on MetS are discussed in the specific sections below. One hypothesis by Scigliano et al. stated that schizophrenia by itself is an independent risk factor for MetS due to sympathetic overactivity which results from psychosis-related stress (Scigliano and Ronchetti, 2013).

3.2. Sedentary behaviour

Studies reported that most patients with schizophrenia spent time in sedentary activities and they did not engage in much physical activities such as sports during their leisure time (Beebe et al., 2005; Roick et al., 2007; Vancampfort et al., 2011). The physical activity level in patients with schizophrenia was found to be lower than that in general population (Faulkner et al., 2006; Roick et al., 2007). Such sedentary lifestyle is a risk factor to develop CVD in patients with schizophrenia. A consistent association between sedentary behaviour and cardio-metabolic comorbidity in schizophrenia has been reported (Vancampfort et al., 2012). Possible causes of sedentary behaviour in schizophrenia might be due to negative symptoms such as lack of drive or social withdrawal, lack of insight and hospitalization where activities are regulated (Ringen et al., 2014).

3.3. Tobacco smoking

The harmful effects of tobacco smoking on cardiovascular system are well-documented (World Health Organization, 2009). The prevalence of tobacco smoking is high in schizophrenia. Meta-analysis has shown that people with schizophrenia had an odds of smoking 5.3 times higher than the general population (de Leon and Diaz, 2005). Heavy smoking is more common in people with schizophrenia, especially in men (Gurpegui et al., 2005; McCreadie, 2002). A large cohort study showed that tobacco-related conditions consist of about 53% of total deaths in the schizophrenia (Callaghan et al., 2014). Several hypotheses explain this increased affinity for smoking such as genetic contribution hypothesis, reward deficiency syndrome hypothesis, and self-medication hypothesis (Blum et al., 2000; Dolan et al., 2004; Wang and Li, 2010). The "self-medication" hypothesis states that patients with schizophrenia smoke nicotine to improve deficits in attention, information processing and cognitive functions and also, to diminish the side-effects of antipsychotics (Dolan et al., 2004).

3.4. Effects of antipsychotics

Antipsychotic medications can disturb the cardiovascular function of people with schizophrenia in various ways. Different groups of antipsychotics vary in their mechanisms of actions and research is still ongoing to explore actions of antipsychotics on the cardiovascular system. Table 3 summarizes the proposed pharmacodynamics of antipsychotics on cardiovascular functions. There have been several case reports of sudden cardiac death in schizophrenia due to antipsychotic use (Ray et al., 2009; Straus et al., 2004). Prolonged QTc interval with the risk of progression to Torsades de Pointes is a fatal side effect of antipsychotic which leads to sudden cardiac death (Ames et al., 2002). Second generation antipsychotics (SGA) are more notorious than first generation antipsychotics (FGA) for causing metabolic syndrome (De Hert et al., 2006a,b). Among SGA, olanzapine and clozapine are the most obesogenic (Rummel-Kluge et al., 2010). As discussed earlier, antipsychotics can produce metabolic syndrome which is an important risk factor for CVD. There are many hypotheses regarding the pathogenesis of metabolic syndrome and CVD by antipsychotics. One mechanistic hypothesis suggests that the root of the pervasive metabolic and cardiovascular disorders in schizophrenia is autonomic nervous system dysfunction which is triggered by the disease and exacerbated by antipsychotic treatment. According to this hypothesis, antipsychotics block both peripheral dopamine and muscarinic receptors which increases sympathetic activity and reduces vagal parasympathetic activity, respectively. As a result, sympathetic activity cannot be countered by parasympathetic activity which in turn leads to impaired

Table 1
Risk factors of CVD among the patients with schizophrenia from selected studies.

