Schizophrenia is associated with increased risk for type 2 diabetes mellitus, resulting in elevated cardiovascular risk and limited life expectancy, translated into a weighted average of 14.5 years of potential life lost and an overall weighted average life expectancy of 64.7 years. The exact prevalence of type 2 diabetes among people with schizophrenia varies across studies and ranges 2–5 fold higher than in the general population, whereas the aetiology is complex and multifactorial. Besides common diabetogenic factors, applied similarly in the general population, such as obesity, hyperlipidemia, smoking, hypertension, poor diet and limited physical activity, the co-occurrence of schizophrenia and diabetes is also attributed to unique conditions. Specifically, excessive sedentary lifestyle, social determinants, adverse effects of antipsychotic drugs and limited access to medical care are considered aggravating factors for diabetes onset and low quality of diabetes management. Schizophrenia itself is further proposed as causal factor for diabetes, given the observed higher prevalence of diabetes in young patients, newly diagnosed with schizophrenia and unexposed to antipsychotics. Furthermore, studies support genetic predisposition to diabetes among people with schizophrenia, suggesting shared genetic risk and disclosing a number of overlapped risk loci. Therefore, special attention should be paid in preventing diabetes in people with schizophrenia, through intervention in all possible modifiable risk factors. Implementation of careful antipsychotic prescription, provision of adequate motivation for balanced diet and physical activity and facilitating access to primary health care, could serve in reducing diabetes prevalence. On the other hand, increasing calls are made for early diagnosis of diabetes, application of the appropriate anti-diabetic therapy and strict inspection of therapy adherence, to limit the excess mortality due to cardiovascular events in people with schizophrenia. Moreover, population health programs could help counseling and preventing diabetes risk, additionally to early screening and diagnosis set, aiming to reduce disparities in populations. Finally, mental health-care providers might greatly promote offered health services to patients with schizophrenia, through a holistic individualized approach, considering additionally the physical health of the patients and working closely, preventively and therapeutically, in collaboration with the physicians and diabetologists.

Key words: Schizophrenia, type 2 diabetes, antipsychotics, prevention.
Introduction

The comorbidity between schizophrenia and increased prevalence of type 2 diabetes mellitus is well established in many different studies on clinical samples, attributed to lifestyle habits and medications, as well as gene-environment interaction factors and shared susceptibility genetic loci for schizophrenia and type 2 diabetes mellitus.

Diabetes is a complex, chronic illness, requiring strict glycemic control beyond continuous medical care, with multifactorial risk-reduction strategies. Its prevalence among adults has risen from 4.7% in 1980 to 8.5% in 2014, more rapidly in middle- and low-income countries, whereas similar increasing prevalence is observed among patients with schizophrenia. Therefore, interventions facilitating the knowledge, skills and abilities necessary to prevent, early diagnose and efficiently control diabetes are important. Promoting such steps could also serve moderate diabetes complications, such as blindness, kidney failure, heart attacks, stroke and lower limb amputation, contributing in limiting cardiovascular risk and mortality rates among people with schizophrenia. A search was conducted across Medline and Scopus and all relevant English articles referring to schizophrenia and type 2 diabetes mellitus (until June 2017) were reviewed.

Prevalence of Type 2 Diabetes among patients with Schizophrenia

The prevalence of diabetes in individuals with schizophrenia varies across different studies, reflecting increasing rates across years, methodological issues (sample size, methods of diabetes detection, inclusion or not of schizoaffective disorders in the case sample, longitudinal, cross-sectional, case-control, cohort, inpatient, outpatient studies), as well as age, sex, ethnicity disparities and further genetic and lifestyle particularities. However, most of them demonstrate elevated diabetes prevalence rates as compared with the general population, with odds estimated to be two to five times elevated.

Particularly, prevalence estimations of diabetes among patients with schizophrenia in the USA range from 14.2% in a retrospective cohort study, 18.7% in a cross-sectional study conducted in 819 patients with schizophrenia, to 23.3% in another cross-sectional with 2231 patients, with an alarming trend of increase over time (6.9% in 1997 to 14.5% in 2004). In the European populations, prevalence is evaluated 15% in the Netherlands, 14.8% in a case-control study conducted in Sweden with 2,058,408 patients, 22% in a cross-sectional study in Finland, whereas the prevalence of diabetes among patients with schizophrenia in the UK is estimated to be 11.3%. Similarly in Asia, prevalence approaches 15.3% in a case-control study in India, 15% in Malaysia and 8% in a case-control study in Singapore, however it included only 164 patients and 200 controls. Accordingly, prevalence in Australia reaches 12.1%. Redefining all causes contributing to excess diabetes comorbidity with schizophrenia constitutes the cornerstone to face the problem.

