Insulin sensitivity, adjusted β-cell function and adiponectinaemia among lean drug-naive schizophrenic patients treated with atypical antipsychotic drugs: A nine-month prospective study


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Abstract

Atypical antipsychotic drugs (AADs) induce weight gain and truncal adiposity, and even the metabolic syndrome (MetS), which may progress to IFG/IGT or DM. AAD effects in lean schizophrenic patients without MetS have not been documented, especially in terms of weight gain and changes in insulin sensitivity (S), beta-cell function (β) and adiponectinaemia. We prospectively determined the effects of nine-month therapy with AADs on anthropometrics, metabolism and adiponectinaemia, including homeostasis model assessment (HOMA) modelling of S changes in insulin sensitivity (S), beta-cell function (β) and adiponectinaemia. We analyzed 36 schizophrenic subjects (M/F: 24/12; Caucasian: n = 23, North African: n = 12, South Asian: n = 1) aged 35 ± years (mean ± one S.D.) free of MetS (NCEP–ATPIII), of whom 19 study completers were evaluated following AAD treatment. S, β, β × S and adiponectin were measured at zero, three and nine months. At nine months, BMI had risen from 22 ± 2 to 25 ± 2 kg/m² (P < 0.001) and waist circumference from 85 ± 8 to 91 ± 11 cm (P < 0.001), while adiponectin decreased from 10.4 ± 5.1 to 7.4 ± 3.8 μg/mL (P < 0.001). Blood pressure and lipids were unaffected. S decreased from 138 ± 49 to 110 ± 58% (P = 0.006) and β increased from 83 ± 24 to 100 ± 40% (P = 0.034). As a result, β × S decreased from 106 ± 19 to 91 ± 27% (P = 0.015). Fasting glycaemia rose from 89 ± 5 to 96 ± 9 mg/dL (P = 0.007). On study completion, 21% had IFG. Long-term use of AADs in lean, drug-naive, schizophrenics initially free of MetS induced weight gain and truncal fat accumulation associated with decreases in adiponectin and hyperbolic product, explaining the increased fasting glycaemia and impaired fasting glucose seen in predisposed individuals.

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Résumé

Sensibilité à l’insuline, fonction β ajustée et adiponectinémie de patients schizophrénes non obèses nouvellement traités par antipsychotiques atypiques : étude prospective de neuf mois.

Les médications antipsychotiques atypiques (APA) favorisent la prise pondérale, l’adiposité tronculaire et peuvent favoriser la survenue d’un phénotype de syndrome métabolique, associé éventuellement à une hyperglycémie à jeun, une intolerance au glucose ou un diabète. L’effet de l’administration d’APA chez des sujets schizophrénes APA-naïfs, maigres et sans syndrome métabolique (SM) n’est pas documenté, en particulier, la relation entre la prise pondérale et les modifications de la sensibilité à l’insuline (S), de la fonction bêta-sécrétoire (β) et de l’adiponectinémie. Nous avons déterminé prospectivement l’évolution après neuf mois d’APA des paramètres anthropométriques, métaboliques (dont la modélisation par homeostasis model assessment (HOMA) de S, β et du produit hyperbolic [β × S], qui mesure la fonction β ajustée selon la S individuelle) et de l’adiponectinémie. Nous avons analysé 36 sujets schizophreniques (M/F : 24/12; caucasiens : n = 23 ; nord-africains : n = 12 ; asiatiques : n = 1 ; 35 ± ans [moyenne ± D.S.J) et sans SM selon NCEP–ATPIII, parmi lesquels 19 ont été évaluables en fin d’étude. S, β, β × S et l’adiponectinémie ont été mesurés à zéro, trois et neuf mois. À neuf mois, l’indice de masse corporelle était en nette élévation de 22 ± 2 à 25 ± 2 kg/m² (P < 0.001), le périmètre abdominal augmentait de 85 ± 8 à 91 ± 11 cm (P < 0.001) et l’adiponectinémie diminuait de 10.4 ± 5.1 à 7.4 ± 3.8 μg/mL (P < 0.001). La pression artérielle et le profil lipidique n’étaient pas modifiés. S diminuait de 138 ± 49 à 110 ± 58% (P = 0.006) et β augmentait de 83 ± 24 à 100 ± 40 % (P = 0.034). Par conséquent, β × S diminuait de 106 ± 19 à 91 ± 27% (P = 0.015). La glycémie à jeun...
s’élèvait en moyenne de 89 ± 5 à 96 ± 9 mg/dL (P = 0,007). En fin d’évaluation (neuf mois), 21 % des sujets avaient développé une hyperglycémie à jeun non diabétique. L’utilisation prolongée d’APA chez des sujets schizophrènes APA-naïfs, maigres et sans SM préalable a induit une prise pondérale avec composante d’accrétion tronculaire, associée à une diminution de l’adiponectinémie et du produit hyperbolique $\beta \times S$, les modifications de ce dernier expliquant l’élévation de la glycémie à jeun moyenne et l’hyperglycémie pathologique observée chez certains sujets prédisposés.

