

Glycosylated hemoglobin as a screening test for hyperglycemia in antipsychotic-treated patients: a follow-up study

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Purpose: To assess the point prevalence of undetected prediabetes (preDM) and diabetes mellitus (DM) in patients treated with antipsychotics and to compare metabolic parameters between patients with normoglycemia (NG), preDM, and DM. Furthermore, conversion rates for preDM and DM were determined in a 1-year follow-up.

Patients and methods: In a naturalistic cohort of 169 patients, fasting glucose (FG) and hemoglobin A_{1c} (HbA_{1c}) criteria were applied at baseline and at follow-up after 1 year. A distinction was made between baseline patients diagnosed according to FG (B-FG) and those diagnosed according to HbA_{1c} (B-HbA_{1c}). Conversion rates in the 1-year follow-up were compared between B-FG and B-HbA_{1c}.

Results: At baseline, preDM and DM were present in 39% and 8%, respectively. As compared to patients with NG, metabolic syndrome was significantly more prevalent in patients with preDM (62% vs 31%). Although the majority of patients were identified by the FG criterion, HbA_{1c} contributed significantly, especially to the number of patients diagnosed with preDM (32%). Regarding the patients with preDM, conversion rates to NG were much higher in the B-FG group than in the B-HbA_{1c} group (72% vs 18%). In patients diagnosed with DM, conversion rates were found for B-FG only.

Conclusion: PreDM and DM are highly prevalent in psychiatric patients treated with antipsychotic drugs. HbA_{1c} was shown to be a more stable parameter in identifying psychiatric patients with (an increased risk for) DM, and it should therefore be included in future screening instruments.

Keywords: severe mental illness, prediabetes, diabetes, fasting glucose, HbA_{1c}

Introduction

Diabetes mellitus (DM) is a chronic illness that has been associated with a two- to three-fold increased incidence of cardiovascular disease independent of other well-known risk factors.^{1,2} For decades, either the fasting glucose (FG) or the 2-hour value in the oral glucose tolerance test was used as a major criterion for the diagnosis of DM. Since glycosylated hemoglobin A_{1c} (HbA_{1c}) is a reliable measure of long-term glycemic exposure and is strongly correlated with diabetic complications, the American Diabetes Association (ADA) included HbA_{1c} for which no fasting conditions are necessary, as an additional diagnostic test.^{3,4} Hyperglycemia that does not fulfill diagnostic criteria for DM is known as prediabetes (preDM). PreDM is commonly associated with (components of) metabolic syndrome (MetS),^{5,6} and is a strong risk factor for the future development of DM and cardiovascular events.^{7,8} Detection of preDM is of special importance to prevent or delay the development of DM by means of lifestyle

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interventions such as dietary change and regular physical exercise.^{9,10} In an effort to identify persons with preDM, diagnostic categories of impaired fasting glucose, impaired glucose tolerance, and HbA_{1c} have been established.⁴

Patients with severe mental illness (SMI) have a disease-related increased risk of both hyperglycemia and DM,^{11–13} which can further be raised by treatment with antipsychotics, known to induce or worsen glycemic dysregulation.^{14–16} There seems to be, however, a lack of monitoring and management of glycemic abnormalities in patients with SMI.¹⁷ Therefore, the treating clinician should be aware of the potential cardiometabolic risk, and a multidisciplinary assessment of psychiatric and somatic health care is warranted.¹⁸

In a recent study, preDM was found to be present in 37% of patients treated with antipsychotics and appeared to be correlated with markers of central obesity, dyslipidemia, and insulin resistance.¹⁹ Furthermore, it was shown that the simultaneous use of the FG and HbA_{1c} criteria identifies the majority of patients with preDM.

