Review Article

Metabolic Syndrome in Schizophrenia

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ABSTRACT

To review the data with respect to prevalence of metabolic syndrome (MetS) and its correlates in schizophrenia. For this review, electronic search engines PUBMED, Sciencedirect, and Google Scholar were used. Available data suggests that most of the studies have been of cross-sectional design. Prevalence rates of MetS have varied from 11% to 69% in medicated patients, and 4-26% in drug naive patients in cross-sectional evaluations. Longitudinal studies have shown the prevalence rates to range from 0% to 14% at the baseline in drug naive patients, which increase to as high as 52.4% by 3 months of antipsychotic medication treatment. The prevalence rates of MetS in patients with schizophrenia are much higher than that seen in general population or healthy controls. Though there is no causal association with any demographic or clinical variables, the risk increases with increase in age. Among antipsychotics, there seems to be an association between MetS and atypical antipsychotics like clozapine and olanzapine. Therefore, the psychiatrists should be more vigilant regarding the presence of MetS in these high risk groups. Research on biological correlates of MetS in schizophrenia is still in its primitive stage, however, these is some evidence to suggest an association of MetS with adiponectin levels, hematological indices, methylenetetrahydrofolate reductase (MTHFR) and Alpha-1A adrenergic receptor (ADRA1A) gene. These areas hold promise, and targeting these with appropriate interventions may help us to prevent the occurrence of MetS in patients with schizophrenia in future.

Key words: *Cardiovascular risk, metabolic syndrome, schizophrenia*

INTRODUCTION

It is a well-established fact that schizophrenia is associated with increased mortality and shortened life span.[1,2] Earlier, the increased risk of mortality in schizophrenia was attributed to high incidence of suicide and other natural causes of death.[3] More recently, research has focused on medical co-morbidities in this disabling disorder, and cardiovascular risk factors have emerged as the major cause of mortality in schizophrenia.[1,2,4] Hence, identification, prevention, and modification of the cardiovascular risk factors should be one of the important therapeutic objectives in the management of schizophrenia. To help the psychiatrists to focus more on these cardiovascular risks in patients with schizophrenia, the concept of Metabolic Syndrome (MetS) has received a lot of attention in psychiatric literature.

The mechanism underlying increased prevalence of MetS among patients with schizophrenia is not well understood. A number of explanations like lifestyle and dietary habits that facilitate the development of obesity among patients with schizophrenia, direct antipsychotic drug action on lipid and carbohydrate metabolism,[5] the tendency to accumulate intra-abdominal adiposity and fat,[6] certain alterations of the hypothalamic pituitary-adrenal axis (HPA) producing hypercortisolemia,[7] and its genotypic

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expression in the form of truncal obesity, poor blood glucose control,[8] and possible associated alterations in hippocampal volume[9] have been proposed.

This review aims to update the existing knowledge regarding prevalence of MetS and its correlates in schizophrenia. For this review, search of electronic databases and manual search of relevant publications or cross references were done. The electronic search engines PUBMED, Sciencedirect, and Google Scholar were searched using the key words like schizophrenia, psychosis, metabolic syndrome, metabolic disturbances, glucose metabolism, obesity, dyslipidemia, and antipsychotics in various combinations. The search was limited to articles published in English. Cross-searches of key references (both electronic and hand-search) often yielded other relevant material. If articles published in any other language were found during the searches of cross references, then these were also included. Abstracts of all the relevant articles were initially reviewed by the first and the second author and only those articles reporting research findings were evaluated further.

PREVALENCE OF METABOLIC SYNDROME IN SCHIZOPHRENIA

Cross-sectional studies

Numerous studies from different countries and ethnic backgrounds have reported the prevalence of MetS in patients with schizophrenia. Though a few researchers have studied the change in prevalence rates over time, largely the estimates have been cross-sectional. Amongst the cross sectional studies, as depicted in Table 1,[10-99] most studies have evaluated the patients who are already on treatment and only a few have assessed the prevalence of MetS in drug naive population. Most of the studies have used National Cholesterol Education Program-Third Adult Treatment Panel (NCEP-ATP-III) criteria for estimating the prevalence rates. Some of the studies have used more than one definition for MetS and show comparable figures for the prevalence of MetS with more than one definition.[12,19,25,26,35-37,39,52,61,73,74,83,95] The sample sizes in studies evaluating the patients already on treatment have varied from 20 to 2,270 patients and the prevalence rates of MetS vary widely from 11% to 69% across different studies. The sample size in the drug naive patients has been less than 100 and prevalence has ranged from 4% to 26%. Most of the authors have limited themselves to patients with schizophrenia; however, few have included patients with schizoaffective disorder[20,21,42,44,59,63,72,83,88] and schizophreniform psychosis.[69]