Clinical and lifestyle causes of Type 2 Diabetes in Schizophrenia

Various factors are involved in diabetes onset among patients with schizophrenia, which also apply in the general population. However they are observed more commonly in schizophrenia. Such factors are obesity, increasing age, hypertension, hyperlipidemia, smoking, lack of physical activity, poor diet, social determinants, poverty, quality of sleep, stress and sedentary lifestyle.

Most, but not all, patients with type 2 diabetes are overweight or obese, or present with an increased percentage of body fat, distributed predominantly in the abdominal region. Obesity is a common comorbidity in schizophrenia, with higher prevalence than the general population. Even in first-episode schizophrenia, 22% of the patients were overweight in a study conducted with 2548 patients. Another study showed that patients diagnosed with schizophrenia were overweight-obese (45–55%, RR: 1.5–2), smokers (50–80%, RR: 2–3), had diabetes (10–15%, RR: 2), hypertension (19–58%, RR: 2–3), dyslipidemia (25–69% RR: 5) and metabolic syndrome (37–63%, RR: 2–3). Additionally, it has been observed rates of BMI greater than 27 to reach 42% in a group of individuals with schizophrenia, compared to 27% in the general population.

Poor diet and physical inactivity result in increased diabetes rates among people with schizophrenia. Deficits in fruits and vegetables intake, excess of fat, sugar and fast food consume characterize the dietary components often preferred by patients with schizo-
Several studies report poor nutritional quality with relevant impact on weight gain and further cardiometabolic adverse effects. Another study estimated the mean number of fruit and vegetable portions per day at 2.8±1.8, whereas over a third patients did not eat any fruit in a typical week. However, choices of poor dietary preferences are likely related to unemployment, household income and lower socioeconomic status, not adequate supportive family environment, cognitive deficits and educational limitations. Homelessness often accompanies patients with schizophrenia, setting many barriers to diabetes prevention, including food insecurity, literacy and numeracy deficiencies, lack of insurance and cognitive dysfunction. Access to health care services for individuals with schizophrenia is often inhibitory by perplexed and bureaucratic health service procedures, unequal legislations, as well as communities' and health providers' racism against persons with mental issues.

Furthermore, negative symptoms, sedating effects of antipsychotic medications and obesity contribute to restricted physical activity of individuals with schizophrenia. Engagement in moderate physical activity is reported less frequently in schizophrenia group than the National Health and Nutrition Examination Surveys group (NHANES group). Specifically, few individuals with schizophrenia reported vigorous physical activity, whereas less than half of the sample followed moderate physical activity. Similar findings are observed by other studies, while a systematic review reported linkage of impaired physical activity with limited socioeconomic status. Besides exercise, sleep alterations, often meet in people with schizophrenia due to desynchronization between melatonin profiles and the sleep–wake rhythms, body temperature, and levels of tryptophan and prolactin, might play a role on diabetes onset. The disturbed circadian clock underlying in schizophrenia contributes to the development of metabolic disorders, affecting further the stress axis (hypothalamic-pituitary-adrenal axis, glucocorticoids, interaction with leptin), the motivation and reward system (dopamine, interaction with hypothalamic-pituitary-adrenal axis) and the orexin/melanin concentrating hormone neuronal network. Additionally, smoking, a known risk factor for type 2 diabetes, among people with schizophrenia is calculated 5.6 times as much as people without, thus increasing the risk for diabetes and its treatment outcome. Likewise, a study estimated smoking rates at 64.9% among people with schizophrenia and in an increased number of them cigarette use was heavy. Additionally to smoking, hypertension and hyperlipidemia contribute to elevated diabetes risk. A cohort study of 2270 patients from 16 European countries reported 69.6% hyperlipidemia rates and 43.4% for hypertension, while the risk was estimated 5fold and 2-3fold higher for these condition respectively, in comparison with the general population. Moreover, odds ratio (OR) of diabetes onset in patients with schizophrenia and hypertension or dyslipidemia, in comparison with patients with schizophrenia without this comorbidity, are reported to be 3.23 [95% Confidence Interval (CI) 2.04–5.11] and 5.99 (3.87–8.92) respectively. Furthermore, hazard ratio for earlier diabetes onset time is evaluated 1.87 (95% CI 1.12–3.09) and 4.67 (2.19–10.00) for patients with schizophrenia under antihypertensive and lipid-lowering treatment respectively.

