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Regular Article

Contribution of baseline body mass index and leptin serum level to the prediction of early weight gain with atypical antipsychotics in schizophrenia

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Aim: This study investigated whether biochemical parameters add predictive information concerning risk for weight gain associated with treatment with atypical antipsychotics (AP) to that provided by baseline weight.

Methods: Weight changes were assessed in 25 patients with schizophrenia after 3–6 months of treatment. These patients were started on AP monotherapy owing to a first psychotic episode or resumed treatment after at least a 6-month period of abandonment. Anthropometric and biochemical data were collected and analyzed as predictors of early weight change.

Results: The baseline biochemical and anthropometric data were not significantly higher in the patients than in the healthy participants. During follow up, the patients had significant increases in body mass index and total cholesterol and apolipoprotein B level. The baseline weight and leptin level were predictive of weight gain during follow up, with an inverse association in both cases.

Conclusion: Baseline weight and leptin level may help to assess the risk of early weight gain with AP.

Key words: clozapine, leptin, olanzapine, risperidone, weight gain.

ATYPICAL ANTIPSYCHOTICS (AP) induce a substantial weight gain in a certain proportion of patients receiving this treatment, which increases their vascular risk.[1] Early weight changes have been shown to be related significantly to longer-term substantial weight gain.[2] Thus, in order to design preventive strategies to counteract such cardiovascular risk, the identification of predictive factors for early weight gain would be useful.

Baseline demographic and anthropometric data may have a role as predictors of AP-associated weight gain. A lower baseline body mass index (BMI) has been associated with the probability of substantial weight gain with olanzapine treatment.[3] Other demographic predictors of AP-induced weight gain include younger age and female sex.[2,4]

It can be suggested that the biochemical parameters involved in lipid metabolism and food intake may also play a role as predictors of weight gain related to atypical AP treatment, which could increase the predictive power of the anthropometric and demographic variables. Among such possible biochemical predictors, leptin is an appetite and metabolic regulator synthesized by adipocytes, the level of which is increased after caloric intake and which has been shown to increase with atypical AP treatment.[5,6] Both bodyweight and leptin significantly increased even in the first month of treatment with clozapine

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or olanzapine.[7] Variation in the leptin gene predicted BMI gain with risperidone in adolescents.[8] Bodyweight and leptin level may not be independent, given that leptin level positively correlated with BMI increase in patients on monotherapy with haloperidol or olanzapine.[9] Although this association suggests that leptin increase is secondary to weight gain following treatment with AP, it is not known if the baseline information provided by both parameters taken together may have a superior predictive value than that of anthropometric measurements alone. Moreover, leptin resistance could in part contribute to weight gain with AP, similar to what has been described in obesity.[10] In this case, a direct association between baseline leptin and weight increase could be detected.

In the present study we assessed the relationship between anthropometric and biochemical baseline indices and early weight gain. We included only patients receiving AP monotherapy because the metabolic effects of atypical AP may be obscured by the treatment combinations often received by patients. The hypothesis was that baseline biochemical data would add predictive value concerning early bodyweight gain with AP compared to that provided by baseline bodyweight.

METHODS

Subjects

We followed 25 psychotic patients during the initial 3–6 months of atypical AP treatment after a first episode (FE) of psychosis or a relapse related to a previous abandonment of their medication for a period >6 months. Patients were included after their admission to a psychiatric unit due to psychotic exacerbation. Using DSM-IV-TR criteria, 14 of the subjects were diagnosed as having FE paranoid schizophrenia, and the other 11 were diagnosed as having: paranoid schizophrenia ($n = 9$); undifferentiated schizophrenia ($n = 1$); or a schizoaffective disorder ($n = 1$). In total, 30 subjects were asked to participate in the study, and five refused to participate.

Follow-up data were available only for 23 patients (12 male). The other two patients stopped taking their medication during the follow-up period and thus their data were not useful for follow-up analysis. The mean follow-up period for the completers was 5.3 ± 3.4 months.

For inclusion in the study the patients had to have received a diagnosis of psychosis and therefore prescription of monotherapy AP with risperidone, paliperidone, olanzapine or clozapine. During follow up they could not receive any other drug with known metabolic effects (lithium, topiramate) or known to interfere with the metabolization of AP (serotonin selective re-uptake inhibitors, carbamazepine or any other drug with recognized potential interference in the metabolization of AP).

During follow up, four subjects were on olanzapine (dose range, 5–10 mg), five were on clozapine (dose range, 250–700 mg/day), 12 were on risperidone (2–9 mg/day), and four were on paliperidone (12 mg/day). One subject on clozapine and one on paliperidone were lost to follow up.

For comparison, we also included the data from 16 healthy controls (nine male), whose biochemical and anthropometric data were assessed using the same methodology.

Healthy controls were recruited through newspaper advertisements and received a small remuneration for their cooperation. They were previously assessed using a semi-structured psychiatric interview by one investigator (VM) to discard major psychiatric antecedents (personal or familial) and treatments.