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Keywords: Atypical antipsychotic drugs; Schizophrenia; Adiponectinaemia; $\beta$-cell function; Insulin resistance

Mots clés : Antipsychotiques atypiques ; Schizophrénie ; Adiponectine ; Fonction $\beta$ ; Résistance à l’insuline

1. Introduction

Over the past decade, second-generation atypical antipsychotic drugs (AADs) have largely superseded conventional antipsychotic drugs in the pharmacological management of schizophrenia [1,2]. Yet, several recent studies have reported a propensity of these newer agents to induce weight gain and predispose to comorbidities such as metabolic syndrome, impaired glucose homeostasis and diabetes mellitus [3–7]. While the mechanisms underlying these metabolic changes remain largely a subject of debate [8–11], decreased insulin sensitivity was proposed as a potential underlying factor for dysglycaemia [12]. Most studies in which patients were assessed prior to AAD administration included heterogeneous populations in terms of clinical characteristics and were biased towards those who were overweight or obese, thereby evaluating patients at risk of concomitant overweight-associated insulin resistance. However, so far, there has been no long-term prospective study of AADs in lean drug-naïve normoglycaemic patients to evaluate the influence of AADs on anthropometrics and determinants of glucose homeostasis.

In the present study, we sought to investigate the sequential (zero, three and nine months) clinical and metabolic changes induced by AADs, including alterations in insulin sensitivity and/or $\beta$-cell function, in a group of lean normoglycaemic individuals, antipsychotic-drug-naïve and free of metabolic syndrome at the time of enrolment.

2. Research design and methods

We prospectively determined the outcome of three and nine months of AAD therapy on the metabolic phenotype, anthropometry and glucose homeostasis determinants of lean patients with schizophrenia, the latter defined according to criteria presented in the Diagnostic and Statistical Manual of Mental Disorders (4th edn) [13]. We also measured adipocyte-derived adiponectin, a key adipokine involved in the regulation of fat oxidation in nonadipose tissue, insulin sensitivity and lipid metabolism. Inclusion criteria were: age 18–55 years; body mass index (BMI: weight [kg] × height [m]$^{-2}$) less than or equal to 25.0 kg/m$^2$; and absence of the metabolic syndrome according to NCEP–ATPIII criteria (waist circumference greater than or equal to 102 cm in men and greater than or equal to 88 cm in women, fasting plasma glucose greater than or equal to 100 mg/dL or diabetes, fasting serum triglycerides greater than or equal to 150 mg/dL, HDL cholesterol < 40 mg/dL in men and < 50 mg/dL in women and blood pressure greater than or equal to 130/85 mmHg, with three or more of these five criteria indicating the presence of the syndrome) [14]. Other exclusion criteria were: previous use of antipsychotic drugs; and concomitant therapy with drugs known to increase weight and/or alter glucose metabolism (including antihistamines, glucocorticoids, $\beta$-blockers, mood stabilizers, antiepileptic drugs and mirtazapine).

As for antipsychotic therapy, all recruited patients received AAD monotherapy with either quetiapine, olanzapine, risperidone or aripiprazole. The patient’s allocation to receive a given agent was decided upon by a psychiatrist, based exclusively on the prevailing psychiatric condition. The same AAD was maintained throughout the study at the same dosage. All patients attended the same psychiatric hospital and all biological samples were assayed at a central laboratory. On inclusion into the study, all subjects received the standard dietary and lifestyle counselling aimed at maintaining normal body weight.