Very few studies have employed proper control groups and studies, which have done so, suggest that the prevalence of metabolic syndrome appears to be higher in schizophrenia than in healthy controls[39,54,81] and comparable to other disorders such as Bipolar affective disorder (BPAD).[14,23,24,30,80,88] Some of the studies have been limited to patients with clozapine and suggest a prevalence of MetS in patients of clozapine to vary from 46% to 62%.[18,35,54,86]

Longitudinal studies

Assessing MetS over a period of time in the same set of patients can help us in understanding the etiological causes responsible for the same, especially the antipsychotic medications. Keeping this in mind many authors have evaluated the drug naïve patients with schizophrenia at the baseline and have followed up them over varying period of time to see the changes in the prevalence of MetS. As shown in Table 2,[100-118] studies involving the drug naïve patients suggest that the prevalence of MetS vary from 0% to 14% at the baseline, which increases to as high as 52.4% by 3 months of antipsychotic medication.[104]

The studies which have taken medicated patients at baseline have followed different study designs. While some have just followed up patients on the same antipsychotics that they have been receiving at baseline,[106,107,111,113] a few have reported the change in prevalence rate after change in antipsychotic.[112,114,116,117] Some of the studies have evaluated the effect of various antipsychotics by randomizing the study sample to different antipsychotic medications.[109,110,118] While most of the studies have included adult patients, two studies longitudinally evaluated MetS in pediatric population.[100,114] Goeb *et al.*, 2010[100] followed up 26 children and adolescents with early onset schizophrenia on risperidone for a period of 6 months. None of the children had MetS at baseline or end of 6 months. Maayan and Vakhruseva, 2010[114] followed up eight children on risperidone for a period of 8 weeks. While none of the children had MetS at baseline, one child developed MetS at the end of 8-week-period.

PREDICTORS OF METS IN SCHIZOPHRENIA

Socio-demographic predictors of metabolic syndrome in schizophrenia

Although many attempts have been made to study the sociodemographic predictors of MetS in patients with schizophrenia, none of the sociodemographic variable has emerged as a consistent predictor of MetS. Among the various sociodemographic variables, many studies have shown higher prevalence of MetS in those who are older.[11,14,15,18,19,30,36,39,40,44,52,54,61,63,64,74,82,83,87,95,98] Kang *et al.*, 2011[48] showed that the relationship of older age with MetS was limited only to males. There

Table 1: Prevalence of MetS in patients with schizophrenia across different cross-sectional studies

Author	Sample	Country	Criteria for MetS	Prevalence of MetS in schizophrenia (%)	Prevalence of MetS in control group (%)
Almeras et al.[10]	42-O 45-R	Canada	NCEP ATP III	33 11	
Arango et al.[11]	1452	Spain	NCEP ATP III	24.6	
Azanza et al.[12]	139	Spain	NCEP ATP III IDF	M-59 F-58 M-71 F-66	
Bai et al.[13]	567	Taiwan	NCEP ATP III	24 C-28, O-24, R-19	
Basu et al.[5]	33 (Schizoaffective)	USA	NCEP ATP III	42	
Baptista et al.[14]	253-Schizophrenia 182-BPAD 617-Other disorders 271-General population	Venezuela	NCEP ATP III	21	29 BPAD 21 Other disorders 27 General population
Bobes et al.[15]	1452	Spain	NCEP ATP III	25	
Boke et al.[16]	231	Turkey	IDF	32	
Bernardo et al.[17]	733	Spain	ADA	24	
Brunero et al.[18]	73 (Clozapine)	Australia	IDF	62	
Cerit et al.[19]	100	Turkey	ATP III ATP III-A IDF	21 34 41	
Cerit et al.[20]	242 (Included BPAD and Schizoaffective)	Turkey	NCEP ATP III	48	
Cohn et al.[21]	240 (Included Schizoaffective)	Canada	NCEP ATP III	M=43 F=48	
Corell et al.[22]	174 (Schizophrenia) 75 (BPAD) 76 (Depression)	USA	NCEP ATP III	50-Polytherapy 34-Monotherapy	
Correll et al.[23]	111 (Schizophrenia 74 (BPAD)	USA	NCEP ATP III	46	43 in BPAD
Correll et al.[24]	871 (Schizophrenia) 1093 (BPAD)	USA	NCEP ATP III	52	54 in BPAD
Dehert et al.[25]	430	Belgium	NCEP ATP III NCEP ATP III A IDF	28 32 36	
Dehert et al.[26]	415	Belgium	ATP III, ATP III A, IDF	Duration of illness <10 yrs= (21,25,28) 10-20 yrs= (35,40,42) >20 yrs= (37,44,49)	
DeHert et al.[27]	238	Belgium	M-NCEP ATP-III	20 incidence	
DeHert et al.[28]	2270	Europe	M-NCEP ATP-III	34	
Ellingrod et al.[29]	58	USA	NCEP ATP III	40	
Ellingrod et al.[30]	127 Schizophrenia 110 BPAD	USA	NCEP ATP III	46	35 in BPAD
Fan et al.[31]	199	USA	M-NCEP ATP-III	54	
Falissard et al.[32]	2270	France	M-NCEP ATP-III	37 (SGA) 31 (FGA)	
Ferreira et al.[33]	125	Europe	NCEP ATP III	21	
Gordon et al.[34]	261	Brazil	NCEP ATP III	29	
Grover et al.[35]	100 (Clozapine)	India	IDF ATP III	46 47	
Grover et al.[36]	227	India	IDF ATP III	43.6 44.5	
Grover et al.[37]	126	India	IDF ATP III	34 36	62 BPAD
Gulzar et al.[38]	56	Ireland	IDF	62	
Guveli et al.[39]	162	Istanbul	ATP III ATP III-A IDF	32 36 42	5.4 5.4 7.1 (Control Group)