Finally, environmental loading is proposed as an etiological factor for diabetes and schizophrenia co-occurrence, influencing susceptibility to both conditions. For instance, poverty and lower educational chances are linked to schizophrenia and obesity. Both increased rates of impaired glucose tolerance and schizophrenia was detected in the cohort born during the Dutch famine in 1944–1945 vitamin D deficit during early life is associated with risk of schizophrenia, whereas it also influences the insulin response to glucose stimulation, although its limited impact on basal insulinemia.

Medication, Schizophrenia and Type 2 Diabetes

There is a considerable literature on the metabolic adverse effects of antipsychotic agents. In particular, comparison between second generation antipsychotics (SGA) with first generation antipsychotics (FGA) revealed a 1.3 fold elevated risk for diabetes. This effect is intermediated either by weight gain, or at 25% of cases – though direct impairment in glucose homeostasis, potentially via blockade of central and peripheral muscarinic M3 receptors. M3 receptors are widely expressed in the brain (ventromedial hypothalamic and arcuate nuclei of the hypothalamus,
dorsal vagal complex of the brainstem,\textsuperscript{60, 61} effecting insulin and glucagon secretion, glucose homeostasis and body weight regulation,\textsuperscript{62, 63} as well as on pancreatic beta cells, modulating the acetylcholine pathway for insulin secretion.\textsuperscript{64, 65} Antipsychotic affinity for the M3 receptors is considered the best indicator for diabetogenic liability.\textsuperscript{66, 67} Interestingly, olanzapine and clozapine have a profile to potently block the M3 receptors, while antipsychotics with a lower risk of metabolic dysfunction side-effect, such as risperidone and ziprasidone, have little effect on the M3 receptors.\textsuperscript{67, 68}

Another study detected elevated risk of diabetes in both patients treated with SGA (adjusted hazard ratio [HR] 1.32, 95% CI 1.01–1.75) and those treated with FGA (adjusted HR 1.82, 95% CI 1.30–2.55) against control patients without schizophrenia.\textsuperscript{69} Furthermore, a meta-analysis on the prevalence of diabetes reported 2.1% diabetes prevalence among antipsychotic-naive patients, whereas the prevalence was 12.8% for antipsychotic receivers.\textsuperscript{17} However, a systematic review of 22 prospective, randomized, control trials, though short-term followed, detected no difference in glycemic abnormalities between placebo and antipsychotic cohorts.\textsuperscript{70} Suggested explanations to those inconsistent findings are beyond methodological problems such as medication pre-exposure of tested groups, duration and dose of medication receive, severity, duration and type of schizophrenia, way of diabetes diagnosis (self-report, anti-diabetes drugs, ADA criteria), homogeneity of case group (schizophrenia, schizoaffective disorders, psychosis), adherence to antipsychotic receive, follow-up period and other unobserved confounding, also the heterogeneity among SGA and FGA groups.

Therefore, other studies attempted to evaluate the diabetogenic role of each antipsychotic regiment separately. Particularly, a large, population-based study conducted in Denmark with 345,937 cases treated with antipsychotics and 1,426,488 controls found 1.45% for clozapine, 1.29% for olanzapine and 1.23% for risperidone, 1.94% for sertindole, 1.57% for perphenazine, 1.94% for ziprasidone and even 1.17 for haloperidol increased diabetes risk,\textsuperscript{71} whereas no increase in diabetes risk was detected for aripiprazole, amisulpride or quetiapine. On the other hand, a study on newly-onset schizophrenia patients revealed diabetes incidence patients with olanzapine initiation therapy (hazard ratio, HR=1.41) and with mid-potency conventional antipsychotics (HR=1.60).\textsuperscript{49} Moreover, an FDA’s database analysis in terms of diabetes, reported the following adjusted ratios hierarchy for diabetes-mellitus-related adverse outcomes: olanzapine 9.6 (95% CI 9.2–10.0), risperidone 3.8 (3.5–4.1), quetiapine 3.5 (3.2–3.9), clozapine 3.1 (2.9–3.3), ziprasidone 2.4 (2.0–2.9) aripiprazole 2.4 (1.9–2.9) and haloperidol 2.0 (1.7–2.3).\textsuperscript{72} Clozapine and olanzapine are consistently associated with greater weight gain risk.\textsuperscript{73}