Risk factors of CVD	Title of the study	Country	Study design	Sample	Study findings
Metabolic syndrome (MetS)	Prevalence of the metabolic syndrome in patients with schizophrenia: baseline results from the clinical antipsychotic trials of intervention effectiveness (CATIE) schizophrenia trial and comparison with national estimates from NHANES III (McEvoy et al., 2005)	USA	Analysis of baseline data from CATIE (clinical antipsychotic trials of intervention effectiveness)	Out of 1460 CATIE baseline subjects, 689 patients with SZ were selected for analysis	The prevalence of MetS was high, over 40% in SZ. It was over 51% for female and 36% for male SZ subjects. CATIE females and males were 251% and 138%, respectively, more likely to have MetS than the matched sample
	Impaired fasting glucose tolerance in first-episode, drug-naive patients with schizophrenia (Ryan et al., 2003)	USA	Hospital based, cross sectional study	Drug-naive, 1st episode Caucasian SZ subjects, N = 26 (M:15 F:11) and matched healthy subjects	Drug-naïve, 1st episode patients with SZ had impaired fasting glucose tolerance and were more insulin resistant and had higher levels of plasma glucose, insulin, and cortisol than healthy comparison subjects
	A 4-fold risk of metabolic syndrome in patients with schizophrenia: the Northern Finland 1966 Birth Cohort study (Saari et al., 2005)	Northern Finland	Birth cohort study	5613 Members of the Northern Finland 1966 Birth Cohort	Four fold increased risk of MetS in patients with SZ than GP
Sedentary behavior	Health habits of patients with schizophrenia (Roick et al., 2007)	Eastern Germany	Comparative study of subjective data (Self–administered questionnaire) from SZ subjects in outpatients with that from GP	194 SZ subjects both from urban and rural area	Patients with SZ showed significantly greater sedentary behaviors than GP. On workdays, SZ subjects spend 9.4 h on average sleeping and 12.7 h with sedentary physical activities. Also, during their leisure time, about 46.6% of SZ did not participate in sports
Tobacco smoking	A meta-analysis of worldwide studies demonstrates an association between schizophrenia and tobacco smoking behaviours (de Leon and Diaz, 2005)	N/A	Meta-analysis of worldwide literature related to smoking behaviour in schizophrenia	N/A	The prevalence of smoking was higher in SZ than the GP and other severe mental illness. Patients with SZ had odds of smoking 5.3 (95% CI: 4.9–5.7) times higher than the general population
	Cigarette smoking among persons with schizophrenia or bipolar disorder in routine clinical settings, 1999–2011 (Dickerson et al., 2013)	USA	To find out prevalence and quantity of smoking among different groups in clinical setting from 1999 to 2011	*N* = 991(SZ = 421, Bipolar = 126, No disorder = 444)	The prevalence of smoking was alarmingly higher in SZ than the control. 64% of SZ patients reported as smokers
	Patterns of tobacco-related mortality among individuals diagnosed with schizophrenia, bipolar disorder, or depression (Callaghan et al., 2014)	USA	Record review of inpatient hospital admission data from 1990 to 2005	SZ: *N* = 174,277	The SMRs for tobacco-linked diseases in SZ was 2.45 (95%CI = 2.41–2.48). Tobacco-related conditions comprised approximately 53% (23,620/44,469) of total deaths in the SZ. The results clearly demonstrated elevated risk of tobacco-related mortality in people with SZ

Table 1 (*Continued*)