The primary aim of the present study was to assess the point prevalence of undetected preDM and DM in patients treated with antipsychotics using the FG and HbA_{1c} criteria, and to compare metabolic parameters between patients with normoglycemia (NG), preDM, and DM. In addition, conversion rates from NG to preDM and DM and vice versa were calculated in a 1-year follow-up to determine the number of patients developing or reversing glycemic abnormalities. To assess stability over time of the diagnostic parameters FG and HbA_{1c}, baseline values of FG (B-FG) and HbA_{1c} (B-HbA_{1c}) were compared with those after 1-year follow-up.

Material and methods

Study design and subjects

This naturalistic cohort study was conducted at the outpatient departments of the Vincent van Gogh Institute for Psychiatry in the Netherlands and approved by the Institutional Review Board of the psychiatric training hospital. Informed consent was obtained from all patients. A health monitor was introduced as a screening instrument in a treatment and recovery program at the outpatient departments. From November 2008 to July 2011, 169 patients had complete assessments at baseline and after 1-year follow-up.

Assessment of parameters

Trained nurse practitioners conducted a standardized patient interview and studied medical records to collect information about DSM-IV (*Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition) diagnoses, smoking status,

substance abuse, prescription of psychiatric and somatic medications, (family) history of cardiovascular disease, and/or DM. Furthermore, a physical examination was performed, including measurements of height (cm), body weight (kg), waist circumference (cm), and arterial blood pressure (mmHg). Laboratory tests comprised FG, HbA_{1c}, triglycerides (TG), total cholesterol, high density lipoprotein (HDL) cholesterol, and low density lipoprotein cholesterol.

All patients and/or their caregivers were clearly instructed that blood sampling had to be performed under fasting conditions.

Evaluation of somatic parameters

Patients were categorized according to the FG and HbA_{1c} criteria from the ADA as having NG (FG <5.6 mmol/L or HbA_{1c} <5.7%), preDM (FG 5.6–6.9 mmol/L or HbA_{1c} 5.7%–6.4%), or DM (FG ≥7.0 mmol/L or HbA_{1c} ≥6.5%).⁴ Body mass index (BMI) was calculated (kg/m²), and obesity was present when BMI ≥30 kg/m².

According to the European guidelines on cardiovascular disease prevention in clinical practice,²⁰ a diagnosis of hypertension was based on a systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg, or use of antihypertensive medication. In addition, high TG (≥1.7 mmol/L), low HDL cholesterol (female <1.3 mmol/L, male <1.0 mmol/L), and high low-density lipoprotein cholesterol (≥3.0 mmol/L or treatment with lipid-lowering agents) were defined.

MetS was defined according to the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel-III) (ATP-III) guidelines,²¹ and the diagnosis was made when patients fulfilled three or more of the following five criteria: waist circumference >88 cm in women and >102 cm in men, fasting blood glucose ≥6.1 mmol/L or treatment with antidiabetic medication, HDL <1.3 mmol/L in women and <1.0 mmol/L in men, TG ≥1.7 mmol/L, and blood pressure ≥130/85 mmHg or treatment with antihypertensives.

Statistical analyses

The percentages of patients who fulfilled criteria for NG, preDM, and DM according to FG or HbA_{1c} criteria were calculated at baseline and follow-up. Independent sample *t*-tests and chi-square tests were used to compare demographic, clinical, and cardiometabolic parameters between patients with NG, preDM, and DM. The percentages of patients developing or reversing preDM or DM were

calculated. All data were analyzed using SPSS 16.0 for Windows. Statistical significance was considered at the level of $P < 0.05$.

