Editorial

Metabolic Syndrome in Schizophrenia: Theoretical, Clinical and Translational Perspectives

Metabolic syndrome in schizophrenia is in many ways, an epitome of the mind-body monism of modern psychiatry and medicine. The focus of this interaction has evolved over the last two decades from the viewpoint that this adverse-effect as mere collateral damage due to the newer antipsychotics' pharmacodynamic profile to a perspective that metabolic dysregulation might have complex and intrinsic link to schizophrenia pathogenesis. Interestingly, this association was indeed alluded to much earlier in Maudsley's work,[1] long before atypical antipsychotics came into clinical practice. Metabolic syndrome adds significantly to the morbidity of schizophrenia and is an important cause of mortality in this population.[2] In contemporary psychiatry, apart from significant clinical implications, the association between schizophrenia and metabolic syndrome has provided a fertile ground for etiological hypothesis generation and testing and has the potential toward facilitating the emergence of newer therapeutics.[3]

Studies have demonstrated that antipsychotic-naïve patients as well as relatives of patients with schizophrenia have impaired glucose tolerance and increased insulin resistance compared with the normal controls.[4,5] An exciting development in the last few years has been the paradigm shift in understanding metabolic disorders consequent to antipsychotic use. A rapidly growing evidence base, although not unequivocal, supports the hypothesis that metabolic side-effects might be intrinsically linked to the efficacy of antipsychotic medication[6] and that without these side-effects, one may not have any effects either.[7,8] Several common genetic and environmental risk factors have putatively been linked with increased risk of both schizophrenia and diabetes, which add an extra layer of complexity in understanding the interactions between these two disorders. Pathophysiological links between schizophrenia (a predominantly dopamine related condition) and metabolic diseases such as obesity, diabetes and hypertriglyceridemia (predominantly insulin related conditions) has been strengthened by independent lines of enquiry as demonstrated in recent studies. Replication of the shared genetic risk between schizophrenia and diabetes in two unrelated population samples,[9,10] both implicating the Transcription factor 7-like 2 (TCF7L2) gene (a gene that has been most consistently replicated in the risk toward type-2 diabetes mellitus[11]) have added substance to a link that was long suspected. That the gene product interacts closely with β-catenin,[12] a member of the Wnt pathway, which has been shown to be dysregulated in patients with schizophrenia, further underscores the biological significance of the finding. The expression of the β-catenin gene itself has been shown to be decreased in patients with schizophrenia.[13] The Wnt pathway is involved in cell proliferation and differentiation. Abnormalities in this pathway have been cited as evidence backing the neurodevelopmental theory of schizophrenia. Other members of the pathway like glycogen synthase kinase 3β (GSK3β) have direct interactions with Disruptedin schizophrenia 1, genetic abnormalities in which, consistently come up in an assessment of the genetic risk factors for schizophrenia.[14] GSK3β has further been shown to be involved in mediation of dopamine action and responds to antipsychotic drugs.[6]

Interestingly, GSK3β influences inflammatory pathways[15] – for example, the ones that involve Toll-like receptors,[16] which are implicated in schizophrenia pathogenesis.[17] This link is significant given the importance of immune-inflammatory aberrations of possible prenatal origin that connects schizophrenia and metabolic syndrome. Prenatal immune activation, due to various kinds of prenatal adversity has been shown to be associated with increase rates of both schizophrenia as well as diabetes.[18] Barker's hypothesis, that malnourishment during critical gestational epochs alters the function and structure of organs, perhaps permanently, but that the effects of this may not be apparent for several years,[19] helps explain how these two, apparently unrelated diseases (schizophrenia and

Access this article online	
Website: www.ijpm.info	Quick Response Code
DOI: 10.4103/0253-7176.116231	

diabetes mellitus), might have a shared pathogenesis secondary to fetal programming aberrations.[20]