Risk factors of CVD	Title of the study	Country	Study design	Sample	Study findings
Effects of antipsychotics	Atypical antipsychotic drugs and the risk of sudden cardiac death (Ray et al., 2009)	USA	Retrospective cohort study	44,218 and 46,089 baseline users of single typical and atypical antipsychotics, respectively and 186,600 matched controls	Current users of typical and of atypical antipsychotic drugs had higher rates of sudden cardiac death than did nonusers of antipsychotic drugs, with adjusted incidence-rate ratios of 1.99 (95%CI, 1.68 to 2.34) and 2.26 (95%CI, 1.88 to 2.72), respectively
Long chain fatty acid deficiency	Adult medication-free schizophrenic patients exhibit long-chain omega-3 fatty acid deficiency: implications for cardiovascular disease risk (McNamara et al., 2013)	USA	Case-control study in inpatient of a hospital. Medication free adult	SZ: M 12, F 6 HC: M 10, F 14 SZ subjects were medication free for 2 weeks prior to the study	SZ subjects exhibited low EPA + DHA status. Most of them (72%) showed erythrocyte EPA + DHA levels $\leq$ 4.0% compared with 37% of controls (Chi-square, $P = 0.001$). It was lower in male than female SZ subjects
Shared genetics between SZ and CVD	Improved detection of common variants associated with schizophrenia by leveraging pleiotropy with cardiovascular-disease risk factors (Andreassen et al., 2013)	A total of 17 samples from 11 countries	Genetic-pleiotropy-informed method with the use of SZ GWASs summary-statistics data. The statistics results were obtained from the PGC	9394 cases with SZ or schizoaffective disorder and 12,462 controls (52% screened)	Of 25 loci associated with SZ, 10 loci are associated with both SZ and CVD risk factors, mainly triglycerides, LDL and HDL but also waist-to-hip ratio, systolic blood pressure, and BMI. The results indicated potential shared mechanisms between SZ and CVD

CI = confidence interval, M = male, F = female, HC = healthy control, *N* = sample size, N/A = not applicable.

control of lipid and glucose metabolism, raised blood pressure and cardiac arrhythmias. The author suggested that levodopa might prevent these effects (Scigliano and Ronchetti, 2013).

3.5. Long chain omega-3 fatty acid deficiency

A study by McNamara et al showed that medication-free adults with schizophrenia, particularly men, had a lower omega-3 index (McNamara et al., 2013). The omega-3 index which is measured by the erythrocyte level of long-chain omega-3 (LCn-3) fatty acids, (principally eicosapentaenoic acid and docosahexaenoic acid) is an important risk marker for cardiovascular diseases (Harris, 2009). Other case-control studies also demonstrated similar deficiency of essential polyunsaturated fatty acids in the erythrocyte membrane of patients with schizophrenia (Arvindakshan et al., 2003; Khan, 2002). The low omega-3 index increases the vulnerability of patients with schizophrenia for developing acute coronary syndromes and sudden cardiac arrest, as well as second generation antipsychotic-induced hypertriglyceridemia and hepatic steatosis (McNamara et al., 2013). In humans, the only source of LCn-3 fatty acids is their diet. The omega-3 index is significantly correlated with dietary intake of LCn-3 fatty acid (Cao et al., 2006). The lower omega-3 index in patients with schizophrenia can be explained by their diets, which have a higher intake of saturated fat and a lower consumption of fibre and fruits compared to the general population (Dipasquale et al., 2013).

3.6. Shared genetics between schizophrenia and CVD risk factors

Genome-wide association studies (GWAS) have identified about 160 loci associated with CVD and its risk factors (Arking and Chakravarti, 2009). A study using genetic-pleiotropy-informed methods detected ten loci which are associated with both schizophrenia and CVD risk factors, mainly triglycerides, low-density lipoproteins (LDL) and high-density lipoproteins (HDL). Body mass index (BMI), waist-to-hip ratio, and systolic blood pressure were also implicated (Andreassen et al., 2013). This indicates that schizophrenia and CVD risk factors share some

Table 2
Six components of the MetS that relate to CVD (American Heart Association, 2002).

1) Abdominal obesity
2) Atherogenic dyslipidemia
3) Insulin resistance with or without glucose intolerance
4) Raised blood pressure
5) Pro-inflammatory state and
6) Pro-thrombotic state

Table 3
The list of mechanisms by which antipsychotics affect cardiovascular functions (Ames et al., 2002).

1) Receptor blockade
2) Conduction disturbance (e.g. bundle branch block)
3) Sinus node abnormalities
4) Delayed ventricular repolarisation (prolonged QTc interval)
5) Left ventricular dysfunction
6) Myocarditis
7) Postural hypotension
8) Polydipsia-hyponatremia syndrome
9) Glucose intolerance and
10) Weight gain

common gene loci. Identification of the genetic basis will help us to understand clearly the association between CVD and schizophrenia.