Results

Demographic and clinical characteristics

In a period of 32 months, 169 patients with SMI, previously known to be nondiabetic, were examined at baseline and after 1-year follow-up. Demographic and clinical characteristics of this group are presented in Table 1. Concerning antipsychotic treatment at baseline, the majority of patients used antipsychotic monotherapy ($n=148$; 88%). Conventional antipsychotics were prescribed to 41 patients (28%) (haloperidol: $n=18$; zuclopenthixole: $n=11$; pimozide: $n=3$; flupenthixol: $n=4$; bromperidol: $n=2$; penfluridol: $n=2$; fluspirilene: $n=1$). A total of 107 patients (72%) received atypical antipsychotics (risperidon: $n=42$; olanzapine: $n=17$; quetiapine: $n=10$; aripiprazole: $n=5$; clozapine: $n=32$; sertindole: $n=1$). Twenty-one patients

(12%) were treated with two antipsychotics (conventional only: $n=3$; atypical only: $n=7$; conventional and atypical: $n=11$). At follow-up after 1 year, there were no significant changes in antipsychotic treatment regimens or cardio-metabolic parameters.

Prevalence of NG, preDM, and DM at baseline and follow-up

At baseline, 90 out of 169 patients (53%) were identified with NG, whereas 66 (39%) fulfilled criteria for preDM (FG only: $n=32$, HbA_{1c} only: $n=21$, both: $n=13$) (Figure 1), and 13 (8%) were diagnosed with DM (FG only: $n=11$, HbA_{1c} only: $n=1$, both: $n=1$). As compared to patients with NG, prediabetic patients had a larger waist circumference (106 cm vs 99 cm, $P < 0.001$), higher BMI (30 kg/m² vs 27 kg/m², $P < 0.001$), higher systolic blood pressure (128 mmHg vs 123 mmHg, $P = 0.011$), higher diastolic blood pressure (86 mmHg vs 81 mmHg, $P < 0.001$), and higher TG levels (2.4 mmol/L vs 1.8 mmol/L, $P < 0.001$) (Table 2). As shown in Figure 2, patients with preDM were more frequently diagnosed with obesity (41% vs 20%, $P = 0.004$), high TG (62% vs 43%, $P = 0.02$), low HDL (58% vs 34%, $P = 0.004$), and MetS (62% vs 31%, $P < 0.001$). No significant differences in age, sex, family history of cardiovascular disease or DM, psychiatric diagnoses, smoking status, number or type of antipsychotic agent(s),

Table 1 Demographic and clinical characteristics of the study group at baseline and follow-up after 1 year

| | N=169 | N=169 |
|---|------------------|------------------|
| Mean age \pm SD | 41 \pm 12 | 42 \pm 12 |
| Male/female | 102/67 (60%/40%) | 102/67 (60%/40%) |
| Caucasian | 125 (74%) | 125 (74%) |
| Smoking | 91 (54%) | 88 (52%) |
| DSM-IV classification | | |
| Schizophrenia | 96 (57%) | 96 (57%) |
| Schizoaffective disorder | 26 (15%) | 29 (17%) |
| Other psychotic disorder | 42 (25%) | 38 (23%) |
| Bipolar disorder | 2 (1%) | 2 (1%) |
| Others | 3 (2%) | 4 (2%) |
| Mean duration of illness (years \pm SD) | 13 \pm 8 | 14 \pm 8 |
| Number of antipsychotic agents | | |
| One antipsychotic | 148 (88%) | 135 (80%) |
| ≥ 2 Antipsychotics | 21 (12%) | 28 (17%) |
| Other psychotropics | | |
| Antidepressants | 38 (23%) | 34 (20%) |
| Mood stabilizers | 28 (17%) | 26 (15%) |
| Benzodiazepines | 63 (37%) | 64 (38%) |
| Cardiometabolic parameters | | |
| BMI (kg/m ²) | 27.9 | 28.1 |
| Waist circumference (cm) | 102.1 | 102.0 |
| Blood pressure (mmHg) | 127/83 | 124/82 |
| Total cholesterol (mmol/L) | 5.4 | 5.2 |
| LDL (mmol/L) | 3.3 | 3.2 |
| HDL (mmol/L) | 1.2 | 1.2 |
| TG | 2.1 | 2.1 |
| FG (mmol/L) | 5.5 | 5.4 |
| HbA _{1c} (%) | 5.4 | 5.5 |

Abbreviations: BMI, body mass index; DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition; FG, fasting glucose; HbA_{1c}, glycosylated hemoglobin; HDL, high density lipoprotein; LDL, low density lipoprotein; TG, triglycerides.