The exclusion criteria included IQ <70; history of neurological illness or trauma with loss of consciousness; past or present substance abuse, except nicotine; any other psychiatric process or treatment, and treatment with drugs acting on the central nervous system. Use of toxic substances was identified at interview and on urinalysis, and those patients were excluded from the study. Patients with metabolic syndrome at baseline were not included.

Written informed consent was obtained from the patients and their families and also from the controls. The research board endorsed the study, in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki).

The baseline and follow-up measurements included weight, BMI and the proportion of fat body mass using bioelectrical impedance measurement. BMI was classified according to the World Health Organization consensus (2010 revision).[11] The biochemical parameters included fasting glucose, cholesterol (total, low-density lipoprotein [LDL] and high-density lipoprotein [HDL]), triglyceride, apolipoprotein B (ApoB), leptin, insulinemia and C-reactive protein level. Blood samples were obtained by venipuncture of the upper forearm.

Nursing personnel ensured the blood samples were obtained in a fasting condition at baseline measurement. As for the follow-up analysis, verbal and written instructions were given to the patients. Follow-up assessment took place in the same hospital. Patients arrived at 08.00 hours and all procedures and measurements were performed in a single session.

Bioelectrical impedance measurement was done using Tanita BC-418MA (Tanita, Tokyo, Japan), with a high-frequency current (50 kHz, 90 μA) through eight electrodes, which yielded the corresponding percentage of fat body mass. To assess the relative fat composition the system uses dual radiological absorptiometry data obtained in Japanese and Western individuals and regression analyses taking into account height, weight, age and impedance values of different parts of the body.

Statistical analysis

Baseline demographic and anthropometric data were compared between the patients and controls using the *t*-test or chi-squared test, when appropriate. The significance of the differences between baseline and follow-up anthropometric and biochemical data was tested using *t*-values for related samples.

The association between BMI changes (follow-up BMI minus baseline BMI) and baseline BMI and the biochemical data (fasting LDL-cholesterol and triglycerides, glucose, insulin, Homeostatic Model of Assessment–Insulin Resistance [HOMA-IR], ApoB, and leptin level) was assessed using partial correlation coefficients, controlling for the effects of age and sex.

To study the predictive capacity of the baseline BMI and biochemical data we used multivariate stepwise linear regression, testing for the normal distribution and homoskedasticity of the residuals.

RESULTS

Comparison of baseline data between the patients and controls did not identify any significant differences between the groups as regards to anthropometric or biochemical data (Table 1).

Comparison of the follow-up and baseline parameters indicated a significant increase in weight, BMI

Table 1. Subject characteristics

	Patients		
	Baseline ($n = 25$)	Follow up ($n = 23$)	Healthy controls ($n = 16$)
Age (years)	34.39 ± 11.56		31.29 ± 12.43
M:F ratio	14:11	12:11	9:7
Illness duration (months)	73.1 ± 60.8		
Weight (kg)	**74.93 ± 17.51**	**78.09 ± 15.56***	73.51 ± 14.50
BMI (kg/m^2)	**26.96 ± 7.66**	**28.17 ± 4.55***	25.21 ± 3.20
DBP (mmHg)	71.54 ± 9.31	66.54 ± 8.26	71.93 ± 11.8
Fat mass (%)	26.37 ± 12.26	23.90 ± 8.59	24.39 ± 7.26
Total cholesterol (mg/dL)	**173.5 ± 39.75**	**194.35 ± 41.45****	183.66 ± 42.05
LDL-cholesterol (mg/dL)	**100.6 ± 33.41**	**119.6 ± 33.61***	111.71 ± 33.32
HDL-cholesterol (mg/dL)	49.5 ± 12.19	48.9 ± 12.27	55.06 ± 14.75
Triglycerides (mg/dL)	133.7 ± 111.7	147.51 ± 123.66	84.24 ± 48.42
Fasting glycemia (mg/dL)	97.4 ± 16.22	92.4 ± 12.49	86.85 ± 17.66
Insulin (μU/mL)	9.5 ± 5.32	11.18 ± 18.78	7.19 ± 7.66
HOMA-IR	2.87 ± 1.55	3.26 ± 5.91	1.57 ± 1.75
ApoB (mg/dL)	**81.6 ± 23.2**	**101.4 ± 31.88***	91.49 ± 30.54
CRP (mg/dL)	0.38 ± 0.74	0.32 ± 0.35	0.119 ± 0.11
Leptin (ng/mL)	18.1 ± 22.1	24.2 ± 20.56	13.31 ± 11.12

*$P < 0.03$; **$P < 0.005$. ApoB, apolipoprotein B; BMI, body mass index; CRP, C-reactive protein; DBP, diastolic blood pressure; HDL, high-density lipoprotein; HOMA-IR, Homeostatic Model of Assessment–Insulin Resistance; LDL, low-density lipoprotein.

Table 2. Prediction of weight change: multivariate analysis

Selected predictor	Variance explained (R^2)	*F* for the model	Beta coefficient
Baseline BMI	0.530	F = 13.54, *P* = 0.03	β = −0.73; t = −3.68, *P* = 0.003
Baseline leptin	0.529	F = 13.45 (0.003)	β = −0.72; t = −3.66, *P* = 0.003

BMI, body mass index.

and ApoB ($P < 0.05$) and total and LDL-cholesterol ($P < 0.005$) in the patients. HOMA-IR differences were not statistically significant.

