Published in final edited form as:

J Psychiatr Res. 2010 June ; 44(8): 493–498. doi:10.1016/j.jpsychires.2009.11.007.

Relationship between Body Mass Index and Insulin Resistance in Patients Treated with Second Generation Antipsychotic Agents

Sun H. Kim, MD, MS¹, Lilla Nikolics, MS², Fahim Abbasi, MD¹, Cindy Lamendola, MSN¹, James Link, PhD¹, Gerald M. Reaven, MD¹, and Steven Lindley, MD, PhD²

¹Department of Medicine, 300 Pasteur Drive, S025, Stanford, CA 94305-5103

²Department of Psychiatry, Veterans Affairs, Palo Alto Health Care System, 795 Willow Road, MC 116A/MHC/MPD, Menlo Park, CA 94025

Abstract

Second generation antipsychotics (SGAs) can increase weight gain and weight-induced insulin resistance. Recent studies have suggested weight-independent effects of certain SGAs on insulin resistance; however the magnitude of these effects and the relationship between BMI and insulin resistance in patients on SGAs are not established. To evaluate, the relationship between body mass index (BMI) and insulin resistance in 54 patients being stably treated with olanzapine (n=19), risperidone (n=16), or aripiprazole (n=19) was compared with data from a large reference population (n=201) not on SGAs. Insulin resistance was directly quantified by measuring the steady-state plasma glucose (SSPG) concentration during the insulin suppression test. The relationship between BMI and SSPG was similar between the SGA ($r=0.58$) and the reference population ($r=0.50$). When SSPG was standardized based on expected values for the reference population, patients on olanzapine had a higher degree of insulin resistance (mean z-score $\pm$ SD, 0.68 ± 0.9) than expected for level of BMI compared with those on aripiprazole (-0.25 ± 1) and risperidone (-0.3 ± 0.9), $F(2, 51) = 6.28$ ($p=0.004$). Thus, olanzapine group was 0.76 SD above the reference population or in the 78 percentile for insulin resistance. SSPG was correlated with fasting plasma insulin concentration (0.78 ($0.64-0.87$), $p<0.001$) but not fasting glucose concentrations (0.15 ($-0.13-0.40$), $p=0.29$). In conclusion, BMI contributes a quarter to a third of the variance in insulin resistance in the SGA population similar to the reference population. Olanzapine also appears to have an independent effect on insulin resistance that is above and beyond obesity.

Keywords

Olanzapine; Second generation antipsychotic medications; Insulin resistance; Obesity

© 2009 Elsevier Ltd. All rights reserved.

Reprint request may be sent to: Sun H. Kim, M.D., M.S., Stanford University Medical Center, 300 Pasteur Drive, Room S025, Stanford, CA 94305-5103, Telephone: 650-723-8284, Fax: 650-725-7085, sunhkim@stanford.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Contributors

Author Sun Kim designed the study, conducted the study, performed the statistical analysis and wrote the manuscript. Authors Lilla Nikolics, Fahim Abbasi, and Cindy Lamendola conducted the study. Author James Link assisted with data collection. Authors Gerald Reaven and Steven Lindley designed the study and contributed to composing the manuscript. All authors contributed to and have approved the final manuscript.

1. Introduction

Treatment with second generation antipsychotic medications is associated with weight gain and untoward metabolic side effects such as glucose intolerance and dyslipidemia (Clark, 2004; Lieberman et al., 2005). Overweight/obesity can increase insulin resistance (Farin et al., 2006) and may explain these abnormalities associated with SGA treatment. Lending support to this line of reasoning, SGAs with the highest risk for weight gain (i.e., olanzapine) also pose the greatest risk for diabetes and lipid abnormalities (Clark, 2004). On the other hand, there has been concern that certain SGAs may have effects on insulin resistance independent of their effect on weight gain and obesity. In particular, patients treated with olanzapine have been found to have higher degrees of insulin resistance compared with nonpsychiatric controls (Henderson et al., 2006) and those treated with first generation antipsychotic medications (Newcomer et al., 2002) and risperidone (Henderson et al., 2005) even when matched for body mass index (BMI).

