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Published in:
Diabetes Care

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2006

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):
Cohen, D., Stolk, RP., Grobbee, DE., & Gispen-De Wied, CC. (2006). Hyperglycemia and diabetes in patients with schizophrenia or schizoaffective disorders. *Diabetes Care*, *29*(4), 786-791.

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Hyperglycemia and Diabetes in Patients With Schizophrenia or Schizoaffective Disorders

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OBJECTIVE — Pharmacoepidemiological studies have shown an increased prevalence of diabetes in patients with schizophrenia. To address this issue, we decided to assess glucose metabolism in a population of patients with schizophrenia or schizoaffective disorder.

RESEARCH DESIGN AND METHODS — Oral glucose tolerance tests (OGTTs) were performed in 200 unselected in- and outpatients. Insulin sensitivity and β-cell function were assessed using the homeostasis model assessment (HOMA) indexes and 30-min glucose and insulin levels.

RESULTS — The mainly Western European (87.7%) study population had a mean age of 40.8 years, was 70% male, and had a mean fasting glucose of 5.1 mmol/l and a mean fasting insulin of 14.8 mU/l. Hyperglycemia was present in 7% of the population: 1.5% with impaired fasting glucose and 5.5% with impaired glucose tolerance. The prevalence of diabetes was 14.5%, of which 8% was previously known and 6.5% was newly diagnosed. Compared with a 1.5% prevalence of diabetes in the age-matched general Dutch population, the prevalence of identified cases was significantly increased in the study population. Comparable figures on the prevalence of hyperglycemia in the general population are not available. Insulin resistance was increased in the study population as a whole (HOMA of insulin resistance: 3.1–3.5), irrespective of the use of antipsychotic medication and, if used, irrespective of its type (typical or atypical). No indication of β-cell defect was found, whereas a nonsignificant increased insulin resistance was found with antipsychotic medication.

CONCLUSIONS — OGTTs in 200 mainly Caucasian patients with schizophrenia or schizoaffective disorder, mean age 41 years, showed that 7% suffered from hyperglycemia and 14.5% from diabetes. The prevalence of diabetes was significantly increased compared with the general population. No differential effect of antipsychotic monotherapy in diabetogenic effects was found. Therefore, a modification of the consensus statement on antipsychotic drugs, obesity, and diabetes is proposed, i.e., measurement of fasting glucose in all patients with schizophrenia, irrespective of prescribed antipsychotic drug.

Diabetes Care 29:786–791, 2006

The first description of disturbances of the glucose metabolism in schizophrenic patients dates from 1879 (1) and was confirmed by many authors (2–6) in the first half of the 20th century. The introduction of neuroleptics was accompanied by a rapid increase in type 2 diabetes in these patients. Numerous case reports and epidemiological studies (7–12) have shown an increased rate of disturbed glucose metabolism in hospitilized patients treated with neuroleptics. The atypical or second-generation antipsychotic drugs, introduced in the 1990s, showed less extrapyramidal side-effects but seemed to have a stronger diabetogenic effect than the classical antipsychotics. The pathophysiologic mechanism of the disturbing glucose metabolism is not well known.

Pharmacoepidemiological research of large databases has recently been the main focus of research (13–22), with two clear methodological restrictions (23). First, database studies are based on an established clinical diagnosis of diabetes, whereas it is known that especially in the care of patients with schizophrenia a substantial proportion of diabetic patients is undiagnosed (19). Second, database studies are unable to shed light on the etiology of glucose intolerance because of lack of information on the preclinical phase of disturbed glucose metabolism, i.e., hyperglycemia.

We decided to investigate the prevalence of impaired glucose tolerance and diabetes and the differences that can be attributed to the type of antipsychotic medication in patients with schizophrenia and schizoaffective disorder using the oral glucose tolerance test (OGTT). Glucose and insulin were measured during the test. Insulin sensitivity and β-cell function were assessed using the homeostasis model assessment (HOMA) indexes and 30-min glucose and insulin levels.