Following the initiation of the AADs ($T_0$), all patients were reassessed at the outpatient clinic after three ($T_3$) and nine ($T_9$) months. Clinical characteristics (BMI, waist circumference, blood pressure) were determined at each visit ($T_0$, $T_3$ and $T_9$), as were fasting plasma glucose, HbA1c, serum adiponectin, ultrasensitive CRP ($\text{hsCRP}$), serum lipids, amylase, lipase, TSH, cortisol, albuminuria and ketonuria. Serum adiponectin was measured using a highly sensitive, enzyme-linked, two-site immunosorbent assay (Adiponectin Quantikine®, R&D Systems, Minneapolis, MN, USA). Homoeostasis model assessment of insulin sensitivity and $\beta$-cell function (HOMA-$S$ and HOMA-$\beta$, respectively), and the $\beta \times S$ product were obtained from the computed triplicate means of fasting glucose and specific insulin taken at five-minute intervals in the fasting state (arterialized venous blood at zero, five and ten minutes) [14–17]. HOMA-$\beta$ values were plotted as a function of HOMA-$S$, defining a HOMA-product ($\beta \% \times S \%$; normal value: 100%). Insulin sensitivity and $\beta$-cell function follow a hyperbolic relationship in individuals with normal or abnormal glucose tolerance. When insulin secretory capacity decreases, HOMA-$S$ increases in subjects with normal glucose tolerance (NGT) and glucose homoeostasis is maintained, albeit with a $\beta \times S$ function exhibiting different geometry. Abnormal glucose tolerance or diabetes mellitus develops when one variable or another fails to compensate, the individual then departing from the normal hyperbolic relationship [15–19]. To assess the magnitude of impaired glucose homoeostasis in schizophrenic patients, the cohort results were plotted against a series of
HOMA products calculated from local reference populations of type 2 diabetics (n = 511), lean and obese normoglycaemics (n = 47 and n = 31, respectively) and subjects with impaired fasting glucose (IFG; n = 30) (Fig. 2).

The inclusion period spanned October 2005 to December 2006. All patients gave their written informed consent to participate, and the research protocol was approved by the ethical committee of the université catholique de Louvain (reference: 2005/29 août/132).

3. Statistical analyses

Results are presented as means ± S.D. or as proportions. Differences in means or proportions were considered statistically significant at P values < 0.05. Numerical variables were compared between the various timepoints using the Friedman test. For comparison of differences in hyperbolic products, error propagation in the product term was taken into account, as described by Preumont et al. [19].

4. Results

Thirty-six consecutive adults (24 men, 12 women) were recruited into the study and treated with quetiapine (n = 12 [33%]), olanzapine (n = 3 [9%]), risperidone (n = 10 [29%]) and aripiprazole (n = 11 [30%]). Daily doses of the AADs were kept constant throughout the study. Mean age (± S.D.) was 35 ± years. The baseline clinical characteristics of the study patients are presented in Table 1. A first-degree family history of dysglycaemia was present in 22% and a personal history of (un)treated high blood pressure or (un)treated dyslipidaemia was found in 6% and 22% of patients, respectively. Current tobacco smoking was recorded in 83% of the patients. None of them had the metabolic syndrome phenotype at inclusion.

Nineteen adult patients (12 men, seven women) were fully evaluable at both T3 and T9. Drop-outs were patients who were lost to follow-up or noncompliant between either T0 to T3 (n = 10) or T3 to T9 (n = 7). The noncompleters’ baseline characteristics were similar to those of completers (data not shown), including clinical characteristics, male-to-female ratio, HOMA-S, HOMA-β and HOMA β × S. The mean age of the completers was 36 ± nine years, and they had been treated with quetiapine (n = 7 [37%]), olanzapine (n = 2 [11%]), risperidone (n = 5 [26%]) and aripiprazole (n = 5 [26%]). A first-degree family history of dysglycaemia was present in 11% and a personal history of high blood pressure and dyslipidaemia was present in 5% and 26%, respectively. Current smoking was recorded in 79% of these patients.

As shown in Table 1 and Fig. 1, there were significant increases in body weight and waist circumference in patients during follow-up, with mean BMI increasing from 22 ± 2 to 25 ± 2 kg/m² at T9 (P < 0.001). Fasting plasma glu-