While these studies raise the possibility of independent drug effects on insulin resistance, there remain questions regarding the findings and the magnitude of the drug effects on insulin resistance. First, the majority of human studies evaluating the effect of SGAs on insulin resistance have used surrogate estimates such as the homeostasis model assessment of insulin resistance (HOMA-IR) (Mackin et al., 2005; Newcomer et al., 2002) or frequently-sampled intravenous glucose tolerance test (FSIVGTT) (Henderson et al., 2005; Henderson et al., 2006). Both are only moderately correlated with the “gold standard” hyperinsulinemic euglycemic clamp ($r < 0.6$) in non-psychiatric populations (McAuley et al., 2001; Saad et al., 1994) and may not accurately portray the effects of SGAs on insulin resistance. For example, using surrogate measures could underestimate the degree of insulin resistance in a psychiatric population. Second, in trying to evaluate direct SGA effects, it would be beneficial to understand the general relationship between obesity and insulin resistance in patients on SGAs as it may not model the association seen in the general population. In the general population, for instance, obesity explains a quarter to a third of the variance in insulin resistance (Farin et al., 2006).

Therefore, to better understand the effect of SGA treatment on insulin action beyond adiposity, we measured insulin resistance using the insulin suppression test in 54 patients treated with SGAs. The insulin suppression test yields essentially identical results to those obtained via the hyperinsulinemic, euglycemic clamp ($r = 0.93$) (Greenfield et al., 1981). The two tests both involve direct measurement of peripheral glucose uptake in response to exogenous infusion of insulin and glucose. Octreotide is also infused during the insulin suppression test to inhibit endogenous insulin production. During the hyperinsulinemic, euglycemic clamp, the measure of insulin sensitivity is the glucose infusion rate which is varied to keep the glucose clamped at a specified level. The higher the glucose infusion rate, the greater is the degree of insulin sensitivity. In contrast, during the insulin suppression test, the glucose concentration is what is allowed to vary; therefore, the higher the glucose concentration in response to exogenous insulin, the greater is the degree of insulin resistance. As opposed to the clamp, one advantage of the insulin suppression test is that the results are not operator dependent; this is important as the glucose infusion rate can be knowingly varied by as much as $16.6\% \pm 4.7\%$ while still conducting a good clamp test (Greenfield et al., 1981). In addition, classification of insulin resistance using the insulin suppression method has been shown to prospectively predict the development of diabetes and other related diseases (Facchini et al., 2001; Yip et al., 1998).

Therefore, using the insulin suppression test in a cross-sectional study, we evaluated the strength of the relationship between BMI and insulin resistance in a psychiatric population being treated with one of three different SGAs thought to have different weight-gain potential: aripiprazole (low), risperidone (intermediate), and olanzapine (high). Second, to understand if

there are any direct effects of these SGAs on the association between BMI and insulin resistance, we compared the degree of insulin resistance as standardized based on a large reference population not on SGAs ($n=201$). Lastly, we also investigated the relationship between surrogate estimates of insulin resistance and a direct measure obtained via the insulin suppression test, which has not been previously performed in psychiatric patients.

2. Materials and methods

Subjects

Subjects included 54 nondiabetic outpatients who provided written informed consent to participate after complete description of the study. The study was approved by the institutional review boards of Stanford University and the Palo Alto Veteran Administration Research and Development Committee and was carried out in accordance with the latest version of the Declaration of Helsinki. Subjects were recruited through outpatient psychiatric clinics associated with Stanford University and Palo Alto Veteran Administration and through local providers and advertisements. Study participants were taking clinically assigned SGA (aripiprazole, risperidone, and olanzapine) for at least three months prior to study entry. Treatment with only one SGA was allowed with stable antipsychotic dose and overall medication regimen for one month preceding the study. No one was treated with first generation antipsychotic medications. In addition, individuals had to be 21–64 years in age and in general good health without diabetes (fasting glucose <126 mg/dL), anemia, or serious heart, liver or kidney disease. Individuals were excluded if they were taking glucose-lowering medications. We allowed concurrent use of mood stabilizers (gabapentin, lamotrigine, lithium, topiramate, and valproic acid), benzodiazepines and antidepressants.

Ethnicity and race were self reported. Psychiatric diagnoses were confirmed by chart review and Mini-International Neuropsychiatric Interview (Sheehan et al., 1998).

Reference Database

Results from our study population were standardized based on values from a large reference population ($n=201$). The reference population was drawn from our registry of subjects who had participated in other studies from 1996 to 2006 and had measurements of insulin resistance using the insulin suppression test. With the exception of SGA usage, inclusion criteria were similar to the SGA study population. Therefore, all individuals were in good general health without diabetes, anemia, serious heart, liver or kidney disease. From an initial group of 402, we excluded 197 individuals who did not have the same age (21–64 years old) and BMI range ($20\text{--}50$ kg/m²) as the SGA population. Two subjects were excluded for missing medication information. Additional two subjects were excluded for taking trifluoperazine and quetiapine for unclear clinical reasons. We did not exclude 32 (16%) subjects who were taking antidepressants. No one was taking a mood stabilizer.