RESEARCH DESIGN AND METHODS

— The research protocol was approved by the medical ethical commission of the University of Utrecht. Participants between the ages of 18 and 65 years were recruited from the mental health care organizations Rijngeestgroep (Oegstgeest, Voorhout, Noordwijkerhout) and De Grote Rivieren (Dordrecht) and Anoiksis, the Dutch organization for patients with schizophrenia. After providing written informed consent, the M.I.N.I. Plus (24), a structured diagnostic interview for DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, 4th edition) diagnosis, and the available medical records were used for a DSM-IV diagnosis of schizophrenia or schizoaffective disorder.

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Received for publication 7 July 2005 and accepted in revised form 28 December 2005.

D.C. has served on an advisory board of and has received honoraria from Bristol-Myers Squibb and has received grant/research support from the Dr. Paul Janssen Foundantion.

Abbreviations: HOMA, homeostasis model assessment; OGTT, oral glucose tolerance test.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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Table 1—*Demographic variables by glucose metabolism*

Classification	Normal	Impaired fasting glucose	Impaired glucose tolerance	Diabetes	*P* value
Schizophrenia	135 (78.5%)	3 (2.3%)	11 (6.4%)	22 (12.8%)	0.197
Schizoaffective disorder	20 (74.1%)	0 (0%)	0 (0%)	7 (25.9%)	
Male	113 (80.7%)	3 (2.1%)	7 (5.0%)	17 (12.1%)	0.39
Female	44 (73.3%)	0 (0%)	4 (6.7%)	12 (20%)	
Inpatient	24 (88.9%)	0 (0%)	0 (0%)	3 (11.1%)	0.24
Outpatient	98 (76.6%)	1 (0.8%)	8 (6.3%)	21 (16.4%)	
Supported living	17 (77.3%)	1 (4.5%)	2 (9.1%)	2 (9.1%)	
Sheltered living	16 (72.2%)	2 (9.1%)	1 (4.5%)	3 (13.6%)	
Total	157 (78.5%)	4 (1.5%)	11 (5.5%)	29 (14.5%)	

Data are *n* patients (proportion). *P* values are adjusted for age and sex, if appropriate.

A 75-g OGTT was performed, with venous plasma measurements of glucose and insulin at −15, 0, 30, 60, and 120 min. In patients with diagnosed diabetes, only a fasting blood sample was taken. Glucose was determined by the Synchron Clinical System (Beckmann Coulter), with a detection limit of 0.3–38.8 mmol/l. The coefficient of variation varied between 2 and 3% at different levels. Serum insulin was measured by radioimmunoassay (Medgenix, Fleurus, Belgium), with a detection limit of 3 mU/l. The coefficient of variation varied between 3.8 and 7.6% at different levels.

Impaired fasting glucose was diagnosed when the mean fasting glucose plasma level at $t = -15$ and $t = 0$ was between 6.1 and 7.0, with a glucose level at $t = 120$ <7.8 mmol/l. Impaired glucose tolerance was diagnosed when the plasma glucose levels at $t = 120$ were between 7.8 and <11.1 mmol/l. Diabetes was defined as a mean fasting glucose ≥7.0 mmol/l and/or a glucose level at $t = 120$ ≥11.1 mmol/l (25). HOMA was used to assess insulin sensitivity and β-cell function, based on fasting insulin and glucose levels and according to published algorithms: HOMA resistance = (insulin × glucose)/22.5 and HOMA β-cell function = 20 × insulin/(glucose − 3.5) (26). β-Cell function was further studied using the 30-min glucose and insulin level during the OGTT. The prevalence of glucose intolerance as well as the results of the OGTT are presented as means ± SD and compared between different subgroups of patients. Linear regression and ANCOVA were used to adjust these differences for potential confounders, notably age, sex, BMI, and waist-to-hip ratio. The difference between types of antipsychotic medications was also analyzed using linear regression. All analyses were performed using SPSS for Windows 11.5.