Further, antidepressants may attribute to increased diabetes risk. Probable suggested mechanisms are their sedative effect, the increase in appetite, and weight gain.\textsuperscript{74–76} A meta-analysis, though included only observational studies, reported increase in diabetes onset likelihood (OR 51.50, 95% CI 1.08–2.10, HR 51.19, 95% CI: 1.08–1.32).\textsuperscript{77} However, most studies\textsuperscript{78, 79} provide evidence for elevated diabetes risk with the concurrent use of tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRIs) (OR=1.89),\textsuperscript{80} the long-term use of both tricyclic antidepressants (incidence rate ratio, IRR=1.77) and SSRIs (IRR=2.06) in at least moderate daily doses,\textsuperscript{81} as well as the use of antidepressants medication in high-risk patients.\textsuperscript{82} Further, amitriptyline, imipramide and mirtazapine are associated substantially with weight gain, nortriptyline and paroxetine appear to have intermediate effect, whereas bupropion and fluoxetine are linked with weight loss.\textsuperscript{48}

Additionally, mood stabilizers, especially valproate itself\textsuperscript{83} and lithium,\textsuperscript{84} have been associated with insulin resistance and diabetes risk,\textsuperscript{22, 85} related possibly to weight gain,\textsuperscript{86} and/or fatty liver infiltration.\textsuperscript{87} However, little research has been performed in terms of concomitant application of different categories of medications\textsuperscript{88, 89} to reveal potential synergic action. One of those\textsuperscript{89} conducted in Medicaid-enrolled youths, reported higher risk for diabetes incident for SGA initiators concomitantly to antidepressant use (OR .54, 95% CI 1.17–2.03, p=0.002), when compared to only SGA initiators. Further, first-episode and antipsychotic-naive patients with schizophrenia as compared to chronic patients, are more vulnerable to severe weight gain, rapidly during the first few weeks, due to antipsychotics.\textsuperscript{79}

Antipsychotics are associated with lipid abnormalities and thus could increase diabetes risk.\textsuperscript{48, 90} On the contrary, most of antidepressants\textsuperscript{91} as well as lithium\textsuperscript{92} observe no associated with dyslipidemia. Valproate
has been associated increased triglycerides and glucose, and insulin abnormalities. Antipsychotics are not associated with hypertension, potentially due to their alpha-1 blocking effects, which can lower blood pressure. Among antidepressants, venlafaxine is most frequently associated with elevated blood pressure, while mirtazapine has been found to be associated less than tricyclic antidepressants. Generally, mood stabilizers have no effect on blood pressure, apart from chronic renal failure related to lithium volume distribution.

**Genetic predisposition for comorbidity Schizophrenia and Type 2 Diabetes**

Metabolic loading in patients with schizophrenia, such as dyslipidemia and insulin resistance, presents also prior to treatment onset, implying genetic vulnerability. Henry Maudsley already proposed the genetic link between diabetes and schizophrenia in his 1897 textbook “The Pathology of Mind”. Prevalence of diabetes is estimated 1.27–1.63 fold higher in medication-naive patients with schizophrenia as compared with the general population in the Netherlands. Furthermore, similarly increased levels of IL-1β, IL-6, TNF-α, but also importantly elevated adiponectin levels were detected in drug naïve, first episode patients with schizophrenia and normal weight, as compared with obese or overweight individuals without schizophrenia, which suggest a potential unique pro-inflammatory role of adiponectin in patients with schizophrenia, leading to later metabolic syndrome.

To explain this comorbidity between schizophrenia and diabetes in genetic terms, linkage studies as well as genome-wide association studies (GWAS) are applied to shed light into this direction. As linkage studies are concerned, one could start with probing the gene involved in both glucose and dopamine pathways. According to the data queried from Genetic Association Database (http://geneticassociationdb.nih.gov/), a total of 37 common genes are detected across these susceptibility genes of schizophrenia and diabetes. For instance, chromosome 1q may harbor genes influencing working memory and diabetes-related traits. Moreover, association studies suggest that chromosome 1q21-24 may harbor risk genes for diabetes. Among others, genes with involvement in both glucose metabolism and cognitive function which may increase the risk of diabetes in patients with schizophrenia vice-versa, are proposed to be nitric oxide synthase 1 (neuronal) adapter, aka, carboxy-terminal PDZ ligand of neuronal nitric oxide synthase protein (CAPON), Nitric oxide synthase 1 adaptor protein (NOS1AP), glycogen synthase kinase 3 gene GSK-3, catecholamine O-transferase gene COMT, tyrosine hydroxylase (TH) gene. Association findings further support that TCF7L2, which is responsible for diabetes, increases risk of schizophrenia in two further studies. Web-based catalog for published genome-wide association studies (GWAS) to search for overlapped findings for diabetes and schizophrenia provided no evidence for shared etiology (with a significance level of p<10^-8). Proposed explanation therefore is that the genetic overlap for schizophrenia and diabetes may depend on combination of rare variants with small effect acting in concert to cause both diseases or to variants other than single nucleotide polymorphisms (SNPs). Another GWAS analysis failed to detect risk variants associating schizophrenia with diabetes in a Japanese population. Moreover, pathway analysis retrieved 2,104 proteins, 364 of them found simultaneously interacting with susceptibility proteins of both diabetes and schizophrenia, therefore proposed as new candidate risk factors for both diseases.