Insulin Sensitivity

Insulin resistance was estimated by a modification (Pei et al., 1994) of the original insulin suppression test (Shen et al., 1970) which has a high correlation ($r=0.93$) with the euglycemic clamp technique (Greenfield et al., 1981). After an overnight fast, an intravenous catheter was placed in each of the subject's arms. One arm was used for the administration of a 180-minute infusion of octreotide (0.27 mcg/m²/min), insulin (32 mU/m²/min) and glucose (267 mg/m²/min); the other arm was used for collecting blood samples. Octreotide is used to inhibit endogenous production of insulin. Blood was drawn at baseline and at 10-minute intervals from 150 to 180 minutes of the infusion to determine the steady-state plasma glucose (SSPG) and insulin concentrations. Because steady-state insulin concentrations are similar between subjects, the SSPG concentration provides a direct measure of the ability of insulin to mediate

disposal of an infused glucose load; therefore, the higher the SSPG concentration, the more insulin resistant the individual. Glucose concentrations were measured by the oxidase method (Beckman Analyzer 2, Brea, CA) and insulin concentrations by radioimmunoassay (Millipore, St. Charles, MO). The intra- and interassay coefficient of variation for insulin ranges between 7.4–8.2%.

Surrogate estimates of insulin resistance included fasting plasma glucose and insulin concentration and homeostasis model assessment of insulin resistance (HOMA-IR) which was calculated as follows: $\text{HOMA-IR} = (\text{fasting plasma insulin (mU/l)} \times \text{fasting plasma glucose (mmol/L)}) / 22.5$ (Matthews et al., 1985).

Statistical Analysis

All statistical analysis was performed using SPSS (version 16 for Windows; SPSS, Chicago, IL). Descriptive data are presented as mean $\pm$ SD unless otherwise specified. Differences in baseline characteristics were assessed by analysis of variance (ANOVA) or Fisher's Exact Test for categorical variables. Pearson's correlations were used to investigate relationships between SSPG and BMI and also fasting plasma glucose and insulin concentration and HOMA-IR; these are reported as the r-value and 95% confidence interval (CI). To evaluate the differences in relationship between BMI and SSPG concentration among the drug groups, we standardized SSPG concentration based on expected values for the reference population given the same BMI and the expected standard deviation of the reference group (z-score). Thus a z-score near 0 would indicate that the degree of insulin resistance for a patient in a drug group was similar to that expected of an individual of the same BMI in the reference group. A z-score of 2 indicates that the patient is two standard deviations above the reference individual, thus a very deviant response from those in the reference sample. The three drug groups were then compared on their z-scores using ANOVA. Statistical significance was defined as a $p < 0.05$.

3. Results

Patients treated with olanzapine, risperidone, and aripiprazole had similar clinical characteristics (Table 1). Majority were overweight/obese, nonHispanic White males who were predominately taking SGAs for schizophrenia or bipolar disorder. Half currently smoked. The reference population had similar age, BMI and fasting glucose. In addition, a majority were non-Hispanic White. Compared with the SGA population, the reference population had fewer males, and they were less likely to smoke and take antidepressants. No one in the reference population was taking a mood stabilizer.

Figure 1 illustrates the relationship between BMI and insulin resistance (SSPG) in the SGA (A) and reference (B) populations separately and together (C). In general, as BMI increased, SSPG concentration also increased, and this was true of both populations. At any given BMI, there was approximately a six-fold variation in SSPG concentration. As can be seen in Figure 1C, the relationship between BMI and SSPG concentration was comparable between the two groups with correlation coefficient and 95% confidence intervals of 0.58 (0.37–0.73) in the SGA population and 0.50 (0.39–0.6) in the reference population. This relationship remained similar in patients with schizophrenia (0.61, 0.28–0.81) and other psychiatric disorders (0.55, 0.24–0.76).

