

# Metabolic Syndrome in Schizophrenia

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## Abstract

Metabolic syndrome (MS), a constellation of interconnected metabolic disorders including obesity (central and abdominal), hyperglycemia, dyslipidemias and hypertension is highly prevalent among patients with schizophrenia. The prevalence of MS varies across countries and ethnic groups. There are multiple determinants of MS among patient with schizophrenia, important being age, sex, ethnic group, longer duration of illness, advanced age, and use of antipsychotics. Early detection and management of metabolic abnormalities could prevent associated premature morbidity and mortality in schizophrenia. Future research is needed to identify and explore genetic determinants of MS in schizophrenia which could help to prevent and manage the illness in better way.

**Keywords: Metabolic Syndrome, Schizophrenia, Obesity**

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## INTRODUCTION

Psychiatric disorders are found among the leading cause of global morbidity.<sup>1</sup> Schizophrenia is one among them which has chronic course with poor prognosis.<sup>2</sup> Patients suffering from schizophrenia have a reduced life expectancy as compared to the general population.<sup>3-7</sup> Moreover, they have 2-3 fold increased risk of dying due to several reasons.<sup>8</sup> Patients with mental illness including schizophrenia are neglected in all societies and their physical health is not given priority and attention. Because of illness itself and chronic use of antipsychotics along with co-morbid substance abuse, patients with schizophrenia are always in high risk of developing metabolic syndrome (MS).<sup>9-12</sup> Undiagnosed and untreated co-morbidities were seen in significant proportion of patients in Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE).<sup>9</sup> There is increased mortality rate observed in schizophrenia due to cardiac cause, so growing concern has been given to the physical illness

especially cardiovascular risk among these patients.<sup>13</sup> The main reason is that these patients are more likely to be overweight, smoke excessively and develop hyperglycaemia, hypertension, and dyslipidaemia.<sup>14,15</sup>

## Schizophrenia

Schizophrenia is a chronic and disabling psychiatric illness<sup>16</sup> that has around 1% lifetime risk and affects young age group.<sup>17</sup> Approximately, half of patients with schizophrenia probably requiring long-term medication due to chronic nature of illness.<sup>18</sup> It has a life time prevalence of 4.0/1000 individuals worldwide.<sup>19</sup> Onset is usually during adolescence or early adulthood affecting both male and female equally.<sup>20</sup> The most prominent characteristic symptoms of schizophrenia are hallucinations, delusions, and disorganization, which may lead to dangerous or bizarre behaviors which are also known as positive symptoms.<sup>16,19</sup> Similar other symptoms so-called negative symptoms such as social

withdrawal and diminished emotional engagement, loss of motivation, poverty of speech and cognitive impairments can significantly impair social and occupational functioning.<sup>16,19</sup> It also result in persistent negative impact on patient ability to maintain relationships and engage in productive work in addition to disorganized thinking and memory impairments.<sup>20</sup> There is evidence that more than 90% of patients with schizophrenia have sleep problems<sup>21</sup> which may exacerbate existing psychopathology by causing distress and negative impact on general functioning.<sup>21</sup> It has serious physical, social and economic consequences,<sup>20</sup> which is often accompanied by relapse even while on treatment.<sup>17</sup> The chronic and deteriorating nature of course makes this illness disabling disorder for patients and their families.<sup>22-4</sup> There is a great negative impact of illness on quality of life of patients and carers.<sup>25-7</sup>

### **Metabolic Syndrome**

MS is characterized by a constellation of interconnected metabolic disorders including obesity (central and abdominal), hyperglycaemia, dyslipidemias and hypertension.<sup>28</sup> It is also commonly known as insulin resistance syndrome or "X syndrome". There are number of definitions of MS along with several diagnostic criteria are used in clinical setting. Majorities of them used in these various definitions include waist circumference, low high density lipoprotein (HDL) level and raised triglycerides (TG), fasting plasma glucose (FPG) and blood pressure (BP). The widely accepted ones are those proposed by (a) National Cholesterol Education Program Adult Treatment Panel III (NCEP- ATP III),<sup>5</sup> (b) updated ATP-III,<sup>29</sup> revised by the American Heart Association/ National Heart, Lung, and Blood Institute, AHA/NHLBI; and (c) International Diabetes Federation (IDF).<sup>7</sup>