Contd...

Table 1: Contd...

Author	Sample	Country	Criteria for MetS	Prevalence of MetS in schizophrenia (%)	Prevalence of MetS in control group (%)
Hatata *et al*.[40]	63	Egypt	IDF	38	
Hagg *et al*.[41]	269	Sweden	NCEP ATP III	35	
Hanssens *et al*.[42]	386 (Schizophrenia and schizoaffective)	Belgium	NCEP ATP III	29	
Heiskanen *et al*.[43]	35	Finland	NCEP ATP III	37	
Huang *et al*.[44]	650 (Schizoaffective)	Taiwan	M-NCEP ATP III	35	
James *et al*.[45]	-	Nigeria	-	19	
Kagal *et al*.[46]	80	India	NCEP ATP	35	
Kang *et al*.[47]	146 (Clozapine)	Korea	M-NCEP ATP III	47	
Kang *et al*.[48]	957	Korea	M-NCEP ATP III	43	
Kato *et al*.[49]	48	-	NCEP ATP III	63	
Kim *et al*.[50]	96	Korea	NCEP ATP III	43	
Krane-Gartiser *et al*.[51]	170	Denmark	-	48	
Kaya *et al*.[52]	87	Turkey	ATP	30	
			ATP III A	36	
			IDF	42	
Kurt *et al*.[53]	296	Turkey	IDF	19	
Lamberti *et al*.[54]	93 (Clozapine)	USA	NCEP ATP III	54	Healthy control: 21
Larsen *et al*.[55]	582	Denmark	NCEP ATP III	43	
Lee *et al*.[56]	145	Korea	M-NCEP ATP III	32	
Lee *et al*.[57]	100	Singapore	AHA	46	
Lee *et al*.[58]	-	Korea	-	35-47	
Lindenmeyer *et al*.[59]	159 (Schizophrenia, schizoaffective)	USA	NCEP ATP III	53	
Lin *et al*.[60]	382	Taiwan	IDF	M: 19-24; F: 29-43	
			NCEP ATP III	M: 26-29; F: 37-44	
McEvoy *et al*.[61]	689	USA	NCEP ATP III	41	
Maslov *et al*.[62]	205	Bosnia Croatia	ATP III	46	
Medeiros-Ferreira *et al*.[63]	76 (Schizophrenia and Schizoaffective)	Europe	NCEP ATP III	37	
Meyer *et al*.[64]	1231	USA	NCEP ATP III	36	
Meyer *et al*.[65]	80	USA	M-NCEP ATP III	51	
Misawa *et al*.[66]	334	Japan	NCEP ATP III	22	
Nurjono and Lee[67]	100	Singapore	-	46	
Oyekcin *et al*.[68]	34	Turkey	NCEP ATP III	35	
Phutane *et al*.[69]	56 (Schizophrenia, Schizoaffective and schizophreniform)	USA	NCEP ATP III	20	
Rahman *et al*.[70]	20	Malaysia	IDF	15	BPAD: 42
Rejas *et al*.[71]	1452	USA	NCEP ATP III	25	
			M-NCEP ATP III	26	
Rivas *et al*.[72]	122 (Schizophrenia plus Schizoaffective)	Florida	-	29.5	
Rezaei *et al*.[73]	372	Iran	ATP III	27	
			ATP III A	38	
			IDF	39	
Roshdy[74]	181	Kuwait	ATP III	19	
			ATP III-A	23,	
			IDF	25	
Said *et al*.[75]	270	Malaysia	NCEP ATP III	47	
Saari *et al*.[76]	31: Schizophrenia 22: Healthy control 5455: Other psychosis	Finland	NCEP ATP III	Schizophrenia: 19 Healthy control: 6 Other psychosis: 5	
Schorr *et al*.[77]	433	Netherlands	NCEP ATP-III	34	
Schorr *et al*.[78]	260	Netherlands	NCEP ATP-III	35	
Srisurapanont *et al*.[79]	57	Thailand	IDF	23	