To evaluate the relative effect of SGAs on insulin resistance, we assessed the relationship between BMI and SSPG concentration in the psychiatric population relative to the reference population. Figure 2 illustrates the mean regression lines between BMI and SSPG concentration in the three drug groups and the reference population. The line for olanzapine appears to be shifted to the left, suggesting higher degree of insulin resistance for any given BMI level. To evaluate this statistically, we standardized insulin resistance based on the

reference population (z-score). As shown in Table 2, olanzapine had a higher mean z-score compared with the reference group and the other two drug groups, confirming higher average SSPG concentration than expected for BMI level. A mean z-score and standard deviation of this magnitude corresponds to the 78% of the reference population compared with the expected 50% if there were no differences in SSPG concentration between the olanzapine group and the reference population. Mean z-score for olanzapine was also significantly higher compared with aripiprazole and risperidone by ANOVA, $F(2, 51) = 6.28$, $p=0.004$. The results were similar when the analysis was isolated to males (Z score $\pm$ SD, olanzapine 0.65 ± 1.1 , aripiprazole -0.44 ± 1.3 , and risperidone -0.68 ± 1.0 , ANOVA, $F(2,32) = 4.96$, $p=0.01$) and to smokers (olanzapine 0.67 ± 1.0 , aripiprazole 0.39 ± 1.7 , and risperidone -0.69 ± 0.8 , ANOVA, $F(2,25) = 3.10$, $p=0.06$).

As a secondary analysis, we also evaluated the relationship between surrogate estimates of insulin resistance and SSPG concentration in the SGA population. Correlation coefficient was significant ($p<0.001$) between SSPG and fasting plasma insulin concentration (0.78, 0.64–0.87) and between SSPG and HOMA-IR (0.77, 0.63–0.86) but not between SSPG and fasting glucose concentration (0.15, -0.13 – 0.40 , $p=0.29$). The relationship between insulin and HOMA-IR was 0.97 ($p<0.001$).

4. Discussion

The findings in the present study show a consistent relationship between obesity and insulin resistance in patients treated with three common SGAs and individuals not treated with SGAs. This relationship was also similar in patients with schizophrenia compared with other psychiatric disorders. Therefore, regardless of the population group, increasing weight tends to worsen insulin resistance with BMI explaining roughly a quarter to a third of the variance in insulin sensitivity.

However, olanzapine treatment had a significant independent effect on insulin resistance beyond adiposity, consistent with many previous findings using surrogate measures of insulin resistance (Henderson et al., 2005; Henderson et al., 2006; Newcomer et al., 2002). For example, Newcomer et al. (Newcomer et al., 2002) and Henderson et al. (Henderson et al., 2005; Henderson et al., 2006) reported higher degrees of insulin resistance in patients treated with olanzapine compared with several other drug groups and controls, when BMI was matched. It is also in line with a recent study using the hyperinsulinemic, euglycemic clamp in healthy volunteers showing an 18% decrease in insulin sensitivity in 14 volunteers after 10 days of olanzapine but not after ziprasidone (Sacher et al., 2008). In this study there was also a significant but modest increase in BMI (by 3%).

But not all studies have shown an independent effect of olanzapine on insulin resistance. In a study by Sowell et al., healthy volunteers were given olanzapine ($n=17$), risperidone ($n=13$) or placebo ($n=18$) for 15–17 days. Although there was a significant increase in weight ($2.8 \text{ kg} \pm 1.7$) and insulin resistance (18%) as measured by the hyperglycemic clamp after olanzapine, the change in insulin resistance was explained by the degree of weight gain in a regression analysis (Sowell et al., 2002). In another study by the same group, there was no effect of 3 weeks of olanzapine (compared with risperidone and placebo) on insulin sensitivity as measured by the hyperinsulinemic euglycemic clamp, although weight ($2.0 \text{ kg} \pm 1.3$), fasting plasma glucose and insulin concentrations significantly increased (Sowell et al., 2003). It is possible that the briefer length of treatment and/or the use of a normal control population accounts for the failure to observe an independent effect of olanzapine although Sacher and colleagues observed a weight independent effect of olanzapine after only 10 days in healthy volunteers (Sacher et al., 2008). Haupt et al. recently evaluated the relationship between BMI and insulin sensitivity in 63 schizophrenia patients on various SGAs and first generation

antipsychotics, using the modified FSIVGTT to measure insulin sensitivity (Haupt et al., 2007). They found an overall correlation between BMI and insulin sensitivity of 0.58, comparable to our results, but found no effect of several SGAs (olanzapine, risperidone, ziprasidone), first generation antipsychotic medications and controls on insulin sensitivity. Nine of the 51 patients on SGAs were also taking first generation antipsychotic medications which may have minimized differences between various SGAs. Our patients were only treated with a single SGA and no first generation antipsychotic medication.