Table 1
Clinical characteristics of schizophrenic patients

<table>
<thead>
<tr>
<th></th>
<th>Inclusion (T0)</th>
<th></th>
<th>T3</th>
<th>T9</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All patients²</td>
<td>Completers²</td>
<td>Completers²</td>
<td>Completers²</td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>36</td>
<td>19</td>
<td>19</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>67 ± 11</td>
<td>68 ± 12</td>
<td>72 ± 11</td>
<td>74 ± 12</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>82 ± 9</td>
<td>85 ± 8</td>
<td>89 ± 9</td>
<td>91 ± 11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Men (n = 24 all patients or 12 completers)</td>
<td>85 ± 8</td>
<td>87 ± 6</td>
<td>92 ± 7</td>
<td>96 ± 8</td>
<td>0.001</td>
</tr>
<tr>
<td>Women (n = 12 all patients or 7 completers)</td>
<td>76 ± 9</td>
<td>79 ± 9</td>
<td>84 ± 9</td>
<td>81 ± 10</td>
<td>0.076</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>22 ± 3</td>
<td>22 ± 2</td>
<td>24 ± 2</td>
<td>25 ± 2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>114 ± 10</td>
<td>112 ± 10</td>
<td>112 ± 11</td>
<td>113 ± 16</td>
<td>NS</td>
</tr>
<tr>
<td>Fasting glucose (mg/dL)²</td>
<td>88 ± 6</td>
<td>89 ± 5</td>
<td>90 ± 7</td>
<td>96 ± 9</td>
<td>0.007</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>5 ± 0</td>
<td>5.2 ± 0.3</td>
<td>5.4 ± 0.3</td>
<td>5.4 ± 0.3</td>
<td>0.103</td>
</tr>
<tr>
<td>Fasting insulin (µIU/mL)</td>
<td>6 ± 2</td>
<td>5.7 ± 2.3</td>
<td>5.5 ± 2.0</td>
<td>9.1 ± 8.7</td>
<td>0.030</td>
</tr>
<tr>
<td>HOMA-β (%)</td>
<td>89 ± 30</td>
<td>83 ± 25</td>
<td>83 ± 21</td>
<td>100 ± 40</td>
<td>0.034</td>
</tr>
<tr>
<td>HOMA-S (%)</td>
<td>134 ± 50</td>
<td>138 ± 49</td>
<td>135 ± 45</td>
<td>110 ± 58</td>
<td>0.006</td>
</tr>
<tr>
<td>HOMA β × S (%)</td>
<td>108 ± 22</td>
<td>106 ± 19</td>
<td>106 ± 20</td>
<td>91 ± 2</td>
<td>0.015</td>
</tr>
<tr>
<td>Adiponectin (µg/mL)</td>
<td>8.7 ± 5.0</td>
<td>10.4 ± 5.1</td>
<td>8.7 ± 4.6</td>
<td>7.4 ± 3.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Men (n = 24 all patients or 12 completers)</td>
<td>6.9 ± 4.7</td>
<td>8.8 ± 5.3</td>
<td>6.8 ± 3.8</td>
<td>5.9 ± 3.4</td>
<td>0.004</td>
</tr>
<tr>
<td>Women (n = 12 all patients or 7 completers)</td>
<td>12.6 ± 3.3</td>
<td>13.5 ± 3.0</td>
<td>12.3 ± 3.8</td>
<td>10.5 ± 2.8</td>
<td>0.069</td>
</tr>
<tr>
<td>hsCRP (mg/dL)³</td>
<td>0.27 ± 0.45</td>
<td>0.32 ± 0.52</td>
<td>0.39 ± 0.49</td>
<td>0.27 ± 0.30</td>
<td>NS</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)³</td>
<td>201 ± 44</td>
<td>209 ± 40</td>
<td>209 ± 41</td>
<td>207 ± 45</td>
<td>NS</td>
</tr>
<tr>
<td>HDL-C (mg/dL)³</td>
<td>46 ± 18</td>
<td>48 ± 20</td>
<td>47 ± 15</td>
<td>47 ± 18</td>
<td>NS</td>
</tr>
<tr>
<td>LDL-C (mg/dL)³</td>
<td>129 ± 36</td>
<td>134 ± 35</td>
<td>139 ± 33</td>
<td>134 ± 44</td>
<td>NS</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)³</td>
<td>129 ± 121</td>
<td>140 ± 138</td>
<td>117 ± 90</td>
<td>146 ± 136</td>
<td>NS</td>
</tr>
<tr>
<td>Albuminuria (mg/dL)</td>
<td>1.1 ± 1.1</td>
<td>0.8 ± 0.5</td>
<td>1.0 ± 0.6</td>
<td>0.9 ± 0.7</td>
<td>NS</td>
</tr>
</tbody>
</table>

Results are expressed as means ± one S.D.; differences in means or proportions were considered significant at P < 0.05; BMI, body mass index; HOMA, homeostasis model assessment; S, insulin sensitivity; β, β-cell function; β × S, HOMA hyperbolic product;

² Data from all study patients (n = 36).