In addition to these intriguing theoretical perspectives, the high prevalence of metabolic syndrome in schizophrenia and its negative effect on the life expectancy emphasizes the need for handling metabolic syndrome in a proactive and thorough manner in contemporary clinical psychiatry.[21] Metabolic syndrome adversely impacts the quality-of-life[22] and its association with other complications like obstructive sleep apnea syndrome further add to the clinical burden. Various factors including lack of knowledge among physicians, patients' and caregivers' attitude toward an increase in weight and often difficult clinical situation act as barriers to implement effective interventions to ameliorate this challenging co-morbidity.[23] The importance of intensive monitoring and early intervention, therefore, cannot be overemphasized.[24] Using the lowest effective dose of antipsychotic, healthy life-style advice and judicious switching between antipsychotics are considered as the most commonly used strategies to handle metabolic complications. Nonetheless, clinicians are, oftentimes, caught between the devil and the deep blue sea when the offending drug has proven to be the most effective in ensuring control of psychotic symptoms. Apart for optimizing the choice as well as the dose of antipsychotics, various add-on medication options are available to treat metabolic syndrome in schizophrenia. For instance, metformin[25] and topiramate[26] have been used quite a lot and often successfully in the management of metabolic problems. The consistency of their efficacy, however, is moderate at best. Recently, approved drugs and combinations such as lorcaserin and topiramate-phentermine combination may help widen the narrow pharmacological repertoire available to a clinician.[27] Interestingly, micronutrients, especially vitamin B_{12}, have been shown to be involved in mediation between insulin resistance and inflammation.[28] Investigating for and correcting vitamin B_{12} deficiency in those who develop metabolic side-effects may prove useful. In addition, there is preliminary evidence for use of immune modulators like minocycline, which may help in the treatment of metabolic complications as well as cognitive and negative symptoms of schizophrenia.[29-31] A healthy balance and prioritization of management issues – symptom control vis-à-vis decreasing the side-effect burden along with an open discussion involving the patient and caregivers often facilitates effective management.[32]

However, it is important to be mindful that these pharmacological strategies need to be complemented with adequate life-style changes like diet management and regular physical exercise to achieve enduring clinical impact. The benefit of regular physical exercise in schizophrenia as a whole and in the presence of metabolic complications in particular cannot be overstated. A recent Cochrane review has summarized the "healthful effects on both the physical and mental health and well-being of individuals with schizophrenia."[33] Exercise aids the individual at many levels. It has a positive impact on symptom control, cognition, immunological parameters and brain protective molecules like brain derived neurotrophic factor and is directly effective in treatment of metabolic complications.[34] That exercise may have a positive stabilizing influence of all links between schizophrenia and metabolic disorders, in the absence of side-effects makes it an attractive therapeutic strategy, which is often underutilized. Yoga - as a combination of life-style modification and physical exercise also has similar beneficial potential, which was validated in a recently published systematic review.[35]

In summary, the interaction between metabolic syndrome and schizophrenia opens up investigative opportunities right from the epidemiological and clinical level to the molecular. In times to come, the common links can potentially unravel the complex etiology of these disorders. At the very least, exploration of molecular links will lead to more targeted, more selective drug targets. One may, at least theoretically, expect to find different isoforms of second messengers, which mediate dopamine and insulin action. Selective action on one, without disturbing the other signaling systems may therefore help in management of symptoms of schizophrenia without invoking the metabolic dysregulation. Until such a time, metabolic complications in schizophrenia are likely to persist as a necessary evil and hence proactive clinical assessment and intervention is of paramount significance in contemporary treatments strategies for schizophrenia.[7]

ACKNOWLEDGMENT

SMA is supported by Wellcome Trust/DBT India Alliance. This work is supported by the Wellcome Trust/DBT India Alliance Senior Fellowship Research Grant to GV.