Some studies in rodents seem to corroborate an independent effect of olanzapine beyond weight gain. Using the hyperinsulinemic euglycemic clamp, Houseknecht et al. showed a 43% decrease in glucose infusion rate with acute, subcutaneous administration of olanzapine compared with no effect after ziprasidone or vehicle (Houseknecht et al., 2007). Although this normally implies a decrease in peripheral insulin sensitivity, the authors did not find impairment in muscle glucose uptake but increase in hepatic glucose output to explain the large fall in glucose infusion rate with olanzapine. Others have substantiated these findings with both acute (Chintoh et al., 2008a) and chronic (4 week) (Chintoh et al., 2008b) subcutaneous administration of olanzapine. While this may be a mechanism by which olanzapine impairs glucose homeostasis, it should be noted that rodents do not model many of the SGA effects seen in humans. For instance, only female rats tend to gain weight with SGA administration and the magnitude of weight gain produced by various antipsychotics varies in a pattern that is not consistent with that seen in humans (Choi et al., 2007). In addition, while techniques have not been similar, human studies suggest a more modest change in insulin sensitivity with olanzapine use: 18% after <3 weeks in healthy volunteers using the hyperinsulinemic euglycemic clamp (Sacher et al., 2008) and hyperglycemic clamp (Sowell et al., 2002) and 19% after 24 weeks based on glucose and insulin measurements during an oral glucose tolerance test (Newcomer et al., 2009). In all three studies, there was also significant weight gain which may explain some of the change in insulin sensitivity. In our study, we accounted for weight effects on insulin sensitivity and showed an independent effect of olanzapine on insulin resistance which was less than a standard deviation from the reference population.

Limitations of our study include the cross-sectional design. It is not entirely possible to distinguish whether our findings reflect a true direct olanzapine effect on insulin action or is related to factors associated with the patients assigned to olanzapine. However, with the heightened awareness of the side effects of olanzapine, it is unlikely that individuals with metabolic abnormalities would be more likely to be placed on olanzapine. Our design also included patients with a number of psychiatric diagnoses, and certain mental illnesses, such as schizophrenia, may be independently associated with insulin resistance (Ryan et al., 2003). However, the study findings were similar in patients with schizophrenia versus those with other diagnoses. Thus, our results suggest the effects of SGAs on insulin resistance are not unique to schizophrenia. As we were not studying patients naïve to SGAs, the effects of prior antipsychotic treatment on the results are not known. In addition, subjects were on medications other than SGAs, e.g., antidepressants. Nevertheless, our findings with olanzapine are consistent with many investigations of single SGA treatment (Henderson et al., 2005; Henderson et al., 2006; Newcomer et al., 2002). We also did not conduct a physical activity assessment which is known to affect variability in insulin sensitivity to a similar degree as BMI (Bogardus et al., 1985). Therefore, it is possible that individuals taking olanzapine were less physically active which may explain their higher degrees of insulin resistance. On the other hand, olanzapine treatment has not been shown to worsen baseline physical activity (Gothelf et al., 2002; Graham et al., 2005) which is generally low in the psychiatric population (Brown et al., 1999). We also used BMI as a surrogate of adiposity which may not be a true reflection of total body fat or visceral fat which may be higher in patients treated with olanzapine. Then again, studies have not demonstrated superiority of more detailed techniques and its relationship to insulin resistance (Reaven, 2005). Lastly, the subjects were compared to a

reference population rather than an experimental population recruited for the same study, although the reference population was studied under similar conditions.

Despite our findings and those of others suggesting an independent effect of olanzapine on insulin resistance, it is unclear if discontinuing olanzapine will result in clinical improvement. Specifically, in a recent multicenter trial, switching from olanzapine to aripiprazole for 16 weeks was associated with worsening in psychiatric outcomes, modest weight loss (mean 1.8 kg), a decrease in triglyceride concentrations (14%), with no change in fasting insulin or glucose concentrations or two hour post glucose concentrations, suggesting no change in insulin sensitivity (Newcomer et al., 2008). The implications of these findings are not clear, but discontinuing olanzapine does not appear to produce dramatic improvements in insulin resistance. These data could be viewed as being contrary to our findings and suggest that olanzapine may not deleteriously affect insulin action. On the other hand, it could also suggest that the adverse effect of olanzapine on insulin action cannot be reversed in four months.

