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Original article

Oral glucose tolerance tests in treated patients with schizophrenia. Data to support an adaptation of the proposed guidelines for monitoring of patients on second generation antipsychotics?

Marc De Hert [a,*], Dominique Van Eyck [a], Linda Hanssens [b], Hendrik Peuskens [a], Erik Thys [a], Martien Wampers [a], Andre Scheen [c], Jozef Peuskens [a]

[a] *University Centre Sint-Jozef, Katholieke Universiteit Leuven, Leuvensesteenweg 517, 3070 Kortenberg, Belgium*
[b] *Department of Epidemiology and Public Health, University of Liège, Liège, Belgium*
[c] *Service of Diabetology, CHU de Sart Tilman, Université de Liège, Liège, Belgium*

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Abstract

***Objective.* –** A recent consensus conference has proposed guidelines for the monitoring for diabetes in patients with schizophrenia and also identifies the need of long-term prospective studies.

***Method.* –** A large scale prospective study on metabolic risks of antipsychotic medication is currently ongoing. At baseline, patients get a full laboratory screening, ECG and an oral glucose tolerance test (OGTT). Baseline data on 100 non-diabetic patients at study inclusion and stable on medication for at least 6 months are presented.

***Results.* –** Glucose abnormalities are found in 22% of patients at baseline. A monitoring protocol based only on fasting glucose would not have detected 63.6% of these patients with classifiable glucose abnormalities in our sample. Fasting insulin and measures for insulin resistance have a high predictive value for abnormalities late in the OGTT.

***Conclusion.* –** Already at baseline, metabolic problems are frequently present in patients with schizophrenia treated with antipsychotics. Adding assessment of fasting insulin in a monitoring protocol improves detection of glucose abnormalities late in an OGTT.

Keywords: Schizophrenia; Diabetes; Metabolic syndrome; Antipsychotics

1. Introduction

In recent years there is a growing awareness of a possible association of both schizophrenia and antipsychotic medication with diabetes [1–3,7,11–13,15,17–20]. Numerous case reports and some large retrospective cohort studies have documented an increased risk of diabetes in patients with schizophrenia and with some second generation antipsychotics (SGA) leading Lean and Pajonk [15] to identify patients on SGA as another high risk group for diabetes in their review article.

A recent American consensus conference dealing with this problem has proposed much awaited guidelines for the monitoring of patients with schizophrenia on SGA [1] and recommended acquiring additional data, especially from large scale prospective studies.

We report from a large scale prospective study which is currently ongoing in Belgium. The screening method adopted is more elaborate than the proposed monitoring protocol. An interim analysis on 100 patients will highlight potential advantages of our approach.

2. Subjects and methods

Patients with a DSM-IV diagnosis of schizophrenia or schizoaffective disorder, both in- and outpatients, under the care of a single psychiatric hospital, are asked to participate in an extensive screening and prospective follow-up of metabolic parameters. At baseline, patients get a full laboratory screening, ECG and a 75 g oral glucose tolerance test (OGTT). Patients were instructed on an overnight fast and were observed during the OGTT.

The aim is to follow patients included in the study prospectively for 1 year, and to retest them at regular intervals (including an OGTT).

* Corresponding author. Tel.: +32 2 758 0546; fax: +32 2 759 5380.
E-mail address: marc.de.hert@uc-kortenberg.be (M. De Hert).

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The present report includes data at baseline from the first contingent of 100 patients who had been stable on their antipsychotic medication regime for at least 6 months and without a prior diagnosis of diabetes mellitus.

For the evaluation of the metabolic syndrome we use the ATP-III criteria [10] and for the diagnosis of diabetes and impaired glucose tolerance (IGT) we follow the criteria of the American Diabetic Association [8].

Descriptive statistics are applied for basic demographic and clinical values as well as for variables relevant for the evaluation of metabolic abnormalities.

The influence of ATP-III criteria for the metabolic syndrome, waist circumference, BMI and diabetic abnormalities on insulin and glucose values of the OGTT is evaluated by means of an ANOVA.

A logistic regression analysis is performed to evaluate the predictive value of results by means of an odds ratio and calculation of the positive predictive value (PPV).

The study is approved by an ethical committee and all patients gave written informed consent.

3. Results

The mean age of patients is 38.0 years (std 8.7 years) and they have been ill for 13.5 years (std 8.4 years) on average. 66% of the patients are male.

All patients are treated with antipsychotic medication. On average they receive 3.8 (std 2.3) different drugs. On average they get 1.4 (std 0.7) antipsychotics, which are combined in 26% with anticholinergics, 48% antidepressants, 38% benzodiazepines, 27% mood-stabilizers and 46% somatic medication.

Thirty-three percent of patients get typical antipsychotics and 89% get SGA: 9% amisulpride; 31% clozapine, 32% olanzapine; 8% quetiapine; 20% risperidone.

The metabolic syndrome is present in 22% of patients, 39% of patients are overweight, 25% are obese. The prevalence of individual metabolic risk factors is: 45% hypertriglyceridemia, 44% increased waist circumference, 29% low HDL, 20% hypertension, 8% impaired fasting glucose (IFG).

Glucose abnormalities are found in 22% of patients: 4% meet criteria for diabetes (two patients had glucose values above 200 mg/dl at 120 min, both with IFG), 16% meet the criteria for IGT and 2% have IFG without other glucose abnormalities in the OGTT. Furthermore, 35% of patients have post-glucose hyperinsulinemia and delayed insulin release.