4. Early detection of CVD in schizophrenia

Delay in seeking health care as well as neglecting CVD risk factors screening in schizophrenia by health care providers can delay early detection of CVD in schizophrenia. To improve quality of life and decrease early deaths in schizophrenia, early diagnosis of CVD is essential. Several guidelines recommended monitoring of some parameters for the purposes of early detection of cardio-metabolic risk during the follow-up of patients with schizophrenia (De Hert et al., 2011). Table 4 shows the list of some suggested screening parameters for detection of CVD risks in schizophrenia. Unsal et al. (2013) proposed three additional screening tests for early detection of subclinical atherosclerosis and diastolic dysfunction in schizophrenia. The three screening tests are: (a) Carotid intima media thickness (CIMT), (b) Ankle brachial index (ABI), and (c) Doppler echocardiography (Unsal et al., 2013). CIMT and ABI are well-established surrogate markers of early atherosclerosis. Tissue Doppler echocardiography can be used to detect diastolic function impairment in its early phase, even when it is asymptomatic (Agarwal et al., 2012). For the early diagnosis of cardiovascular diseases, Monitoring diastolic functions via echocardiography could be potentially useful in all patients with schizophrenia (Unsal et al., 2013).

Use of CVD risk assessment algorithms could be a good option for predicting 10 years CVD risk in schizophrenia. But McLean et al found that the existing standard CVD risk algorithms such as Joint British Societies Score (JBS2) or Framingham CVD algorithm underestimated the risk of CVD in schizophrenia due to several reasons like much younger age of onset of CVD in schizophrenia than the general population (McLean et al., 2014). The author recommended for the development of a schizophrenia-specific risk scores which have better ability to predict CVD risk in schizophrenia (McLean et al., 2014).

These additional screening tools have the advantage of being non-invasive, but might impose additional costs and manpower, so might not be feasible in some low resource areas.

5. Prevention of CVD in schizophrenia

Prevention of CVD in schizophrenia can reduce disease burden and increase longevity. Modifiable risk factors of CVD, such as smoking, sedentary and unhealthy life style, metabolic syndrome and obesity can be controlled in people with schizophrenia in the same way as in the general population. However, life style modification alone may not be enough, since people with schizophrenia have additional risk factors such as the effects of antipsychotics. Some important potential preventive measures are discussed below.

Table 4
Recommended monitoring measures for cardio-metabolic risks in schizophrenia (De Hert et al., 2011).

1) Blood pressure
2) BMI
3) Hip circumference
4) Waist circumference
5) Fasting triglycerides
6) Fasting cholesterol
7) High-density lipoprotein/low-density lipoprotein ratio
8) Fasting glucose, and
9) Diabetes symptoms

5.1. Exercise programmes to improve physical fitness

Exercise can reduce CVD risk factors and improve the quality of life of people with schizophrenia. A study by Scheewe et al. showed that exercise therapy improved cardiorespiratory fitness (CRF) in patients with schizophrenia (Scheewe et al., 2012). Improved CRF reduces risk of CVD (Kodama et al., 2009). Physical fitness (PF) which is measured as peak oxygen uptake (VO_{2peak}) plays a more important role than physical activity in controlling CVD risk factors (Sassen et al., 2009). A study by Heggelund et al. (2011) found that high aerobic intensity training could effectively improve physical fitness in people with schizophrenia and consequently, reduce the risk of CVD.