We expected that the use of typical and atypical antipsychotics would be about equal in these patients. To detect a difference of fasting plasma glucose 0.5 mmol/l, two groups of 101 patients are needed (SD 1.0, two-sided α 0.05, power 0.85).

RESULTS

Descriptives

Most participants of the study were recruited from the semirural part of the Dutch province Zuid-Holland. A total of 87.7% of the study population was of Western European origin, with the remaining 12.3% equally divided between the Asian, African, Mediterranean, and Hindustan population. Nearly two-thirds (64%) of the participants were outpatients; the remaining 35.4% was equally divided over the different forms of more intensive psychiatric care: supported living (11.1%), sheltered living (10.6%), and inpatients (13.6%) (Table 1).

Twelve patients, currently not using antipsychotic medication, had significantly lower BMI and waist-to-hip ratios (25.3 vs. 28.2 kg/m^2, 0.87 vs. 0.95, respectively; both comparisons $P < 0.05$ adjusted for age and sex). Of the remaining 188 patients, 182 used antipsychotic monotherapy and 6 antipsychotic polypharmacy: two typical antipsychotic drugs ($n = 2$) or a combination of typical and atypical agents ($n = 4$).

Patients were classified as on typical ($n = 55$) and atypical ($n = 133$) medication, the latter including the four patients with classical plus atypical drugs. The two groups did not differ in age, BMI, or waist-to-hip ratio (all comparisons $P > 0.4$ adjusted for age and sex).

Glucose metabolism

Before every OGTT, the fasting status of the patient was confirmed. In the cases where the patient was not fasting, the OGTT was canceled and a new appointment was made. In the study population ($n = 200$), we found 157 patients (78.5%) with normoglycemia, 14 (7%) with hyperglycemia, and 29 (14.5%) with diabetes (Table 1). No significant differences were found by sex ($P = 0.39$), psychiatric diagnosis ($P = 0.197$), or psychiatric setting ($P = 0.24$) (Table 1). Further subdivision of hyperglycemia showed impaired fasting glucose present in 4 patients (2%) and impaired glucose tolerance in 11 patients (5.5%). Diabetes was an established diagnosis in 16 patients (8%) and newly diagnosed in 13 patients (6.5%).

Insuline resistance and β-cell function

The fasting values of glucose and insulin levels as well as HOMA estimates for the whole study population are presented in Table 2. There were no differences between men and women ($P = 0.39$). Higher age was associated with increased plasma glucose and HOMA of insulin resistance values ($P < 0.05$). The glucose and insulin levels during the OGTT are presented in Fig. 1.

Table 2—*Clinical characteristics of the study population*

Characteristics	
Age	40.8 ± 10.2
BMI (kg/m²)	28.1 ± 5.2
Waist-to-hip ratio	0.95 ± 0.08
Fasting glucose (mmol/l)	5.1 ± 1.1
Fasting insulin (mU/l)	14.8 ± 16.7
HOMA of β-cell function	192 ± 730
HOMA of insulin resistance	3.4 ± 4.0

Data are means ± SD.

Table 3—*Antipsychotic medication and glucosemetabolism on OGTT*

	No AP	Classic	Atypical	*P* value
n	12	52	136	
Fasting glucose (mmol/l)	4.8 ± 0.4	5.1 ± 1.1	5.1 ± 1.1	0.65
Fasting insulin (mU/l)	8.2 ± 3.7	14.6 ± 16.4	15.7 ± 18.0	0.99
HOMA of β-cell function	222 ± 306	173 ± 388	197 ± 849	0.95
HOMA of insulin resistance	3.1 ± 4.8	3.5 ± 4.5	3.4 ± 3.7	0.95
$\Delta ins_{30}/glu_{30}$	22.76 ± 31.13	28.76 ± 33.52	18.00 ± 30.92	0.73
Normoglycemia	10 (83.3)	43 (82.7)	103 (75.5)	0.741
Hyperglycemia	1 (8.3)	2 (3.8)	12 (8.8)	
Diabetes	1 (8.3)	7 (13.5)	21 (15.4)	

Data are means ± SD or *n* (%). *P* values are adjusted for age and sex. AP, antipsychotic medication.