Fourteen of the 16 patients with IGT have normal fasting glucose levels, while as a group, patients with IGT have significantly higher fasting insulin levels compared to patients with normal glucose tolerance ($P = 0.0003$).

A monitoring protocol based only on fasting glucose would have accounted for only 12.5% of IGT, an identified pre-diabetic stage, and 50% of diabetes cases in our sample. Overall, 63.6% of patients with classifiable glucose abnormalities would not have been detected.

Patients meeting ATP-III criteria for the metabolic syndrome have higher fasting glucose ($P = 0.0089$), higher glucose at 120 min in the OGTT ($P = 0.0032$), higher fasting insulin ($P = 0.009$) and higher HOMA-IR (a measure of insulin resistance calculated from fasting glucose and fasting insulin; $P = 0.0035$). Patients with elevated waist circumference only have higher glucose at 120 min in the OGTT ($P = 0.0171$) and higher insulin levels at each point in the OGTT. Comparing obese and non-obese patients only identifies significant differences in insulin values at each point in the OGTT.

Table 1
Influence of fasting insulin and HOMA-IR on IFG and IGT

	IFG		IGT
	Odds ratio (95% CI)	PPV	Odds ratio (95% CI) PPV
FINS >20	8.2 (1.77–38)	29	10.1357 (2.91–35.26)
	$P = 0.0099$		$P = 0.0003$
IR >5	4.92 (1.02–23.76)	61	8.06 54 (2.28–28.42)
	$P = 0.0638$		$P = 0.0013$

IFG = impaired fasting glucose, IGT = impaired glucose tolerance, FINS = fasting insulin, IR = HOMA-IR.

Hemoglobin A1c values is not different between patients with or without diabetic abnormalities ($P = 0.1725$).

Both fasting insulin values ($P = 0.0015$) and HOMA-IR ($P = 0.0003$) are significantly different between non-diabetic, IGT and diabetic cases.

A logistic regression analysis shows that both fasting insulin >20 microU and HOMA-IR >5 are predictors of both IFG and IGT (Table 1).

Of the four cases of detected diabetes three patients are on olanzapine (one combination with clozapine) and one on a classical antipsychotic. Diabetes was confirmed with a test on another day and none of the patients had symptoms of diabetes when diabetes was detected. Among the patients with IGT, five are treated with olanzapine (one in combination with clozapine, one in combination with classical antipsychotics), six with clozapine, three with risperidone, two with classical antipsychotics and one with quetiapine.

4. Discussion

Our study confirms that metabolic abnormalities are frequent in a cohort of relatively young, treated, patients with schizophrenia. Twenty-two have a full metabolic syndrome and the elaborate screening identified 4% of the patients with diabetes (all abnormal values confirmed on another day) and 18% of the patients with pre-diabetic abnormalities.

In routine practice metabolic consequences of antipsychotics often remain undetected and untreated. This is also suggested in two recent large scale naturalistic studies of treatment practices in Belgium [4,22]. Only 3% of ambulatory and 1.7% of hospitalized patients with schizophrenia receive antidiabetic medication, while the estimated prevalence of diabetes in this population is at least double. Only one out of

three ambulatory patients had a laboratory screening looking at metabolic parameters in the last 6 months.

Recent consensus statement gives much awaited guidelines for screening for metabolic disturbances linked to antipsychotic treatment [1,5,9]. A wide distribution of these guidelines is important to raise the awareness of clinicians.

With a monitoring protocol based only on fasting glucose however, 63.6% of patients with classifiable glucose abnormalities would not have been detected. Combining fasting glucose measurements with fasting insulin, using a cut-off value for fasting insulin of 20 microU/ml, improved the prediction of IGT threefold, yielding a PPV of 57. The long-term follow-up of patients with repeated measures of fasting glucose may improve the sensitivity.

Metabolic risk factors such as the presence of ATP-III defined metabolic syndrome and obesity correlate more closely with abnormal insulin values in the OGTT than with glucose levels.

Our data suggests that the assessment of fasting insulin together with fasting glucose is useful [18]. Fasting insulin levels and the HOMA-IR are highly correlated with glucose abnormalities in the OGTT. High fasting insulin levels should be an indication for closer monitoring and more rigorous evaluation. HOMA-IR is useful in follow-up of patients to indicate whether insulin resistance increases over time [6,14]. A recent Belgian consensus conference on metabolic problems associated with antipsychotic medication advocates a closer and more frequent monitoring system than proposed in the APA/ADA guidelines, and proposes the assessment of fasting insulin levels [1,5].

Hemoglobin A1c measurements which are useful in the long-term follow-up of diabetic patients may of little use in screening for possible diabetes in schizophrenic patients.

In conclusion, we propose to include measurements of fasting insulin in the screening protocol allowing for improved detection of metabolic disturbances and useful in the long-term follow-up after calculation of insulin resistance. We propose to perform a full OGTT, or at least glucose and insulin measurements 2 h after glucose challenge, in patients with high fasting insulin values and with risk factors for diabetes additional to the use of antipsychotics. Although performing on OGTT is considered costly and inconvenient by some [16,21], our experience suggests that, with appropriate information to patients, performing an OGTT in this group at risk for diabetes is feasible in the majority of patients and should not be delayed.

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