5.2. Omega-3 fatty acid supplement

Randomized controlled trials (RCTs) have documented that omega-3 fatty acid supplements can reduce CVD and decrease the progression of atherosclerosis in coronary patients (Kris-Etherton, 2003). But more evidence is needed to confirm the effect of omega-3 on CVD as suggested by a Cochrane systematic review (Hooper et al., 2004). An example of beneficial effect of omega-3 fatty acid intake might be the Japanese whose annual seafood consumption is 3-times greater than the consumption by USA population and their mortality due to CVD is 6-times lower than the USA population (World Health Organization, 1995). The mechanisms by which omega-3 fatty acids reduce risk for CVD are not clearly understood. Some proposed mechanisms are: (1) prevention of ventricular arrhythmias, (2) hypotriglyceridaemic effect, (3) antithrombogenic effect, (4) antiinflammatory effect, (5) inhibition of synthesis of cytokines and mitogens, (6) stimulation of endothelial-derived nitric oxide, (7) inhibition of atherosclerosis, and (8) mild hypotensive effect (Connor, 2000; Kris-Etherton, 2003).

Since people with schizophrenia show omega-3 deficiency, omega-3 fatty acid rich foods such as fish oil or its supplement can be considered as a preventive diet for them. Moreover, Mellor et al gave omega-3 supplement to patients with schizophrenia and concluded that the supplement improved both schizophrenic symptoms and tardive dyskinesia (Mellor et al., 1996). Thus, it could be hypothesized that omega-3 fatty acid can help to prevent and ameliorate cardiovascular diseases as well as psychotic symptoms and extrapyramidal syndromes such as tardive dyskinesia among patients with schizophrenia.

However, we need to be aware that omega 3 supplements are taken mainly in the form of oily fish or fish oil (often fish liver) capsules and there are reports of presence of high levels of various toxic compounds such as mercury, dioxins, polychlorinated biphenyls (PCBs) in oily fish and fish oils (Hooper et al., 2004). Long exposure to fish oils contaminated with dioxins or PCB might increase cancer in humans and mercury contamination might give rise to neurological deficits. Another concern is that omega 3 fats might promote haemorrhagic stroke by reducing thrombotic tendency (Hooper et al., 2004).

5.3. Statin therapy

The use of statins in secondary prevention of CVD patients is well established. The benefits of statin for the primary prevention of CVD in high risk individuals, such as those with hyperlipidaemia, hypertension or diabetes are found in the literature (Moride et al., 2008). Since, people with schizophrenia are also a high risk group for the development of CVD, a statin could be considered as a primary preventive method in schizophrenia, especially, with use of second generation antipsychotics (Andrade, 2013). At present, there is no long-term, prospective study to evaluate beneficial

effects of statins for primary prevention of CVD in schizophrenia. But some short term, small sample size studies reported beneficial effects of statins for primary prevention of CVD in schizophrenia and schizoaffective disorders (De Hert et al., 2006a,b; Hanssens et al., 2007). There are a few drawbacks of statin therapy to consider, for example, the addition of a statin will increase the number of prescribed medications and treatment cost, which ultimately, might affect compliance to the treatment (Andrade, 2013).

6. Conclusion

People with schizophrenia are at high risk of developing CVD due to multiple factors. Understanding of the aetiology and mechanism of the elevated CVD risk will help us to deal effectively with CVD in schizophrenia. Some risk factors, for example, the genetic association between CVD and schizophrenia, long chain fatty acid deficiency and mechanism of antipsychotic effects need further exploration. Health care providers should be aware of the side effects of antipsychotics and cautiously choose the regimen which causes least harm to the cardiovascular system of each patient. Regular monitoring of carotid intima media thickness, ankle brachial index or Doppler echocardiography might be recommended for early diagnosis of CVD in schizophrenia. Furthermore, novel risk assessment tools such as schizophrenia-specific CVD risk algorithm could be created and used for early identification of CVD in schizophrenia. Cardiologist, dietician and physiotherapist/exercise therapist play important roles in schizophrenia care and should either be part of or liaise with the multi-professional team. Physical fitness rather than physical activity might need more attention to control CVD risk factors in schizophrenia. For primary prevention of CVD in schizophrenia, the role of statins and omega-3 fatty acid need more investigations and a consensus guideline is needed for prescribing them. More research is needed from Asia, since causes of excess mortality and response to interventions is likely to be different.

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