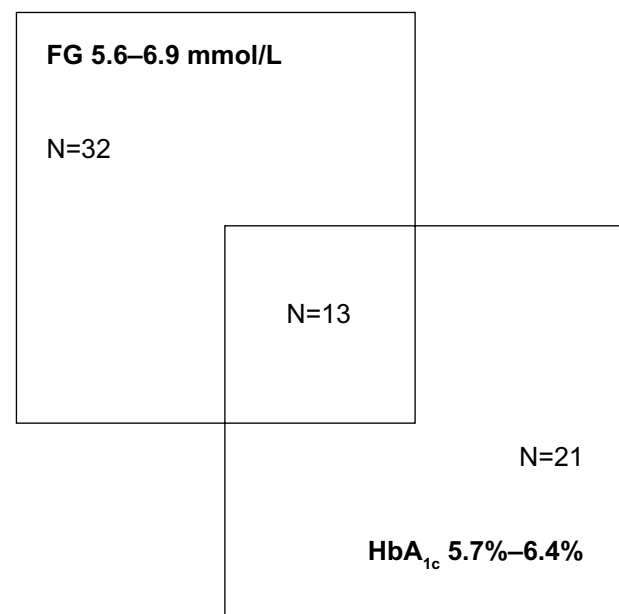


Figure 1 Number of baseline patients with preDM ($n=66$) according to FG only ($n=32$), HbA_{1c} only ($n=21$), or both ($n=13$).

Abbreviations: FG, fasting glucose; HbA_{1c}, glycosylated hemoglobin; preDM, prediabetes.

Table 2 Cardiometabolic parameters in patients with NG, preDM, and DM

| | NG (n=90) | PreDM (n=66) | DM (n=13) |
|---------------------------------|--------------|-----------------|--------------|
| Waist circumference (cm) | 99 | 106* | 105 |
| BMI (kg/m ²) | 27 | 30* | 29 |
| Systolic blood pressure (mmHg) | 123 | 128* | 136 |
| Diastolic blood pressure (mmHg) | 81 | 86* | 87 |
| Total cholesterol (mmol/L) | 5.3 | 5.4 | 1.4 |
| HDL (mmol/L) | 1.3 | 1.1 | 1.1 |
| LDL (mmol/L) | 3.3 | 3.3 | 3.3 |
| TG (mmol/L) | 1.8 | 2.4* | 3.0 |

Note: *Significant difference between preDM and NG ($P < 0.05$).

Abbreviations: BMI, body mass index; DM, diabetes mellitus; HDL, high density lipoprotein; LDL, low density lipoprotein; NG, normoglycemia; preDM, prediabetes; TG, triglycerides.

or co-medication with antidepressants and/or mood stabilizers were found.

In comparison to diabetic patients, patients with preDM were younger (42 years vs 50 years, $P = 0.001$). There were no significant differences in sex, family history of cardiovascular disease or DM, cardiometabolic parameters, smoking status, psychiatric diagnoses, and psychotropic treatment variables between prediabetic and diabetic patients.

After 1 year, 49 out of 169 patients (29%) were diagnosed with preDM (FG only: $n = 25$, HbA_{1c} only: $n = 16$, both: $n = 8$) and 14 (8%) with DM (FG only: $n = 11$, HbA_{1c} only: $n = 1$, both:

$n = 2$). The remaining 106 patients (63%) did not fulfill the criteria for hyperglycemia and were classified as NG.

Follow-up data of patients with NG at baseline (n=90)

Of the 90 normoglycemic patients at baseline, after 1 year, 74 patients (82%) were still normoglycemic. In 13 patients (15%), conversion to preDM was found (FG only: $n = 11$, FG and HbA_{1c}: $n = 2$), whereas three (3%) had developed DM (FG only: $n = 3$).