Finally, surrogate estimates of insulin resistance had a high degree of correlation with a specific measure in the SGA population. In the general population, the relationship between fasting insulin or HOMA-IR and SSPG concentration is ~ 0.6 (Kim et al., 2004); the relationship strengthens with obesity (Kim et al., 2004) and may partially explain the higher r-values in the overweight/obese SGA population ($r=0.77-0.78$). It should also be noted that insulin and HOMA-IR are highly correlated and have the same relationship with a specific measure. Therefore, HOMA-IR likely provides no additional information regarding insulin resistance than fasting plasma insulin concentration alone. This is not surprising given the weak correlation between SSPG concentration and fasting plasma glucose concentration, which is the second component of the HOMA-IR formula in addition to fasting insulin.

In conclusion, our results suggest that outpatients treated with SGAs have similar relationship between BMI and insulin resistance as the general population, and that olanzapine-treated patients are more insulin resistant at any degree of adiposity as compared with patients treated with risperidone and aripiprazole. Our study is the first to use the insulin suppression test, a specific measure of insulin action, to study the effects of SGAs on insulin resistance and to employ a large reference population as a comparison group. Thus our findings likely depict the nature of the relationship between adiposity and insulin action and the quantitative impact of olanzapine on insulin action above and beyond its tendency to produce weight gain. Given both the indirect and direct effects of olanzapine on insulin resistance, the clinical impact of olanzapine treatment may be significant. Insulin resistance has been associated with the development of many adverse clinical outcomes such as diabetes mellitus, cardiovascular disease, nonalcoholic steatohepatitis, sleep-disordered breathing and certain forms of cancer (Reaven, 2003). Therefore, when olanzapine treatment is necessary for psychiatric health, there must also be intensive efforts in place to monitor, prevent and treat potential outcomes associated with insulin resistance.

Acknowledgments

Role of funding source

Funding for this study was provided by Eli Lilly and NIH Research Grants RR-00070 and K23MH079114 (Dr. Kim). The funders had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Reference

Bogardus C, Lillioja S, Mott DM, Hollenbeck C, Reaven G. Relationship between degree of obesity and in vivo insulin action in man. *Am J Physiol* 1985;248:E286–E291. [PubMed: 3883799]