World Health Organization(WHO)<sup>30</sup> defined MS as insulin resistance and/or impaired fasting glucose and/or impaired glucose tolerance and two or more of the following: (i) waist-hip ratio >0.90 (men), >0.85 (women) or body mass index >30 kg/m<sup>2</sup>., (ii) triglyceride level >1.7 mmol/L or high-density lipoprotein <0.9 mmol/L(men), <1.0 mmol/L (women), (iii) blood pressure >140/90 mm Hg (or treated hypertension), and (iv) microalbuminuria. Similarly, NCEP ATP III

<sup>5</sup> had proposed the definition of MS which was later revised in 2005 by the American Heart Association/National Heart, Lung, and Blood Institute (updated ATP III).<sup>30</sup> Waist circumference, blood pressure, HDL and TG are found common in these two definitions whereas FPG measurement is found to be different. Similarly, IDF proposed another definition on it.<sup>7</sup> Diagnostic of MS depend upon the criteria used and population being studies. As Asian population have small build, the metabolic risk profile in Asian descent has been reported to be more adverse than that in European descent at the same waist circumference.<sup>31</sup> Thus, the recommended cut-off for waist circumference in the NCEP ATP III definition is inappropriate for Asian populations. The most current definition done by IDF focused on the importance of waist circumference, using both more stringent and ethnic-/race-specific criteria. Waist circumference is smaller than ATP III and updated ATP III. Emphasis is given on abdominal obesity in this definition where (abdominal circumference of ≥90 and ≥80 cm respectively for male and female of Asian origin, and of 102 cm and 88 cm respectively for non-Asians). The other criteria are triglyceride levels ≥150 mg/dl, high density lipoproteins (HDL) <40 mg/dl and 50 mg/dl for men and women respectively, a systolic blood pressure ≥130 mm of mercury (Hg) or a diastolic blood pressure ≥85 mm of Hg, and fasting plasma glucose levels ≥100 mg/dl.<sup>7</sup> The IDF and updated ATP III criteria overlap and identify essentially the same individuals as having MS.<sup>28</sup> The major difference between these is the necessity of central obesity for making a diagnosis; while the IDF definition needs central obesity plus any other two or more out of five criteria, the updated ATP III definition requires any three or more of the five criteria for a diagnosis. Past studies revealed variation in outcome rates in same population when different criteria were used to calculate MS.<sup>9,10,32-3</sup> These study found IDF criteria usually generated the highest rates and NCEP-ATP III modified criteria generated the lowest rates.

MS is associated with a four times relative risk of developing diabetes<sup>31</sup> and approximately a 2-fold risk of coronary heart disease, stroke, and premature mortality.<sup>9</sup> As a result, MS has been proposed as an alternative or an augmentation

to the Framingham<sup>10</sup> or systematic coronary risk evaluation<sup>11</sup> calculations to assess the risk of cardiovascular disease and death. Similar results for the MS as a predictor of the risk of coronary heart disease have been found previously in schizophrenia.<sup>32</sup>