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Table 1: Contd...

Author	Sample	Country	Criteria for MetS	Prevalence of MetS in schizophrenia (%)	Prevalence of MetS in control group (%)
Sicras *et al*.[80]	178	Spain	NCEP ATP III	26	BPAD: 25
Subashini *et al*.[81]	131 (Schizophrenia) 524 (Healthy control)	India	IDF	34	Healthy control=24
Straker *et al*.[82]	56	USA	NCEP ATP III	29	
Sugawara *et al*.[83]	1186 (Schizophrenia and Schizoaffective)	Japan	NCEP ATP-III A IDF JASSO	27 25 18	
Sugawara *et al*.[84]	759 (Inpatients) 427 (Outpatients)	Japan	M-NCEP ATP III	16 48	
Suvisaari *et al*.[85]	8028	Finland	NCEP ATP III	36	Healthy control: 30
Steylen *et al*.[86]	50 (Clozapine)	Venray, Rottedam	NCEP ATP III	58	
Sweileh *et al*.[87]	250	Palestine	NCEP ATP III	44	
Teixeira and Rocha[88]	44 (Schizophrenia plus+Schizoaffective)	Brazil	NCEP ATP III	32	38 (BPAD) 48 (Depression) 5 (Alcohol dependence) 23 Other psychiatric disorders
Tirupati and Chua[89]	231	Australia	IDF	69	
Van Der Heiden *et al*.[90]	452 (Schizophrenia and other psychotic disorders)	Netherlands	NCEP ATP III	50	
Van Winkel *et al*.[91]	518	Belgium	M-NCEP ATP III	33	
Van Winkel *et al*.[92]	503: Schizophrenia 112: BPAD 92: Schizoaffective	Belgium	M-NCEP ATP III	29	BPAD: 23 Schizoaffective: 50
Vancampfort *et al*.[93]	106	Belgium	NCEP ATP III	35	
Vuksan Cusa *et al*.[94]	46-Psychosis 36-BPAD	Croatia	NCEP ATP III	37	31 in BPAD
Yaziki *et al*.[95]	319	Netherlands	ATP III ATP III A IDF	34 37 42	
Yoon *et al*.[96] Drug Naïve Patients	214	Korea	NCEP ATP III	23	
Padmavati *et al*.[97]	51	India	IDF	4	
Pallava *et al*.[98]	50	India	IDF	26	50 in medicated group
Grover *et al*.[99]	47	India	IDF M-ATP III	11 13	

NCEP ATP-III – National cholesterol education program-Third adult treatment panel-III; M-NCEP ATP-III – Modified national cholesterol education program-Third adult treatment panel-III; IDF – International diabetes federation; AHA – American heart association; JASSO – Japan society for the study of obesity; O – Olanzapine; C – Clozapine; R – Risperidone; M – Males; F – Females

is no conclusive evidence regarding the relationship of gender with MetS. Some studies have reported that MetS is more common in females,[16,44,64,73,87-89] while others have reported no gender differences in the prevalence rates of MetS[10,15,18,31,41,54,82] and only a few studies have reported higher prevalence in males.[96,111] Occasional studies have reported association of MetS with higher education level,[35,98] urban background,[38] employed status,[37,38] and marital status.[11,37]