Follow-up data of patients with preDM at baseline (n=66)

At baseline, 32 patients were diagnosed with preDM according to the FG criterion only (B-FG). As depicted in Figure 3A, after 1 year, 23 patients (72%) reversed to NG, eight patients (25%) still fulfilled criteria for preDM (FG only: $n = 6$, FG and HbA_{1c} only: $n = 2$), and only one patient (3%) developed DM (FG only).

Of the 34 B-HbA_{1c} patients with preDM, six patients (18%) reversed to NG, 24 (70%) were still diagnosed with preDM (FG only: $n = 5$, HbA_{1c} only: $n = 13$, both: $n = 6$), and four (12%) fulfilled criteria for DM (FG only: $n = 3$, HbA_{1c} only: $n = 1$) (Figure 3B).

Thus, after 1 year, 28% (25% + 3%) of the B-FG patients vs 82% (70% + 12%) of the B-HbA_{1c} patients remained in a hyperglycemic state.

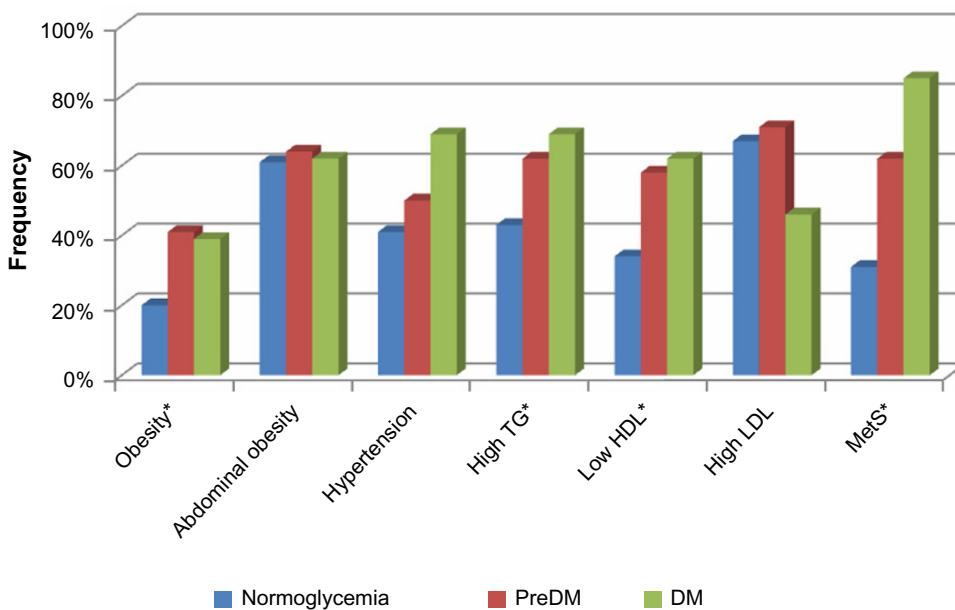


Figure 2 Frequencies of cardiometabolic parameters in patients with NG (n=90), preDM (n=66), and DM (n=13).

Note: *Significant differences ($P < 0.05$) between patients classified as preDM vs NG.

Abbreviations: DM, diabetes mellitus; HDL, high density lipoprotein; LDL, low density lipoprotein; MetS, metabolic syndrome; NG, normoglycemia; preDM, prediabetes; TG, triglycerides.