- Brown S, Birtwistle J, Roe L, Thompson C. The unhealthy lifestyle of people with schizophrenia. *Psychological Medicine* 1999;29:697–701. [PubMed: 10405091]
- Chintoh AF, Mann SW, Lam L, Lam C, Cohn TA, Fletcher PJ, et al. Insulin resistance and decreased glucose-stimulated insulin secretion after acute olanzapine administration. *Journal of Clinical Psychopharmacology* 2008a;28:494–499. [PubMed: 18794643]
- Chintoh AF, Mann SW, Lam TK, Giacca A, Remington G. Insulin resistance following continuous, chronic olanzapine treatment: An animal model. *Schizophrenia Research* 2008b;104:23–30. [PubMed: 18675538]
- Choi S, DiSilvio B, Unangst J, Fernstrom JD. Effect of chronic infusion of olanzapine and clozapine on food intake and body weight gain in male and female rats. *Life Sciences* 2007;81:1024–1030. [PubMed: 17822717]
- Clark N. Consensus development conference on antipsychotic drugs and obesity and diabetes. *Diabetes Care* 2004;27:596–601. [PubMed: 14747245]
- Facchini FS, Hua N, Abbasi F, Reaven GM. Insulin resistance as a predictor of age-related diseases. *Journal of Clinical Endocrinology and Metabolism* 2001;86:3574–3578. [PubMed: 11502781]
- Farin HM, Abbasi F, Reaven GM. Body mass index and waist circumference both contribute to differences in insulin-mediated glucose disposal in nondiabetic adults. *Am J Clin Nutr* 2006;83:47–51. [PubMed: 16400048]
- Gothelf D, Falk B, Singer P, Kairi M, Phillip M, Zigel L, et al. Weight gain associated with increased food intake and low habitual activity levels in male adolescent schizophrenic inpatients treated with olanzapine. *Am J Psychiatry* 2002;159:1055–1057. [PubMed: 12042200]
- Graham KA, Perkins DO, Edwards LJ, Barrier RC Jr, Lieberman JA, Harp JB. Effect of olanzapine on body composition and energy expenditure in adults with first-episode psychosis. *Am J Psychiatry* 2005;162:118–123. [PubMed: 15625209]
- Greenfield MS, Doberne L, Kraemer F, Tobey T, Reaven G. Assessment of insulin resistance with the insulin suppression test and the euglycemic clamp. *Diabetes* 1981;30:387–392. [PubMed: 7014307]
- Haupt DW, Fahnestock PA, Flavin KA, Schweiger JA, Stevens A, Hessler MJ, et al. Adiposity and insulin sensitivity derived from intravenous glucose tolerance tests in antipsychotic-treated patients. *Neuropsychopharmacology* 2007;32:2561–2569. [PubMed: 17375138]
- Henderson DC, Cagliero E, Copeland PM, Borba CP, Evins E, Hayden D, et al. Glucose metabolism in patients with schizophrenia treated with atypical antipsychotic agents: a frequently sampled intravenous glucose tolerance test and minimal model analysis. *Archives of General Psychiatry* 2005;62:19–28. [PubMed: 15630069]
- Henderson DC, Copeland PM, Borba CP, Daley TB, Nguyen DD, Cagliero E, et al. Glucose metabolism in patients with schizophrenia treated with olanzapine or quetiapine: a frequently sampled intravenous glucose tolerance test and minimal model analysis. *Journal of Clinical Psychiatry* 2006;67:789–797. [PubMed: 16841629]
- Houseknecht KL, Robertson AS, Zavadski W, Gibbs EM, Johnson DE, Rollema H. Acute effects of atypical antipsychotics on whole-body insulin resistance in rats: implications for adverse metabolic effects. *Neuropsychopharmacology* 2007;32:289–297. [PubMed: 17035934]
- Kim SH, Abbasi F, Reaven GM. Impact of degree of obesity on surrogate estimates of insulin resistance. *Diabetes Care* 2004;27:1998–2002. [PubMed: 15277430]
- Lieberman JA, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *New England Journal of Medicine* 2005;353:1209–1223. [PubMed: 16172203]
- Mackin P, Watkinson HM, Young AH. Prevalence of obesity, glucose homeostasis disorders and metabolic syndrome in psychiatric patients taking typical or atypical antipsychotic drugs: a cross-sectional study. *Diabetologia* 2005;48:215–221. [PubMed: 15688206]
- Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 1985;28:412–419. [PubMed: 3899825]
- McAuley KA, Williams SM, Mann JJ, Walker RJ, Lewis-Barned NJ, Temple LA, et al. Diagnosing insulin resistance in the general population. *Diabetes Care* 2001;24:460–464. [PubMed: 11289468]