Clinical predictors of metabolic syndrome in schizophrenia

While a longer duration of illness has been demonstrated to be associated with higher prevalence of MetS in some of the studies,[10,19,36,39,50,87] some studies have shown

no association of MetS and duration of illness.[52,96] Another clinical variable inconclusively associated with MetS is age of onset with Yaziki *et al*.[95] demonstrating the prevalence to be higher in those with late age at onset of illness, while Kaya *et al*.[52] refuting such an association. Old age at hospitalization[95] and more number of hospital admissions[11] have also been shown to be associated with MetS. Similarly, smoking has been inconsistently associated with presence of MetS; with some studies reporting higher prevalence of MetS in patients who smoke[30,87] while others have reported no association between MetS and smoking.[18,38,54] Poor lifestyle habits are associated with MetS,[45] but data with regards to the level of exercise in patients with and without MetS in inconclusive.[11,38]

Table 2: Prevalence of MetS in longitudinal studies

Author	Sample	Country	Criteria for MetS	Prevalence of MetS in schizophrenia	
				Baseline (%)	Follow up (%)
Studies with Drug Naïve patients at the Baseline					
Goeb *et al*.[100]	26	France	NCEP ATP III	0	6 months=0
Dehert *et al*.[101]	122 Historic cohort	Belgium	NCEP ATP III	5.7	3.7 yrs: 13
	108 Current cohort			5.6	3.2 yrs: 32
Medved *et al*.[102]	94	Croatia	NCEP ATP III	14	3 months: 25
Sahoo *et al*.[103]	21	India	IDF	9.5	3 months: 52.4
Sahoo *et al*.[104]	30	India	IDF	3.3	3 months: 31.81
Sahoo *et al*.[105]	99	India	IDF		Endpoint (6 weeks): 18.2 10.1
			ATP III		
Studies with patients already on psychotropics at the Baseline					
Attux *et al*.[106]	44	Brazil	NCEP ATP III	2.2	6 months on same treatment: 9.1
Chiu *et al*.[107]	33	Taiwan	-	-	8 wks after switching to O: 33
Fleischhacker *et al*.[108]	-	Austria	-	6	52 weeks on same treatment: Increased
Gautam and Meena[109]	120 Mixed group-Drug naïve/ off treatment for 6 months	-	ATP-III	-	4 months: New MetS-O: 23.3; R: 10; C: 13.3; H: 0
Krakowski *et al*.[110]	93	USA	NCEP ATP III	-	12 weeks: New MetS C-60; O-21; R-23
Kraemer *et al*.[111]	Mixed group	-	AHA/NHLB	44.3 Drug naive: 25	3 months after initiation or switch of antipsychotic: 49.6
Lin *et al*.[112]	46 (Schizophrenia and schizoaffective)	Taiwan	NCEP ATP III	65	1 year after switching from SGA to amisulpride: 30
Malhotra *et al*.[113]	53	India	IDF	32	6 months on same treatment 41
			ATP III	32	41
			Prevalence without pre-existing HTN and DM	30	41
Maayan and Vakhruseva[114]	8	USA	M-NCEP ATP III	None	8 wks continuing on R: 12.5
Meyer *et al*.[115]	660	USA	NCEP ATP III	37 O: 35 Z: 38 R: 31 Q: 37	3 months: 51 O: 44 Z: 30 R: 31 Q: 38
Meyer and Pandira[116]	71 (Schizophrenia plus schizoaffective)	USA	NCEP ATP III	53 on olanzapine	20 weeks after switching to risperidone 36
Nebhinani *et al*.[117]	60	India	Consensus definition	33	3 months after clozapine: 53.3
Patel *et al*.[118]	400	USA	NCEP ATP III	4	52 weeks: 19

NCEP ATP-III – National cholesterol education program-Third adult treatment panel-III; M-NCEP ATP-III – Modified national cholesterol education program-Third adult treatment panel-III; IDF – International diabetes federation; AHA – American heart association; O – Olanzapine; R – Risperidone; Z – Ziprasidone; Q – Quetiapine; C – Clozapine; H – Haloperidol

Psychotropics and metabolic syndrome in schizophrenia

Use of atypical antipsychotics has been cited as one of the reason for increased prevalence of MetS in schizophrenia. Literature suggests that the prevalence of MetS is in the range of 3-26%[98,104] in drug naïve patients with schizophrenia, while the same reaches up to 69% in medicated patients.[89] Pallava *et al*.[98] compared the prevalence rates between drug naïve patients and those on treatment and demonstrated that the prevalence was nearly double in those on treatment. Studies that have followed up drug naïve patients after institution of antipsychotics have demonstrated increment of prevalence rate ranging from 7% to 42% over a period ranging from 3 months