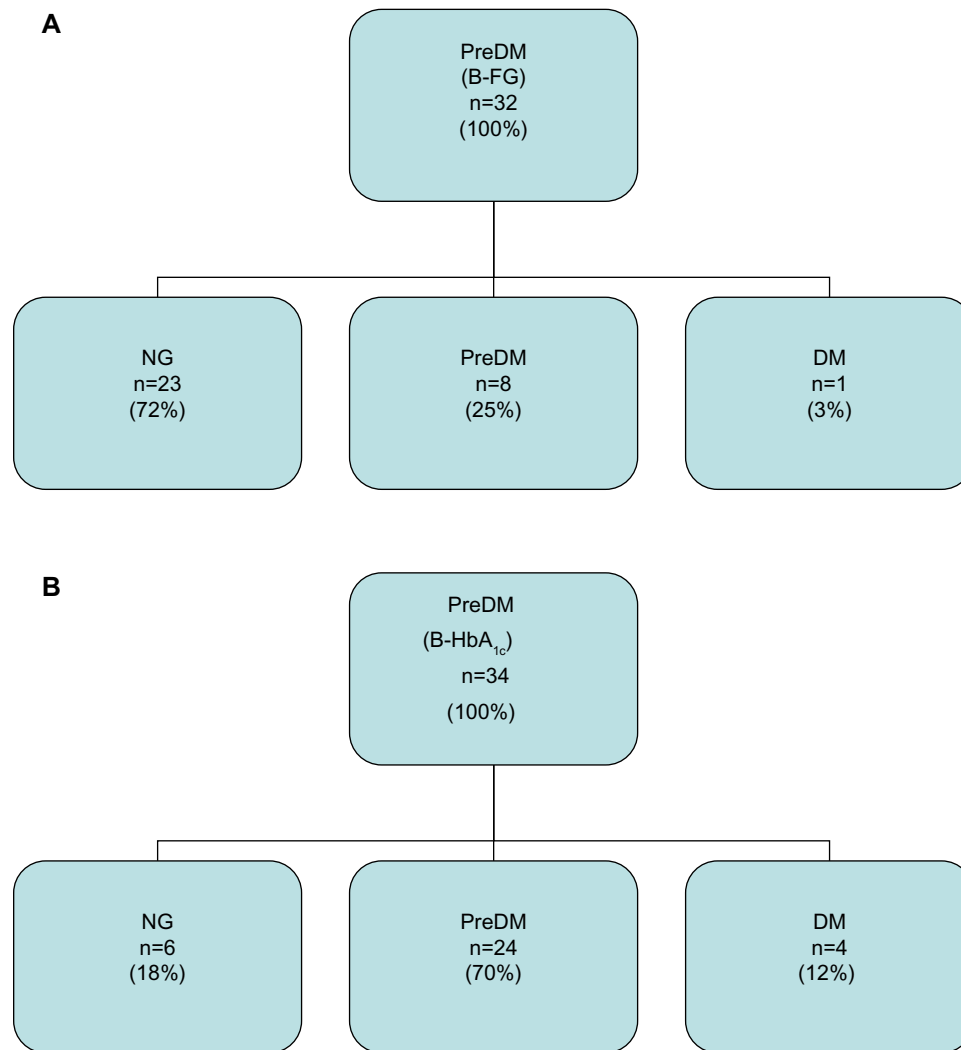


Figure 3 Follow-up on patients with a baseline diagnosis of preDM according to **(A)** FG criteria only (B-FG) (n=32) and **(B)** HbA_{1c} criteria (B-HbA_{1c}) (n=34).

Abbreviations: B-FG, baseline patients diagnosed according to FG; DM, diabetes mellitus; FG, fasting glucose; HbA_{1c}, glycosylated hemoglobin; NG, normoglycemia; B-HbA_{1c}, baseline patients diagnosed according to HbA_{1c}; preDM, prediabetes.

Follow-up data of patients with DM at baseline (n=13)

After 1 year, three of the eleven B-FG patients (28%) reversed to NG, four patients (36%) fulfilled criteria for preDM (FG only: n=3, HbA_{1c} only: n=1), and four patients (36%) still fulfilled criteria for DM (FG only: n=4). The two B-HbA_{1c} patients still fulfilled criteria for DM at follow-up.