Antipsychotic medication

After adjustment for age and sex, fasting glucose, insulin, and HOMA estimates were not associated with type of antipsychotic medication (Table 3). Further adjustment for BMI or waist-to-hip ratio did not change the results. The prevalences of disturbed glucose levels for the individual atypical patients were as follows: patients with hyperglycemia: clozapine 18% (7 of 39), olanzapine 2.3% (1 of 44), quetiapine 0% (0 of 5), and risperidone 11.6% (5 of 43); patients with diabetes: clozapine 12.8% (5 of 39), olanzapine 18.2% (8 of 44), quetiapine 0% (0 of 5), and risperidone 16.3% (7 of 43). After excluding patients currently not using antipsychotic medication ("no AP"), the difference did not reach statistical significance ($P = 0.2$).

The first-phase insulin response, measured by Δ30 (Table 3) and graphically presented in Fig. 1, was the same in all patients, irrespective of their treatment modality. Patients using antipsychotic medications had (nonsignificant) increased insulin levels during the second half of the OGTT, which was more pronounced in those using atypical drugs.

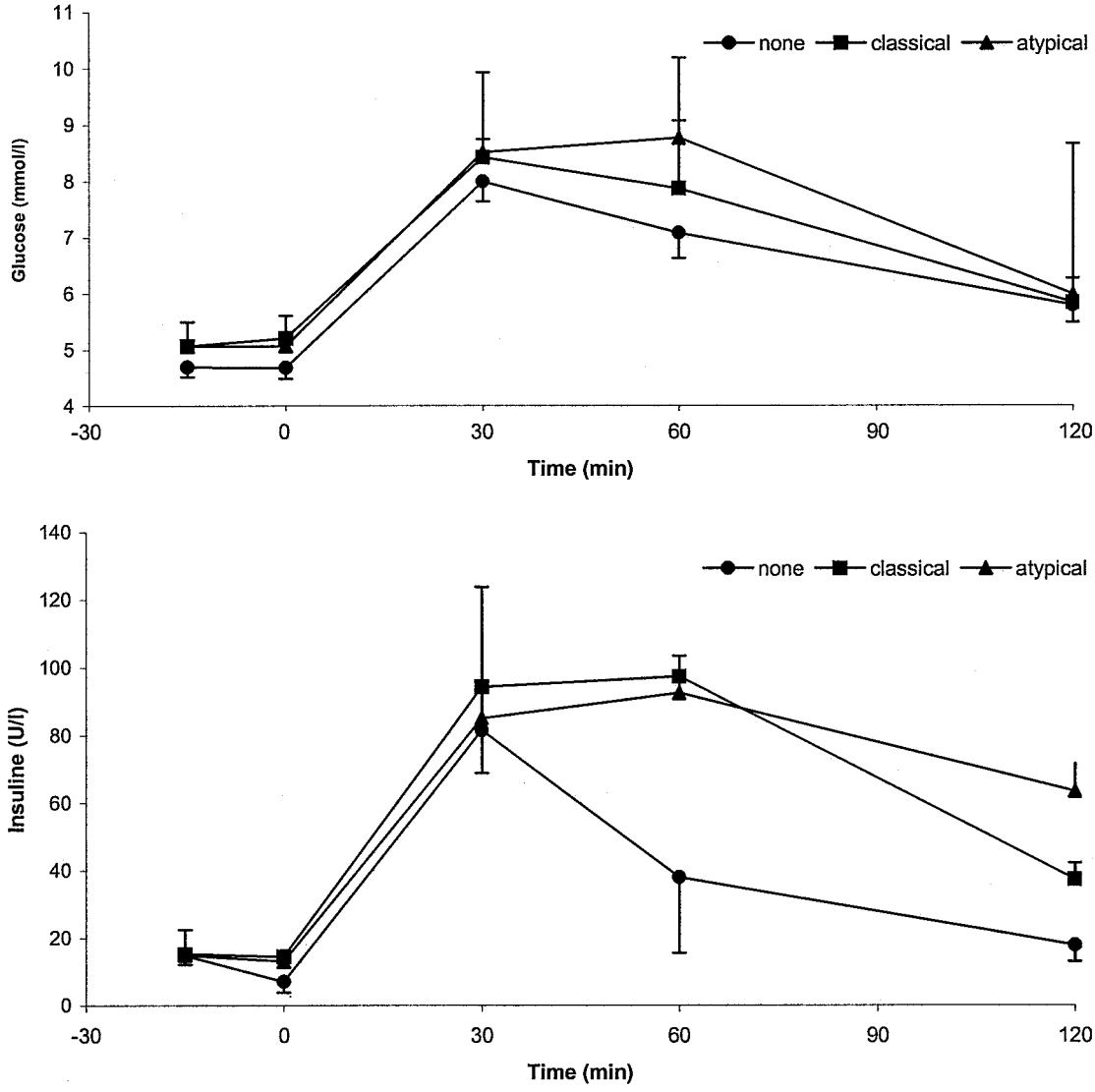

Figure 1—*Glucose and insulin levels during the OGTT by antipsychotic drug use. Error bars indicate SE.*

CONCLUSIONS — In accordance with the recommendations by the World Health Organization, we used the OGTT to assess the glucose regulation in our cross-sectional study. In 200 mainly Caucasian patients with schizophrenia or schizoaffective disorder, hyperglycemia was found to be present in 7% and diabetes in 14.5% of this relatively young population. Impaired fasting glucose accounted for 1.5% of the hyperglycemia and impaired glucose tolerance for the remaining 5.5%. The 14.5% with diabetes consisted of 8% previously known and 6.5% newly diagnosed cases.

The results reveal that the less severe form of glucose metabolism (hyperglycemia) was less prevalent (7%) compared with the 14.5% with the more severe form (diabetes). This result seems to confirm earlier findings that disturbance of glucose metabolism tends to be more severe in patients with schizophrenia than in the general population (27,28). The differences in prevalence of impaired fasting glucose (1.5%) and impaired glucose tolerance (5.5%) reflect the differences in sensitivity between fasting and 2-h measurements.