to 4 years. Though many authors have failed to demonstrate an association of MetS with a specific atypical antipsychotic,[34,38,39,43,51,82,96] or the mean chlorpromazine (CPZ) dose,[50] still there is some evidence to suggest that atypical antipsychotics do differ in their propensity to cause metabolic syndrome. Highest association was seen with clozapine and olanzapine in cross-sectional studies.[10,75] Longitudinal studies have also demonstrated that the patients on clozapine and olanzapine are more likely to develop metabolic syndrome when compared to other atypical antipsychotics.[101,109,111,118] In a study done by Dehert *et al*.[101] data from an historic cohort of consecutively admitted first episode patients with schizophrenia treated with typical antipsychotics were compared

with an age and sex matched series of consecutive first episode patients treated only with atypical antipsychotics. Rates of MetS were compared at baseline and after 3 years of treatment exposure. At first episode, there was no difference in the prevalence of MetS between the historic and the current cohort. Rates of MetS increased over time in both groups, but patients started on atypical antipsychotics had a three times higher incidence rate of MetS. The difference between the two groups was no longer significant when patients started on clozapine and olanzapine were excluded. Gautam and Meena[109] randomized 120 patients with schizophrenia who were either drug naive or had not received any antipsychotic in the last 6 months into four treatment groups receiving haloperidol, olanzapine, clozapine, and risperidone and followed up the patients for 4 months. None of the patients in the haloperidol group developed MetS, 23.3%, 10%, and 13.3% of the patients developed metabolic syndrome in olanzapine, risperidone, and clozapine group, respectively. In another study[111] 110 patients with schizophrenia on antipsychotics were randomized to three groups receiving clozapine, olanzapine, and haloperidol. This study reported that the incidence of metabolic syndrome over a period of 12 weeks was significantly higher in clozapine as compared to the other two antipsychotics. Meyer *et al*.[115] estimated the prevalence rates of MetS in patients with schizophrenia included in Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) trial twice at an interval of 3 months and demonstrated a significant increase in incidence of MetS in olanzapine group when compared to perphenazine, quetiapine or risperidone group. Also, a significant reduction by 8% was observed in ziprasidone group over a period of 3 months. Patel *et al*.[118] also demonstrated that a higher proportion of patients in olanzapine group developed MetS as compared to quetiapine and perphenazine over a period of 1 year. Nebhinani *et al*., 2013[117] estimated the prevalence of MetS in patients with schizophrenia on antipsychotics before and 3 months after switching them to clozapine, and reported the prevalence to increase from 33.3% to 53.3%. Lin *et al*.[112] followed up patients after switching from an atypical antipsychotic to amisulpride and demonstrated a decrease in prevalence of MetS from 65% to 30% within a year. Meyer and Pandira[116] followed up 71 patients with schizophrenia of schizoaffective disorder for 20 weeks after switching from olanzapine to risperidone and demonstrated that the prevalence rates decreased from 53% to 36%, suggesting a differential effect of antipsychotics on development of MetS.

Though many of the aforementioned studies have demonstrated higher risk of MetS with atypical, however, many authors have also concluded that atypical or typical antipsychotics do not differ in their propensity to cause MetS.[22,28,31] Few studies, which have measured the prevalence of MetS in patients receiving clozapine suggest that the presence of MetS is not dependent on dose and duration.[18,86] While there is some evidence to suggest association of MetS with polypharmacy,[22,44,66] a few authors have refuted such association.[32,51] There is no conclusive evidence regarding the association of duration of antipsychotic use with MetS. Though multiple studies have demonstrated that the duration of treatment does not influence the prevalence,[11,54,64] a few have demonstrated a definite relationship of MetS with the duration of treatment.[19,50,54]

Biological correlates of metabolic syndrome in schizophrenia

Some researchers have attempted to identify biological markers for MetS in schizophrenia and have shown that low levels of adiponectin,[13,42,119] low levels of leptin,[119] lower uric acid,[107] hyperhomocyseniemia,[94] high alanine transferase,[58] high white blood cell count,[120,121] high monocytes, and high C-reactive protein[121] to be associated with MetS in schizophrenia. Lee *et al*.[122] studied the association of cardiac autonomic control with MetS and failed to show any positive association.

Some authors have tried to study the genetic basis of high prevalence of MetS in schizophrenia. Methylenetetrahydrofolate reductase (MTHFR) gene has been the most often studied and a few studies have demonstrated that MTHFR 677T allele[30] and MTHFR 677C/T as compared to 677C/C allele[29] is more likely to be associated with MetS. Arg347 allele in Alpha-1A adrenergic receptor (ADRA1A)[123] has been demonstrated to be associated with a high prevalence and alpha-2A adrenergic receptor (ADRA2A) 1291-G allele with lower prevalence of MetS.[124] Similarly COMT158Val allele was shown to be associated with MetS prevalence in one of the studies.[30] Kang *et al*.[32] studied the relationship of MetS and 5-hydroxytryptamine (serotonin) receptor 2C (HTR2C), but failed to demonstrate any association.