Sri Mahavir Agarwal[1,2], Ganesan Venkatasubramanian[1,2]

[1]Department of Psychiatry, The Metabolic Clinic in Psychiatry, National Institute of Mental Health and Neurosciences, [2]Translational Psychiatry Laboratory, Cognitive Neurobiology Division, Neurobiology Research Centre, National Institute of Mental Health and Neurosciences, Bangalore, Karnataka, India
E-mail: venkat.nimhans@yahoo.com

REFERENCES

1. Maudsley H. The Pathology of Mind. 3rd ed. London: Macmillan; 1979.
2. Tandon R, Nasrallah HA, Keshavan MS. Schizophrenia, "just the facts" 4. Clinical features and conceptualization. Schizophr Res 2009;110:1-23.
3. Altar CA, Hunt RA, Jurata LW, Webster MJ, Derby E, Gallagher P, *et al*. Insulin, IGF-1, and muscarinic agonists modulate schizophrenia-associated genes in human neuroblastoma cells. Biol Psychiatry 2008;64:1077-87.
4. Fernandez-Egea E, Bernardo M, Parellada E, Justicia A, Garcia-Rizo C, Esmatjes E, *et al*. Glucose abnormalities in the siblings of people with schizophrenia. Schizophr Res 2008;103:110-3.
5. Venkatasubramanian G, Chittiprol S, Neelakantachar N, Naveen MN, Thirthall J, Gangadhar BN, *et al*. Insulin and insulin-like growth factor-1 abnormalities in antipsychotic-naive schizophrenia. Am J Psychiatry 2007;164:1557-60.
6. Girgis RR, Javitch JA, Lieberman JA. Antipsychotic drug mechanisms: Links between therapeutic effects, metabolic side effects and the insulin signaling pathway. Mol Psychiatry 2008;13:918-29.
7. Venkatasubramanian G. The 'boon and bane' of antipsychotic-induced metabolic syndrome. Acta Psychiatr Scand 2009;120:500-1.
8. Venkatasubramanian G, Chittiprol S, Neelakantachar N, Shetty TK, Gangadhar BN. A longitudinal study on the impact of antipsychotic treatment on serum leptin in schizophrenia. Clin Neuropharmacol 2010;33:288-92.
9. Hansen T, Ingason A, Djurovic S, Melle I, Fenger M, Gustafsson O, *et al*. At-risk variant in TCF7L2 for type II diabetes increases risk of schizophrenia. Biol Psychiatry 2011;70:59-63.
10. Alkelai A, Greenbaum L, Lupoli S, Kohn Y, Sarner-Kanyas K, Ben-Asher E, *et al*. Association of the type 2 diabetes mellitus susceptibility gene, TCF7L2, with schizophrenia in an Arab-Israeli family sample. PLoS One 2012;7:e29228.
11. Tong Y, Lin Y, Zhang Y, Yang J, Zhang Y, Liu H, *et al*. Association between TCF7L2 gene polymorphisms and susceptibility to type 2 diabetes mellitus: A large human genome epidemiology (HuGE) review and meta-analysis. BMC Med Genet 2009;10:15.
12. Cauchi S, Froguel P. TCF7L2 genetic defect and type 2 diabetes. Curr Diab Rep 2008;8:149-55.
13. Cotter D, Kerwin R, al-Sarraji S, Brion JP, Chadwich A, Lovestone S, *et al*. Abnormalities of Wnt signalling in schizophrenia – Evidence for neurodevelopmental abnormality. Neuroreport 1998;9:1379-83.
14. Bradshaw NJ, Porteous DJ. DISC1-binding proteins in neural development, signalling and schizophrenia. Neuropharmacology 2012;62:1230-41.
15. Rayasam GV, Tulasi VK, Sodhi R, Davis JA, Ray A. Glycogen synthase kinase 3: More than a namesake. Br J Pharmacol 2009;156:885-98.
16. Hofmann C, Dunger N, Schölmerich J, Falk W, Obermeier F. Glycogen synthase kinase 3-β: A master regulator of toll-like receptor-mediated chronic intestinal inflammation. Inflamm Bowel Dis 2010;16:1850-8.
17. Venkatasubramanian G, Debnath M. The TRIPS (Toll-like receptors in immuno-inflammatory pathogenesis) hypothesis: A novel postulate to understand schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry 2013;44:301-11.