### **Metabolic Syndrome among Patient with Schizophrenia**

Metabolic abnormalities have consistently been identified among patient with schizophrenia since decade.<sup>34</sup> Schizophrenia does not just affect mental health of a person but is found to be associated with increased mortality and shortened life expectancy.<sup>15</sup> Patients are more likely to die prematurely due to physical health problems especially metabolic abnormalities.<sup>35-6</sup> The reason for excess mortality among patient with MS is mostly related to circulatory, respiratory, digestive, genitourinary and endocrine diseases including diabetes.<sup>37</sup> As past studies pointed out the mortality in schizophrenia was especially due to suicide and other natural causes, however more recent study found co-morbid medical conditions along with cardio-metabolic illnesses is the leading cause.<sup>38</sup> MS increases mortality from cardiovascular diseases from numerous causes. Schizophrenic patients are always at a greater risk of developing obesity, diabetes mellitus type 2, hypertension and dyslipidemia than other due to a number of reasons, including sedentary lifestyle, poor dietary choices, decreased physical activity, smoking, alcohol & substance abuse and side effects of antipsychotic medications.<sup>39</sup> It has been well established fact that metabolic abnormalities among schizophrenic patients not only have an impact on physical health but also on poorer quality of life,<sup>40</sup> non-compliance,<sup>41-5</sup> and lower functional outcome.<sup>46</sup> The CATIE study found that MS are often under-recognized as well as undertreated in schizophrenia in which 88% of patients with dyslipidaemia were not receiving treatment, 62% were found to be hypertensive patients and 38% of them had diabetes.<sup>47</sup> Thus special attention has been given to prevent mortality and morbidity related to MS in schizophrenia since last several years.<sup>14</sup>

### **Prevalence**

The prevalence of MS in populations around the world varies in urban populations from 8% in India to 24% in USA among men and from 7% in France to 46% in Iran among women.<sup>48</sup> A study involving around 14,425 participants in Eastern Nepal estimated that the prevalence of MS using the IDF criteria was 22.5% and 20.7% based on NCEP ATP III criteria.<sup>49</sup> Globally prevalence of MS among patient with schizophrenia is found to be higher than general population. It is found approximately two-to three-folds higher than in the general population.<sup>9, 50-1</sup> The prevalence study of metabolic syndrome in schizophrenia differs from ethnic group and geographic location. Studies among Asian population reported lower rates of MS in schizophrenia and on the other hand western population showed high rates of MS. Prevalence of MS ranges from 20% in Thailand<sup>52</sup> to 22% in Taiwan.<sup>53</sup>

Research carried out among patient with severe mental disorder in Hong Kong<sup>54</sup> has estimated the unadjusted prevalence of MS to be 35%. The study revealed the relative risk of MS in comparison with the general Hong Kong population was 2.008 (95% CI 1.59-2.53,  $p < 0.0001$ ). A Korean cross-sectional study<sup>55</sup> has estimated the prevalence of 43.4% of MS and was found approximately similar among men (43%) and women (43.9%). The MS prevalence among 1186 patients with schizophrenia and schizoaffective disorder in Japan based on ATP-III definition was 27.5%.<sup>56</sup> The study found out higher rate (29.8%) in male than in female patients (25.3%). Few studies have been carried out in South Asian countries. Studies about prevalence rates of MS in South Asians region tend to be somewhat different from East Asian countries. A study regarding MS among 227 patients with schizophrenia in India using IDF criteria found 43.6%, and 44.5% using NCEP ATP III met the criteria for MS.<sup>57</sup> Similarly, another study carried out in similar setting using the IDF criteria found out the prevalence of 37.8%.<sup>58</sup> Studies carried out in the USA has estimated the prevalence of MS in schizophrenia to be between 28.7%<sup>59</sup> and 60%.<sup>60</sup> Research done in other western countries apart from USA and Australia revealed approximately similar study findings that of Asian countries. A Canadian study<sup>61</sup> found out the prevalence rate of 44.7%,

and a Finnish Project<sup>62</sup> estimated the rate of 37.1%.