Discussion

The present study demonstrates that, using FG and HbA_{1c} criteria, undetected preDM and DM were present in 39% and 8% of SMI patients treated with antipsychotics, respectively. Although in the present study the majority of prediabetic and diabetic patients were diagnosed by the FG

criterion, HbA_{1c} appeared to contribute significantly to the number of patients identified, especially those with preDM (32%). As compared to patients with NG, cardiometabolic parameters, including MetS, were more prevalent in patients with preDM. These findings are in line with data reported elsewhere.¹⁹

After 1 year, the prevalence of preDM had decreased about 10% but that of DM did not change. A more detailed analysis of the conversion rates, however, disclosed that over a period of 1 year, 15% vs 3% of the baseline normoglycemic patients developed preDM and DM, respectively. Of the patients with preDM at baseline, in 7% (five out of 66) DM was diagnosed at follow-up. The incidence rate of DM in these SMI patients is about ten-fold as high as compared to the general population in the Netherlands (0.2%–0.3%).²²

These findings stress the high cardiometabolic risk of patients with SMI. On the other hand, it cannot be ruled out a fortiori that during this 1-year period, changes in lifestyle have contributed to a change in glucose state.

It should be underlined, however, that a substantial number of patients with a baseline diagnosis of preDM or DM showed conversion to NG at follow-up, ie, 44% or 23%, respectively. This phenomenon may be explained by the dynamic course of glucose metabolism, which stresses the need for systematic and repeated evaluation of glucose parameters.²³ The reversion into a normoglycemic state also raises the question about the use of FG as a diagnostic test. In this study, it was shown that the conversion rates were higher in patients with hyperglycemia according to FG in comparison to HbA_{1c}. After 1 year, 82% of the B-HbA_{1c} patients remained in a hyperglycemic state as compared to only 28% of the B-FG patients. Therefore, HbA_{1c} seems to be a more stable parameter over time in diagnosing glucose abnormalities in patients with SMI. Nevertheless, in contrast to the ADA, the World Health Organization states that there is currently insufficient evidence to make a formal recommendation on the interpretation of HbA_{1c} levels below 6.5%.²⁴ Furthermore, it is worth mentioning that, since HbA_{1c} reflects the average glucose levels over the past 6–8 weeks, acute changes in glucose metabolism potentially induced by antipsychotics cannot be detected.

It is worth noting that a diagnosis of preDM or diabetes was established according to only one laboratory assessment. When glycemic abnormalities were found, patients were sent to their general practitioner for further analysis, lifestyle advice, and somatic treatment when indicated. Unfortunately, information about the number of patients in whom lifestyle modification took place was not collected and therefore its possible contribution to change in glucose metabolism could not be assessed. Another limitation is the relatively small sample size, so the results may not be representative of all antipsychotic-treated patients. Long-term follow-up studies of glucose metabolism in larger sample sizes are warranted to better understand glucose metabolism in patients with SMI.

In conclusion, systematic evaluation of glucose parameters in antipsychotic-treated patients is necessary, in order to detect glucose dysregulations at an early stage and to prevent premature metabolic and cardiovascular complications. As there is no need for a fasting condition and HbA_{1c} is more stable over time, this test should be used, in addition to FG, to screen for glucose abnormalities in psychiatric patients at risk for DM. Further studies are warranted to assess the course of glucose dysregulation in patients with SMI in order to establish an appropriate screening instrument and somatic treatment protocol.

Acknowledgments

The authors are indebted to the patients, their caregivers, and the nursing staff for their willingness to participate in the study. All patients provided informed consent that was noticed in their medical records. Somatic screening was performed by Hans DH Kok, general practitioner at the Vincent van Gogh Institute for Psychiatry. Laboratory analyses were performed by the biochemical laboratories of the general hospital VieCuri in Venray/Venlo, the Netherlands. This study was partially supported by unrestricted grants from Astra-Zeneca, Janssen Pharmaceuticals, and Lundbeck BV.

Disclosure

The authors report no conflicts of interest in this work.

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