18. Kinney DK, Hintz K, Shearer EM, Barch DH, Riffin C, Whitley K, *et al*. A unifying hypothesis of schizophrenia: Abnormal immune system development may help explain roles of prenatal hazards, post-pubertal onset, stress, genes, climate, infections, and brain dysfunction. Med Hypotheses 2010;74:555-63.
19. Osmond C, Barker DJ. Fetal, infant, and childhood growth are predictors of coronary heart disease, diabetes, and hypertension in adult men and women. Environ Health Perspect 2000;108 Suppl 3:545-53.
20. Bale TL, Baram TZ, Brown AS, Goldstein JM, Insel TR, McCarthy MM, *et al*. Early life programming and neurodevelopmental disorders. Biol Psychiatry 2010;68:314-9.
21. Hennekens CH, Hennekens AR, Hollar D, Casey DE. Schizophrenia and increased risks of cardiovascular disease. Am Heart J 2005;150:1115-21.
22. von Hausswolff-Juhlin Y, Bjartveit M, Lindström E, Jones P. Schizophrenia and physical health problems. Acta Psychiatr Scand Suppl 2009;438:15-21.
23. Hasnain M, Fredrickson SK, Vieweg WV, Pandurangi AK. Metabolic syndrome associated with schizophrenia and atypical antipsychotics. Curr Diab Rep 2010;10:209-16.
24. De Hert M, Vancampfort D, Correll CU, Mercken V, Peuskens J, Sweers K, *et al*. Guidelines for screening and monitoring of cardiometabolic risk in schizophrenia: Systematic evaluation. Br J Psychiatry 2011;199:99-105.
25. Wang M, Tong JH, Zhu G, Liang GM, Yan HF, Wang XZ. Metformin for treatment of antipsychotic-induced weight gain: A randomized, placebo-controlled study. Schizophr Res 2012;138:54-7.
26. Hahn MK, Cohn T, Teo C, Remington G. Topiramate in schizophrenia: A review of effects on psychopathology and metabolic parameters. Clin Schizophr Relat Psychoses 2013;6:186-96.
27. Henry RR, Chilton R, Garvey WT. New options for the treatment of obesity and type 2 diabetes mellitus (narrative review). J Diabetes Complications 2013;pii: S1056-8727 (13) 00106-2.
28. Chen AR, Zhang HG, Wang ZP, Fu SJ, Yang PQ, Ren JG, *et al*. C-reactive protein, vitamin B12 and C677T polymorphism of N-5,10-methylenetetrahydrofolate reductase gene are related to insulin resistance and risk factors for metabolic syndrome in Chinese population. Clin Invest Med 2010;33:E290-7.
29. Soory M. A role for non-antimicrobial actions of tetracyclines in combating oxidative stress in periodontal and metabolic diseases: A literature review. Open Dent J 2008;2:5-12.
30. Levkovitz Y, Mendlovich S, Riwkes S, Braw Y, Levkovitch-Verbin H, Gal G, *et al*. A double-blind, randomized study of minocycline for the treatment of negative and cognitive symptoms in early-phase schizophrenia. J Clin Psychiatry 2010;71:138-49.
31. Jhamnani K, Shivakumar V, Kalmady S, Rao NP, Venkatasubramanian G. Successful use of add-on minocycline for treatment of persistent negative symptoms in schizophrenia. J Neuropsychiatry Clin Neurosci 2013;25:E06-7.
32. Morrison AP, Hutton P, Shiers D, Turkington D. Antipsychotics: Is it time to introduce patient choice? Br J Psychiatry 2012;201:83-4.
33. Gorczynski P, Faulkner G. Exercise therapy for schizophrenia. Cochrane Database Syst Rev 2010;(5):CD004412.
34. Knöchel C, Oertel-Knöchel V, O'Dwyer L, Prvulovic D, Alves G, Kollmann B, *et al*. Cognitive and behavioural effects of physical exercise in psychiatric patients. Prog Neurobiol 2012;96:46-68.

35. Vancampfort D, Vansteelandt K, Scheewe T, Probst M, Knapen J, De Herdt A, *et al*. Yoga in schizophrenia: A systematic review of randomised controlled trials. Acta Psychiatr Scand 2012;126:12-20.

How to cite this article: Agarwal SM, Venkatasubramanian G. Metabolic syndrome in schizophrenia: Theoretical, clinical and translational perspectives. Indian J Psychol Med 2013;35:117-20.