The prevalence of previously known diabetes in our study population with a mean age of 41 years (8%) is comparable with the prevalence in the general Dutch population 20 years older, in the age-group 60–65 years (29). This suggests that an early aging effect is present in the population of patients with schizophrenia or schizoaffective disorder.

When we turn to the hypothesis, i.e., the absence of an effect of the class of antipsychotic medication on glucose metabolism, we see that both in absolute terms (means of fasting glucose, insulin level, HOMA of β-cell function, and HOMA of insulin resistance; Table 3) and in relative terms (distribution of the three possible outcomes of the OGTT; Table 3), no difference between the two classes of medication was found, thereby confirming the hypothesis. The results of Fig. 1 suggest that antipsychotic drugs increase peripheral insulin resistance in patients with schizophrenia.

As far as the power of the study is concerned, the study may have been slightly underpowered, but the lack of difference in absolute terms between means and percentages indicates that no small differences were missed. The design therefore did not effect the results in a negative way. The result of this study differs from some (30–33) but confirms other (34–36) studies in patient populations. Hägg et al. (30) found no significant difference in the prevalence of hyperglycemia or diabetes between patients on typical antipsychotic medication or clozapine. The study is complicated by 19% antipsychotic polypharmacy in the clozapine group. In a study with four treatment conditions, typical, clozapine, olanzapine, and risperidone, and healthy control subjects, Newcomer et al. (31) found a significant increase of glucose levels for olanzapine and clozapine in comparison with typical antipsychotic and healthy control subjects. Antipsychotic polypharmacy (±15%), differences in treatment duration (19 days to >1 year), different distribution of BMI, and high-risk African Americans over the four treatment conditions complicate the interpretation of the results.