IMPACT OF METABOLIC SYNDROME

Although studies have evaluated the prevalence of MetS in schizophrenia, there is a serious lack of data about its impact. There is inconclusive evidence that MetS influences the quality of life.[64] Some of the studies have shown that patients of schizophrenia with MetS tend to have higher residual psychopathology scores on Positive and Negative Syndrome Scale (PANSS) and Computer-generated imagery (CGI).[11] Studies have also linked presence of MetS with presence of more anxiety symptoms.[62] Others have not found

any association between MetS and symptom severity, depression, and self-rated mental health.[64]

Poor cognitive functioning has been inconsistently associated with MetS.[59,64] Patients with MetS have also been reported to have significantly lower physical health as assessed by Short Form-12 (SF-12).[64] Padmavati *et al.*, 2010[97] demonstrated that malnutrition is very common in patients with schizophrenia having MetS.

DISCUSSION

First study measuring the prevalence of MetS in schizophrenia was published in 2004 by Almeras *et al.*[10] As per this study, the prevalence rate of MetS in schizophrenia varied from 11% to 33% depending on the antipsychotic patients were receiving. Over the years, many studies have accumulated and the estimates have ranged from 15% to 69% in cross-sectional studies in medicated patients. The available research has many shortcomings. Though a few have estimated the prevalence rates in large sample sizes, most of the studies have been on small sample sizes. Secondly, most of the research has been on medicated patients. Thirdly, the research has largely been cross-sectional. There is a large variation in the prevalence rates across various countries. This can partly be explained by the fact that different definitions have been used and different cut-offs for waist circumference have been used in different ethnic populations. Among the various definition, the definition of NCEP ATP-III[125] has been the most commonly used criteria-set for defining MetS and it requires presence of at least three out five criteria (abnormal blood pressure, raised triglycerides, reduced high density lipoprotein, raised fasting blood glucose, and increased waist circumference) for diagnosing MetS. Some authors have used the criteria of International Diabetes Federation (IDF);[126] which are identical to NCEP ATP III, with a fundamental difference of mandatory requirement of fulfilment of abnormal waist circumference criteria along with presence of two other criteria. Other definitions (World Health Organization, European Group for the Study of Insulin Resistance, American Association of Clinical Endocrinology, American Heart Association)[127-130] of MetS, which have been used differ slightly in cut offs of subcomponents but most of these require the fulfilment of three criteria for the diagnosis of MetS. Recently, in an attempt to harmonize various definitions of MetS a joint interim statement of the IDF has provided a consensus definition, according to which, abdominal obesity is no more a pre-requite criterion and presence of any three of the five risk factors is sufficient for considering MetS. Additionally, in a major change from the NCEP-ATP III criteria, the consensus definitions requires use of population and country-specific cut

offs for waist circumference. Moreover, it has been suggested that while defining MetS those with established diabetes mellitus and known cardiovascular disease should be excluded so as to consider MetS as a premorbid condition to predict the development of diabetes mellitus and cardiovascular disease in future as once diabetes develops MetS is invariably present.[131]

WHAT CAN BE CONCLUDED FROM THE DATA?

Review of the available data suggests that MetS is fairly prevalent in patients with schizophrenia. The prevalence rate is similar to other severe mental illness like BPAD and other psychotic conditions and is much higher than that seen in general population or healthy controls.[39,54,81] Though there is no causal association with any demographic or clinical variables, the risk appears to be higher in older people.[11,14,15,18,19,30,36,39,40,44,52,54,61,63,64,74,82,83,87,95,98] and in those with long duration of illness.[11,19,36,39,50,87] Effect of psychotropics on prevalence of MetS is inconclusive but there is some evidence to suggest higher association with atypical antipsychotics like clozapine and olanzapine.[101,109,111,118] Therefore, the psychiatrists should be more vigilant regarding the presence of MetS in these high risk groups. Research on biological correlates of MetS in schizophrenia is still in its primitive stage; however, data on adiponectin levels, hematological indices appear to be promising. There is some evidence base to suggest association of MetS with MTHFR and ADRA1A gene; however it is still in its juvenile phase. These areas hold promise, and targeting these with appropriate interventions may help us to prevent the occurrence of MetS in patients with schizophrenia in future.