The partial correlation controlling for the effect of sex and age indicated a significant and inverse association between BMI gain and BMI ($r = -0.707$, $P = 0.010$), total cholesterol ($r = -0.701$, $P = 0.01$) and leptin ($r = -0.577$, $P = 0.05$) level at baseline.

Multivariate linear regression identified baseline BMI as a predictor of weight change, the association being negative (Table 2).We checked whether the analytical parameters had any predictive power by repeating these analyses without including baseline BMI in the model. We found that baseline leptin was inversely associated with BMI change in the present patients, the association also being inverse (Table 2).

We investigated the post-hoc association between baseline BMI and leptin level, which was found to be significant ($r = 0.78$, $P < 0.001$). Total cholesterol was also significantly associated with baseline BMI ($r = 0.47$, $P < 0.05$). There was no association between follow-up changes in leptin level and BMI.

DISCUSSION

In the present patients, the increase in BMI with atypical AP was predicted by baseline BMI, the association being negative, in agreement with the results of a recent review.[3] This relationship has also been shown for FE patients[12] and chronic patients receiving clozapine[13] and may become evident as early as 6 weeks after starting treatment.[14] The direction of the association between baseline weight and weight gain, however, was the opposite in a retrospective study with an average length of treatment of 5 years.[15] In that same study, a low BMI prior to the first AP treatment predicted a higher acceleration of BMI change, suggesting an accelerated gain during the initial months of treatment related to a lower BMI, which at least in some patients may plateau later on.

Baseline leptin level was inversely related to a higher weight gain in the present sample only after excluding baseline weight from the model. This indicates that baseline leptin did not add predictive value in the present sample to baseline weight, contrary to the hypothesis. Given the role of leptin in intake regulation, an association between BMI and its level seems likely, which could explain why leptin was not primarily selected as a weight gain predictor. Indeed, in the present patients there was an association between baseline BMI and leptin. The genes influencing the leptin-signaling pathway have been reported to exert no significant effect on weight gain in FE schizophrenia,[16] which seems consistent with the possibility that the effect of leptin on the risk of weight gain with atypical AP would be mediated by BMI. The early change in BMI with AP treatment, correlated with an increase in leptin level,[17] is consistent with this possibility, as well as the early increase in leptin level described for treatment with olanzapine.[17]

Nevertheless, this does not completely rule out the possibility that lower baseline leptin level may pose a significant risk for weight gain secondary to AP treatment in some cases. Data from other groups suggest the importance of studying in a greater sample the predictive role of leptin for AP-induced weight gain, such as the association reported between variation in the leptin gene and weight gain with risperidone,[8] and the association between lower leptin level and greater weight gain in prepubertal children after 12 months of follow up.[17] If confirmed, this would suggest a role for decreased leptin function in AP-induced weight gain in a subgroup of patients, perhaps related to deficient appetite regulation.

The present patients had significant early increases in ApoB and cholesterol level. Previous studies have reported significant increases of ApoB in patients receiving olanzapine, in comparison to risperidone-treated patients,[18] and in phenotiazine-treated patients as compared to healthy controls.[19] A higher level of ApoB in patients treated with olanzapine as compared to risperidone has been reported.[20] This effect on ApoB may be more evident with atypical AP, given that no increase in ApoB was detected in

patients receiving typical AP.[21] The involvement of ApoB in metabolic risk in schizophrenia is also supported by the finding of higher ApoB level in metabolically obese but normal weight patients, based on a HOMA-IR cut-off.[22]

In the present patients, circulating lipids increased with atypical AP in the initial months of treatment together with BMI, in agreement with the described link between increased plasma lipid level and weight gain.[23,24] This highlights the clinical relevance of AP-induced weight gain. Excessive weight gain in diabetic subjects has been associated cross-sectionally with higher ApoB.[25]

In the present sample, lipid changes were found but with no significant change in glucose or insulin level. According to the present data, lipid disturbance precedes glycemic problems in schizophrenia patients treated with AP. Along the same line, early lipid changes (8 weeks) in both risperidone- and olanzapine-treated patients have been reported to be more severe in the latter.[26]

It is also interesting to note that, although not statistically significant, patients had higher glucose and insulin and lower HDL-cholesterol baseline level, suggesting a possible higher insulin resistance, which could contribute in turn to differences in leptin level. Similarly, the larger BMI in the patients (probably associated with central adiposity) might also contribute to insulin resistance. These possibilities could be explored using a larger sample size.

The present patients received different treatments in follow up, notably AP with a high (clozapine, olanzapine) versus low (risperidone, paliperidone) histaminergic affinity. Given the proposed role for both H1 and H3 blockade in weight gain and food intake control,[27] diverse mechanisms may have contributed to weight changes in the present sample.

Given the small sample size, the present data are clearly preliminary. They do, however, suggest the need for further investigation of the possibility that baseline biochemical data can be used, in addition to the better established anthropometric parameters, to predict the risk of life-threatening events such as those associated with metabolic syndrome.

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