**Prevention and therapy**

Clinical practice guidelines and individualized medicine are keys to improve health of patients with schizophrenia. The American Diabetes Association (ADA) highlights the importance of patient-centered care, defined as care that is respectful of and responsive to individual patient preferences, needs, and values and ensuring that patient values guide all clinical decisions. Annual screening for people with schizophrenia for prediabetes or diabetes is recommended. Changes in weight, glycemic control, blood pressure and cholesterol levels should be carefully monitored and the treatment regimen should be reassessed.

Motivation in the direction of healthy lifestyle choices, such as healthy eating, physical activity, tobacco cessation, weight management and effective strategies for coping with stress, should belong to health providers’ priorities. Providers should assess social context, including potential food insecurity, housing stability, and financial barriers, and apply that infor-
Η σχιζοφρένεια συνδέεται με αυξημένο κίνδυνο για εμφάνιση σακχαρώδους διαβήτη τύπου 2, συμβάλλοντας σε επίταση του καρδιαγγειακού κινδύνου και περιορισμό του προσδόκιμου επιβίωσης σε ασθενείς με σχιζοφρένεια. Σε ό,τι αφορά στο προσδόκιμο ζωής, αυτό ανέρχεται συνολικά σε 14,5 έτη πιθανής απώλειας ζωής και συνολικό μέσον όρο προσδόκιμου ζωής τα 64,7 έτη. Ο ακριβής επιπλασμός του διαβήτη τύπου 2 στα άτομα με σχιζοφρένεια διαφέρει στις μελέτες και κυμαίνεται από 2–5 φορές υψηλότερος σε σχέση με τον γενικό πληθυσμό. Η αιτιολογία του σακχαρώδους διαβήτη στους ασθενείς με σχιζοφρένεια είναι πολύπλοκη και πολυπαραγοντική. Εκτός από τους κοινούς διαβητογόνους παράγοντες, που απαντώνται και στον γενικό πληθυσμό, όπως η παχυσαρκία, η υπερλιπιδαιμία, το κάπνισμα, η υπέρταση, η κακή διατροφή και η περιορισμένη σωματική δραστηριότητα, η συνύπαρξη σχιζοφρένειας και διαβήτη αποδίδεται σε επιπλέον ιδιαίτερους παράγοντες. Συγκεκριμένα, ο καθιστικός τρόπος ζωής, κοινωνιοοικονομικοί παράγοντες, οι ανεπιθύμητες ενέργειες των αντιψυχωτικών φαρμάκων και η περιορισμένη πρόσβαση στις υπηρεσίες υγείας θεωρούνται επιβαρυντικοί παράγοντες για την εμφάνιση του διαβήτη και τη χαμηλή ποιότητα διαχείρισης του. Η ίδια η σχιζοφρένεια θεωρείται αιτιολογικός παράγοντας για εμφάνιση σακχαρώδους διαβήτη, δεδομένου του παρατηρούμενου υψηλότερου επιπλασμού του διαβήτη σε νεαρούς ασθενείς, που έχουν πρόσφατα διαγνωσθεί με σχιζοφρένεια και δεν έχουν εκτεθεί σε αντιψυχωτικά. Επιπλέον, οι μελέτες υποστηρίζουν γενετική προδιάθεση για διαβήτη μεταξύ των ατόμων με σχιζοφρένεια, υποδηλώνοντας ότι κοινοί γενετικοί παράγοντες ευθύνονται τόσο για τη σχιζοφρένεια όσο και για τον σακχαρώδη διαβήτη, ενώ έχει προσδιορισθεί ένας αριθμός αλληλεπικαλυπτόμενων υπεύθυνων
References


45. Muller DP, de Haan L. Smoking cessation and schizophrenia. Tijdschrift voor psychiatrie 2017, 59:297–301


86. Masuccio F, Verrotti A, Chiavaroli V, de Giorgis T, Giannini C, Chiarelli F et al. Weight gain and insulin resistance in children


104. Zeggini E, Damcott CM, Hansson RL, Rayner NW, Groves CJ et al. Variation within the gene encoding the upstream stimulatory factor 1 does not influence susceptibility to type 2 diabetes in samples from populations with replicated evidence of linkage to chromosome 1q. *Diabetes* 2006, 55:2541–8, doi: 10.2337/db06-0088


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