### **Risk factors for Metabolic Syndrome**

Central obesity is a key feature of the MS reflecting the fact that there is strong relationship between waist circumference and increasing adiposity.<sup>28</sup> Many components of the MS are associated with sedentary life style including increased central obesity, reduced HDL cholesterol level, high blood pressure, increased triglyceride level and increase glucose level.<sup>63</sup> Many life style factors such as poor dietary habits, smoking, drinking may increase risk of MS.<sup>64</sup>

It is estimated that approximately 75% of patient with type-2 DM or impaired glucose tolerance (IGT) have MS. The presence of MS in this population group is found to be related to higher prevalence of cardiovascular disorder compared with those patients having type-2 DM or IGT without syndrome.<sup>63</sup> MS is found more among those people having cardiac diseases and hypertension.<sup>63-7</sup> Prevalence of MS demonstrated by the study in coronary heart disease is approximately 50% among which 37% is premature.<sup>65</sup> The age dependency of MS prevalence is seen in most population throughout the world and prevalence was found to be increased in older age.<sup>56, 68-73</sup>

### **Socio-demographic predictors**

Many attempts have been made to study the socio-demographic predictors of MS in patients with schizophrenia; however none of the socio-demographic variable has emerged as a consistent predictor of MS.<sup>10,55-6,74-7</sup>

### **Metabolic syndrome and sex**

The relationship of gender and occurrence of MS in schizophrenia is mixed. Many studies compared prevalence rates between men and women, and found no gender difference between patients with schizophrenia with or without MS.<sup>74-7</sup> Other studies reported high rate of MS prevalence among female population.<sup>10,51,70,72,78-9</sup> However, very few studies reported high prevalence of MS among male population.<sup>73</sup>

### **Metabolic syndrome and age**

The relationship of metabolic syndrome with age is almost established fact. The prevalence of MS increases with age in the general population and a similar findings were demonstrated by several past studies<sup>56,68-72</sup>, however, fewer studies reported no age differences.<sup>60</sup> A contrast study finding of Kang et al.<sup>55</sup> showed the limited relationship of older age with MS to males only. Correlation of peak MS rate with age demonstrated mixed result. MS was found to be peak in the third, fourth or fifth decade of life which subsequent decline in later life.<sup>56</sup> This study finding was not consistent through all studies, as other study found sex variation in peak MS rates.<sup>56</sup>

### **Metabolic syndrome and ethnicity**

Metabolic syndrome among patients with schizophrenia is common in all ethnic groups. However, limited studies have addressed the issue of ethnicity in estimating the metabolic rates.<sup>60,68,74</sup> These studies found out black African and Hispanic patients appeared to have higher rates of MS.

### **Metabolic Syndrome and Educational Status**

Education is seen as a good indicator for social position, socio-economic status and health status of an individual. It helps to shape the healthy behavior of a person through knowledge, attitude and healthy practice. In recent years increase prevalence of metabolic syndrome is seen among educated people due to life style changes.<sup>80</sup> Similar trend is seen in Schizophrenia as some studies finding reported higher education level among patient with schizophrenia.<sup>81-2</sup> However, no correlation of MS with educational status was also reported in the past study.<sup>57</sup>

### **Metabolic syndrome and other factors**

Few studies have reported association of MS with living in urban areas,<sup>57</sup> employed status<sup>75,83</sup> and marital status.<sup>83</sup>

### **MS and duration of illness**

Several studies<sup>10,57,70</sup> correlated duration of illness with MS in patients with schizophrenia. These studies reported that longer duration of illness increased the chance of having high rate of MS. However, no association of MS and

duration of illness were also reported by some studies.<sup>84</sup>

#### **Drug naive patients versus medicated patients**

There is vast difference on occurrence of metabolic syndrome between patient who are under medication and who never been on medication. The prevalence rates to range from 11% to 69% in patient under antipsychotics, and 4-26% in drug naive patients.<sup>85</sup> Initially base line prevalence in drug- naive patients vary from 0% to 14% and it increases to approximately 52.4% by 3 months of antipsychotic medication treatment. MS rate is depending upon the type of antipsychotic medication prescribed to the patient. Patients under second generation antipsychotics tend to develop higher rate of MS than patient who are taking first generation antipsychotic.<sup>86</sup> A study among patients with schizophrenia in 2000 to 2006 compared with 1984 to 1995 explored that patient who were under second generation antipsychotic had more than twice the rate of new incident cases of MS after 3 years, compared with those treated with first generation antipsychotics (27.8% vs 9.8%).<sup>47</sup> The pioneer study in schizophrenia , CATIE study showed concordance finding.<sup>9</sup>