In a comparative, cross-sectional study of BMI-matched, nonobese, stable patients treated with atypical antipsychotics (treatment duration not mentioned), Henderson et al. (32), using the frequently sampled intravenous glucose tolerance test, found significant impairment of glucose effectiveness in patients treated with olanzapine and clozapine when compared with risperidone. No significant differences in age or BMI were reported. In a prospective study of patients treated with clozapine during 2–4 months, Howes et al. (34) found a significant increase of plasma glucose levels, independent of change in either insulin resistance or BMI. In another study with OGTT on three atypicals, Smith et al. (35) failed to find a significant difference in 2-h glucose between olanzapine, risperidone, and clozapine. In these three studies, with significant increase of glucose levels, the small size (104 patients alltogether) and high proportion of high-risk African Americans (varying between 17 and 83%) preclude any definite conclusions.

The results of the prospective study by Lindenmayer et al. (33) might be indicative of the influence of treatment duration on study outcome. In a comparison of haloperidol with the atypicals clozapine, olanzapine, and risperidone, a significantly raised glucose level was found at 8 weeks in the clozapine and haloperidol groups. After an extension of 6 weeks, the increased glucose level was only found in a third group of olanzapine.

Recently, it was suggested that screening for diabetes in hospitalized patients is more intensive when atypical antipsychotics are prescribed (37). This may explain the higher prevalence of diabetes found with these atypical agents. The lack of association between drug therapy and disturbed glucose metabolism, both on a group level (typical versus atypical) and on the level of the individual atypical AP in this study, seems to confirm *1*) earlier reports on increased prevalence of diabetes in patients treated with typical antipsychotics (38–40), *2*) clinical studies in inpatients with schizophrenia (34–36,41) and bipolar and schizoaffective disorders (42), and *3*) two recently published, long-term prospective 52-week randomized studies: a double-blind trial of clozapine versus chlorpromazine in treatment-naive first-episode inpatients (43) and an investigator-blinded parallel-group comparison of flexible doses of haloperidol and quetiapine (44). Moreover, due to the combination of a mixed in- and outpatient study population with a strong emphasis of 64% on the outpatient population, this study extends the results obtained in inpatients to the majority, i.e., the outpatient population.

The patients in our study stem from three different psychiatric settings: inpatient care, outpatient care, and supported/sheltered living, thereby covering the whole spectrum of severity and disability found in the population of patients suffering from schizophrenia or schizoaffective disorder. We think, therefore, that the study population, and its results, fairly represents the Caucasian patient population of the Netherlands.

With diabetes increasingly recognized as a serious health problem in the treatment of schizophrenia with the second-generation antipsychotics, the discussion on the health risks of antipsychotic drugs is turning away from the drug-related neurological motor side-effects to, among other things, the endocrinological problem of disturbed glucose metabolism. Irrespective of the uncertainty that surrounds the still-open question of the pathophysiological mechanisms involved (iatrogenic or endogenic), the implications are both distinct and severe. The results of this study clearly indicate the importance, if not necessity, of assessment of glucose metabolism in patients with schizophrenia or schizoaffective disorder. In case of doubt, the OGTT is the more sensitive measurement but in clinical practice is less feasible then a fasting glucose.

The monitoring protocol of the consensus development conference (45) restricts fasting glucose measurement to

patients treated with atypical antipsychotics. We suggest a modification of this consensus to extend this measurement to all patients with schizophrenia or schizoaffective disorder, irrespective of the use or type of antipsychotic drug applied.

Acknowledgments— This study was made possible by unrestricted grants from Dr. Paul Janssen Stichting (Tilburg) and Rijngeestgroep (Oegstgeest).

We thank Peter Edelbroek, Hugo van Engelsdorp, Marijke Fröhlich, Karen Gehring, Nil Kaymaz, Roel de Rijk, Jeannine Stelck, and Tinie van der Tang for their contributions.

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