³ Data from study completers (n = 19).

⁴ To convert values for blood glucose to millimol per liter, multiply by 0.05551.

⁵ To convert values for total cholesterol, HDL cholesterol and LDL cholesterol to millimol per liter, multiply by 0.02586.

⁶ To convert values for triglycerides to millimol per liter, multiply by 0.01129.
Fig. 1. Individual values for BMI, waist circumference, adiponectin levels, HOMA-S, HOMA-β, HOMA β × S and fasting glycaemia at baseline and after nine months of AAD treatment. The broken line in the lower right panel corresponds to the upper threshold for normal fasting glycaemia (100 mg/dL).

cose increased from 89 ± 5 at $T_0$ to 96 ± 9 mg/dL at $T_9$ ($P = 0.007$). Four patients developed abnormal fasting glycaemia (> 100 mg/dL), although none surpassed the threshold defining diabetes in the fasting state (> 126 mg/dL).

On study completion, a significant decrease in HOMA-S was observed, from 138 ± 49 to 110 ± 58% ($P = 0.006$), as well as an increase in relative insulin secretion, as reflected by HOMA-β (from 83 ± 25 to 100 ± 40%, $P = 0.034$). As a consequence of the former decreasing to a greater extent than the latter, HOMA β × S decreased from 106 ± 19 to 91 ± 27% ($P = 0.015$), as shown in Table 1 and Fig. 2. Comparison of HOMA products obtained in normoglycaemic subjects and other common conditions with well-established β-cell function showed significant differences in hyperbolic values at baseline for patients with type 2 diabetes versus obese and lean normoglycaemic, IFG or schizophrenic subjects, and for IFG versus lean normoglycaemic or schizophrenic subjects.

On inclusion, although none of the patients had the metabolic syndrome as required by the inclusion criteria, at nine months, three patients (16%; two men and one woman) had developed the metabolic syndrome phenotype according to NCEP–ATPIII criteria. The incremental gains in each of the components resulting in the metabolic syndrome over the study period were ascribable to either waist enlargement and/or plasma glucose levels beyond normoglycaemia.

Significantly lower adiponectin concentrations were observed at $T_3$ and $T_9$ compared with $T_0$ (Table 1 and Fig. 1). There was a significant decrease in serum amylase levels during follow-up (86 ± 51 to 73 ± 35 U/L [$P = 0.020$]), but no significant changes in lipase were observed (34 ± 18 to 34 ± 35 U/L, NS). In addition, holoCRP, lipid profile, TSH, cortisolaemia (16 ± 5 to 15 ± 4 μg/dL, NS) and albuminuria remained unaffected and ketonuria was not detected at any time during the study.

5. Discussion

To our knowledge, this was the first prospective study to demonstrate that AADs as a class induce weight gain and insulin resistance in lean subjects free of metabolic syndrome, and that the impaired fasting blood glucose induced by this class of drugs is related to insufficient compensatory β-cell secretion in the wake of reduced insulin sensitivity. Although the small size of the population under scrutiny in this study is an obvious limitation that precludes any inferences as to differences in metabolic effects among AADs, no long-term prospective study in AAD- or other antipsychotic-naïve patients has ever been previously carried out to provide data from the simultaneous assessment of both insulin sensitivity and β-cell function in lean, normoglycaemic subjects not normally at risk of developing insulin resistance, the metabolic syndrome and/or impaired glucose homoeostasis.

Numerous case reports and observational studies have suggested that the prevalence of impaired fasting glucose, diabetes and diabetes-associated ketoacidosis is increased in schizophrenic patients treated with AADs. However, the precise pathophysiological mechanisms underlying dysglycaemia remain poorly documented. Abnormal glucose homoeostasis is generally considered to be a consequence of insulin resistance associated with the rapid weight gain induced by these drugs, although the magnitude of these effects may vary according to the type of medication [1–3,12,20–25]. However, this mechanism has not been definitively proven due to the fact that, in most studies, the patients were already overweight or
Over the course of the study, 16% of our patients developed the metabolic syndrome clinical phenotype, mostly as a result of waist diameter enlargement or glucose dysregulation, the latter in keeping with the measured diminution in $\beta \times S$ product. Such changes may account for the convergent occurrence of insulin resistance in these previously lean and otherwise metabolically normal individuals over the course of AAD therapy. Thus, at nine months, we observed a significant impairment in insulin sensitivity, as assessed from HOMA modeling. While the latter changes are in agreement with data obtained from schizophrenic patients with BMI less than 30.0 kg/m² [5], the latter study did not allow for simultaneous changes in adjusted $\beta$-cell function.