- Newcomer JW, Campos JA, Marcus RN, Breder C, Berman RM, Kerselaers W, et al. A multicenter, randomized, double-blind study of the effects of aripiprazole in overweight subjects with schizophrenia or schizoaffective disorder switched from olanzapine. *J Clin Psychiatry* 2008;69:1046–1056. [PubMed: 18605811]
- Newcomer JW, Haupt DW, Fucetola R, Melson AK, Schweiger JA, Cooper BP, et al. Abnormalities in glucose regulation during antipsychotic treatment of schizophrenia. *Archives of General Psychiatry* 2002;59:337–345. [PubMed: 11926934]
- Newcomer JW, Ratner RE, Eriksson JW, Emsley R, Meulien D, Miller F, et al. A 24-week, multicenter, open-label, randomized study to compare changes in glucose metabolism in patients with schizophrenia receiving treatment with olanzapine, quetiapine, or risperidone. *Journal of Clinical Psychiatry* 2009;70:487–499. [PubMed: 19358783]
- Pei D, Jones CN, Bhargava R, Chen YD, Reaven GM. Evaluation of octreotide to assess insulin-mediated glucose disposal by the insulin suppression test. *Diabetologia* 1994;37:843–845. [PubMed: 7988789]
- Reaven G. All obese individuals are not created equal: insulin resistance is the major determinant of cardiovascular disease in overweight/obese individuals. *Diab Vasc Dis Res* 2005;2:105–112. [PubMed: 16334591]
- Reaven GM. The insulin resistance syndrome. *Curr Atheroscler Rep* 2003;5:364–371. [PubMed: 12911846]
- Ryan MC, Collins P, Thakore JH. Impaired fasting glucose tolerance in first-episode, drug-naïve patients with schizophrenia. *American Journal of Psychiatry* 2003;160:284–289. [PubMed: 12562574]
- Saad MF, Anderson RL, Laws A, Watanabe RM, Kades WW, Chen YD, et al. Insulin Resistance Atherosclerosis Study. A comparison between the minimal model and the glucose clamp in the assessment of insulin sensitivity across the spectrum of glucose tolerance. *Diabetes* 1994;43:1114–1121. [PubMed: 8070611]
- Sacher J, Mossaheb N, Spindelegger C, Klein N, Geiss-Granadia T, Sauermann R, et al. Effects of olanzapine and ziprasidone on glucose tolerance in healthy volunteers. *Neuropsychopharmacology* 2008;33:1633–1641. [PubMed: 17712347]
- Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry* 1998;59:22–33. quiz 34–57. [PubMed: 9881538]
- Shen SW, Reaven GM, Farquhar JW. Comparison of impedance to insulin-mediated glucose uptake in normal subjects and in subjects with latent diabetes. *Journal of Clinical Investigation* 1970;49:2151–2160. [PubMed: 5480843]
- Sowell M, Mukhopadhyay N, Cavazzoni P, Carlson C, Mudaliar S, Chinnapongse S, et al. Evaluation of insulin sensitivity in healthy volunteers treated with olanzapine, risperidone, or placebo: a prospective, randomized study using the two-step hyperinsulinemic, euglycemic clamp. *Journal of Clinical Endocrinology and Metabolism* 2003;88:5875–5880. [PubMed: 14671184]
- Sowell MO, Mukhopadhyay N, Cavazzoni P, Shankar S, Steinberg HO, Breier A, et al. Hyperglycemic clamp assessment of insulin secretory responses in normal subjects treated with olanzapine, risperidone, or placebo. *Journal of Clinical Endocrinology and Metabolism* 2002;87:2918–2923. [PubMed: 12050274]
- Yip J, Facchini FS, Reaven GM. Resistance to insulin-mediated glucose disposal as a predictor of cardiovascular disease. *Journal of Clinical Endocrinology and Metabolism* 1998;83:2773–2776. [PubMed: 9709945]

Fig. 1. Relationship between BMI and insulin resistance (SSPG) in patients treated with SGAs (A), individuals not on SGAs (reference population) (B), and both populations combined (C). R-value (95%CI) between BMI and SSPG concentration is similar in the two populations: SGA, 0.58 (0.37–0.73) and reference population, 0.50 (0.39–0.6).

Fig2.

Relationship between BMI and insulin resistance (SSPG) by specific SGA or no SGA (reference population). Mean regression line for olanzapine is shifted to the left compared with the two other SGA groups and the reference population.

Baseline characteristics

Table 1

Variable	Aripiprazole		Risperidone		Olanzapine		p ¹		Reference		p ²
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
N	19		16		19				201		
Age (years)	45	8	48	10	47	11	0.67		48	9	0.55
BMI (kg/m ²)	33.9	5.0	30.0	5.4	31.6	5.8	0.11		31.8	3.7	0.88
Fasting glucose (mg/dL)	93	13	96	8	100	11	0.14		96	10	0.97
Medication dose (mg)	22.6	8.7	4.1	2.7	13.9	10.6	--		--	--	--
	N	%	N	%	N	%			N	%	
Male	9	47	13	81	13	68	0.12		97	48	0.03
NonHispanic White	13	68	9	56	16	84	0.19		148	74	0.61
Current smoker	9	47	9	56	10	53	0.94		37	18	<0.001
Psychiatric Diagnosis											
Schizophrenia/Schizoaffective	4	10	10		11				0		
Bipolar	12	4	4		5				0		
Depression	2								14		
Anxiety			2		1				2		
Posttraumatic Stress Disorder	1				1				0		
Obsessive Compulsive					1				0		
Concurrent mood stabilizer	11	58	6	38	9	47	0.55		--	--	<0.001
Concurrent antidepressant	10	53	8	50	13	68	0.55		32	16	<0.001

¹ Differences among the three drug groups were analyzed by ANOVA.

² Differences between the three drug groups combined and the reference population were analyzed by independent t-tests.

Table 2

Comparison of standardized scores for insulin resistance among the groups

	Reference Group	Aripiprazole	Risperidone	Olanzapine
Z-score (mean $\pm$ SD)	0 ± 1	-0.25 ± 1	-0.3 ± 0.9	0.68 ± 0.9
Standard deviation from reference population	0	-0.25	-0.33	0.76
% of reference population	50%	40%	37%	78%