LIMITATIONS AND FUTURE DIRECTION

The major limitations of many of the studies reviewed here are small sample size and cross-sectional study design. Even many of the longitudinal studies have included only medicated patients, hence not providing the prevalence rates in patients who have never been exposed to antipsychotics. Data with regards to the role of different antipsychotics are also scarce. In addition, very few studies have tried to study the association of MetS with demographic and clinical variables and there is hardly any data on the impact MetS has on patients with schizophrenia. Future studies should focus more on prevalence of MetS in drug naive patients and follow-up these patients longitudinally to understand the factors which contribute to development of MetS. In addition, large randomized controlled trials are warranted to compare the potential of different

antipsychotics to cause MetS. The risk factors for development of metabolic abnormalities as well as their pathophysiology in schizophrenia also need further research. Also, we need to focus on the impact MetS has on course and outcome of schizophrenia. In addition, the impact of MetS on quality of life, and psychological functioning of the patients with schizophrenia also warrants further research.

ALTERNATIVES TO METABOLIC SYNDROME IN UNDERSTANDING THE CARDIOVASCULAR MORTALITY

It has been established that when present, MetS is highly predictive of cardiovascular disease. Cardiovascular risk has also been estimated in schizophrenia using Systematic Coronary Risk Evaluation (SCORE) function[132] for cardiovascular mortality risk (CVM) (including coronary death, sudden death, stroke, aortic aneurism, and heart failure) and the Framingham function[133] to estimate the overall risk of any fatal or non-fatal coronary heart disease (CHD) (including, in addition to the fatal CHD events mentioned above, any type of angina, myocardial infarction, other type of coronary ischemia, congestive heart failure, intermittent claudication, or peripheral arterial ischemia) within 10 years. Both functions are mathematical probability models obtained using multivariate analysis techniques from follow-up studies of individuals in the general population, in which the incidence of a fatal or non-fatal CHD event is related to the individual risk factors of each subject. In the SCORE function, the CVM risk is calculated from the values for age, sex, total cholesterol, High-density lipoprotein (HDL) cholesterol, systolic blood pressure (SBP), and smoking status. The Framingham function calculates the risk from the same values as the SCORE function, but with the addition of diabetes. Some of the risk factors which estimate the cardiovascular risk as per SCORE and Framingham function are similar to those constituting MetS. Arango *et al.*[11] compared the CHD 10-year risk in patients of schizophrenia with and without MetS using both SCORE and Framingham function. Higher percentage (6.6%) of patients with MetS as against 2.8% without MetS showed high/very-high CVM risk (SCORE ≥ 3%), and 44.2% with MetS as against 12.9% without MetS showed high/very-high CV event risk (Framingham ≥ 10). Similarly, Correll *et al.*[134] reported the 10 year cardiovascular risk as per Framingham function to be significantly higher in patients with MetS. Bobes *et al.*[15] estimated mean overall 10-year cardiovascular risk in patients with schizophrenia which was 0.9 (SCORE) and 7.2 (Framingham). Eight percent and 22.1% of patients showed a high/very high risk according to SCORE

and Framingham function, which is higher than in general population. Similarly Cohn *et al.*[21] reported Framingham 10-year risk of myocardial infarction to be greater in the patients with schizophrenia as compared to general population. Correl *et al.*[23] reported Framingham 10-year risk of cardiovascular events in schizophrenia to be similar to BPAD. However, there is a need to study this area further to understand the best predictors of cardiovascular mortality in patients with schizophrenia.

DO WE NEED TO MONITOR THE SCHIZOPHRENIA FOR METABOLIC SYNDROME?

MetS is one of the primary reasons for increased mortality in patients with schizophrenia. This very fact merits routine screening of these patients for the prevalence of MetS. It is important to identify the high risk patients and educate them regarding the preventive measures. Attempts should be made to change unhealthy lifestyle like inactivity; overeating, smoking, and use of appropriate psycho-educational programs in this regard need to be developed. Although, the data with respect to association of MetS and psychotropics in schizophrenia remain inconclusive, nonetheless, a cautious approach in prescribing psychotropics is advisable. Studies in schizophrenia patients do suggest that atypical like clozapine and olanzapine pose a higher risk of metabolic abnormalities hence, due consideration should be given to their potential to cause metabolic disturbances while prescribing an agent, and whenever used, the prescription should be revised frequently to maintain a balance between appropriate control of symptoms and minimal metabolic abnormalities.

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