Kahn et al. previously showed that the hyperbolic product corresponds to the true underlying $\beta$-cell function adjusted for individual sensitivity and, therefore, is an accurate reflection of a given patient’s glucose homeostasis status [15]. Considered as a whole, we observed in our study population an increase in relative $\beta$-cell secretion, as illustrated by the rise in unadjusted HOMA-$\beta$ values. However, the latter response proved to be clearly insufficient in absolute terms, as the $\beta \times S$ product was significantly altered after nine months with every AAD used in our study, but with different effects in terms of the subsequent rise in fasting glucose. In other words, an early, drug-induced impairment in insulin sensitivity was associated with insufficient compensation in insulin secretory capacity, accounting for the concomitant alteration of the $\beta \times S$ from the normal hyperbolic relationship. This suggests that, in addition to reduced insulin sensitivity, there is an early and independent genuine impairment in $\beta$-cell secretion following AAD use. Comparisons with HOMA products obtained in other common conditions showed significant differences in hyperbolic values between the AAD group and obese normoglycaemic subjects, and patients with impaired fasting glucose or type 2 diabetes. The latter group had close to the 25% hyperbolic value, hence displaying a much more severe deficit in $\beta$-cell function adjusted for insulin sensitivity.

As a consequence of the decrease in the $\beta \times S$ product in schizophrenic patients receiving AADs, a slight but significant increase in fasting blood glucose was recorded at nine months compared with study baseline levels. Our data are in accordance with and go beyond previous reports in overweight and obese schizophrenic patients who developed major dysglycaemia during AAD treatment (and were likely to have acquired insulin resistance). The dysglycaemia could be the consequence of either further deterioration of insulin sensitivity induced by AADs or the inadequacy of $\beta$-cell compensatory response, or both. It is also possible that a predisposing genetic background in some individuals may account for variations in terms of individual $\beta$-cell adaptive responses to decreased insulin sensitivity and the ensuing dysglycaemia. In the present study, HOMA modelling of insulin sensitivity and $\beta$-cell function in the basal state was used to compute the $\beta \times S$. Although other $\beta$-cell function tests often rely upon post-load stimulation, the relationship between HOMA and various dynamic tests reveals an excellent discriminatory ratio and unbiased equation of equivalence with HOMA in relation to other tests, including CIGMA, intravenous glucose tolerance test (IVGTT) and minimal modelling of an IVGTT [16,17].
Caution is needed in interpreting our results with the individual AADs due to the small sample sizes of patients treated with these drugs. The drop-out rate, while seemingly high compared with other metabolic conditions (such as diabetes, hypertension or dyslipidaemia), was nevertheless within the range reported for the psychiatric condition under study [33].

On the other hand, the strength of the present analysis lies in its prospective nature and in having enrolled only lean normo-glycaemic subjects free of the metabolic syndrome, as well as the simultaneous assessment of insulin sensitivity and β-cell function along with other metabolic markers such as adiponectin. Indeed, while our sample size and drop-out rate should be considered possible limitations of the present report, the population under study is not only difficult to follow-up on a prospective basis, hence the dearth of longitudinal data on AAD effects [20]. Our limited sample size also prevented any comparisons between first- and second-generation antipsychotic drugs. This would have required a considerably greater number of patients, while the seriousness of the condition would have made some patients ineligible for receiving one class of drugs versus another because of the known side-effects and efficacy within each respective drug generation. To efficiently assess the respective metabolic effects of the first- and second-generation antipsychotics, a double-blind, crossover study design is required.

In conclusion, our results show that AADs induce rapid weight gain and insulin resistance, and that impaired fasting blood glucose is related to an insufficient compensatory adjustment of β-cell secretion in the wake of reduced insulin sensitivity. The progressive decrease in adiponectinaemia observed in our lean, drug-naive patients suggests that the latter could represent an early marker/factor of impending metabolic deterioration in such patients that is developing prior to any measurable impairment in HOMA parameters. It is, therefore, of paramount importance, irrespective of the prescribed drug, to assess and monitor glucose metabolism on both a short- and long-term basis in patients with schizoaffective disorders treated with AADs. Studies that include larger patient populations and longer durations of antipsychotic drug exposure are needed to confirm and expand on the present findings.

References