#### **Clinical predictors**

Number determinants were found to be associated with clinical predictors of MS in schizophrenia. Conflicting results regarding age of onset, duration of the disorder, smoking and number of hospitalization have been observed.<sup>52,56</sup> Some studies have shown no association of MS and duration of illness,<sup>84</sup> however, other studies with a longer duration of illness has been demonstrated to be associated with higher prevalence of MS in some of the studies.<sup>10,70</sup> Late age of onset is viewed as potential predictor of MS,<sup>52</sup> while contrast finding is also exist relating to such association.<sup>87</sup> It also depend upon modality of treatment. Patient who treated as out- patient were more prone to develop MS than those who treated as in-patient.<sup>56</sup> There are inconsistent findings regarding association of smoking and MS shown by past studies. Some studies reported higher prevalence of MS in patients who smoke,<sup>70,88</sup> while other studies reported no differences in terms of smoking.<sup>10,60,71,75</sup>

Researchers reported higher body mass index (BMI) in patients with schizophrenia with MS.<sup>72,89</sup> Most patients with schizophrenia diagnosed with MS have raised waist circumference,<sup>57,71-3</sup> while the least have raised FPG level.<sup>57,72</sup> De Hert and colleagues<sup>40</sup> concluded that adding FPG measurement to waist circumference was the most sensitive (100%) method to follow MS in patients with schizophrenia. Patient with schizophrenia tend to smoke more than general population, however, smoking was found no difference between patients with or without MS .<sup>10,68,71</sup>

#### **Psychotropics and metabolic syndrome**

Patient with schizophrenia have to take antipsychotic medication for the longer duration which has potential risk of MS. Use of atypical antipsychotics has been cited as one of the reason for increased prevalence of MS in schizophrenia.<sup>33,69,82,90-7</sup> Most common antipsychotics associated with MS are second generation antipsychotics, important being clozapine, olanzapine and risperidone.<sup>33,69,93</sup> Risk of MS is lower for amisulpride, aripiprazole, sertindole, ziprasidone, haloperidol and chlorpromazine.<sup>33,90,92</sup> Literature suggests that the prevalence of MS is approximately reaches up to 69% in medicated patients<sup>91</sup> while it is lower in the range of 3-26% in drug naive patients.<sup>93</sup> Another study revealed the concordance finding regarding the prevalence rates between drug naive patients and those on treatment and demonstrated that the prevalence rates was nearly double in those treatment.<sup>92</sup> Although most of the studies found difference in weight gain property between typical and atypical antipsychotics, some studies<sup>96-7</sup> have concluded that there is no difference in their propensity to cause MS. The increased risk to develop MS under antipsychotic drugs is in part related to drug induced weight gain.<sup>93</sup> Although all antipsychotics can induce weight changes, the relative risk to induce clinically relevant weight changes difference approximately more than 7% is clearly seen between antipsychotic drugs.<sup>94-5</sup> Poly-pharmacy is associated with some degree of weight change and MS <sup>51,67</sup> , however contrast findings are also existing with some literature.<sup>76,98</sup>

## CONCLUSION

MS is a major public health problem in patient with schizophrenia and multiple contributing factors determine the high prevalence of metabolic disturbances. Morbidity and mortality associated with MS in schizophrenia is preventable and special attention should be given to high risk patients. All patients undergoing antipsychotic treatment should be screened prior to starting medication and then after initiating it on regular basis. The cornerstone of early detection and management of MS is comprehensive monitoring as recommended by different available guidelines. Psychiatrist should employ multiple strategies to minimize the metabolic risk by using medication with less adverse effect of metabolic abnormalities and promoting healthy lifestyle habits. Focus on future research to identify genetic determinants of MS in schizophrenia could be cornerstone in the prevention and management.

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