# Bodyweight gain and β-antagonist associated with hyperinsulinaemia during bipolar mania

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**Running title:** Hyperinsulinaemia in bipolar disorder

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**ABSTRACT**

Background: Hyperinsulinaemia, a pre-clinical condition considered to predict metabolic syndrome, has not yet been sufficiently investigated in bipolar disorder. It does, however, seem that bipolar disorder patients are at risk of developing insulin resistance. This study sets out to determine the alternation of fasting insulin and to evaluate the factors associated with hyperinsulinaemia during bipolar mania.

Methods: Fasting plasma insulin and leptin levels were measured in 42 bipolar manic (DSM-IV) patients aged ≤45, Young Mania Rating Scale (YMRS) scores of ≥26, as well as in subsequent remission (YMRS ≤12).

Results: Fourteen patients (33.3 %) in acute mania, and thirty patients (71.4 %) in subsequent remission, met the Taiwanese criterion for hyperinsulinaemia: 8.7 μIU/mL for men, and ≥11.3 μIU/mL for women. By logistic regression, the use of classic β-adrenoceptor antagonists (beta-blocker), proparnolol, in remission (odds ratio [OR] = 10.04, with 95 % confidence interval [95% CI]= 1.03-97.96), and the increase in BMI (OR= 1.35, with 95% CI= 1.01-1.80) were found to have independent associations with hyperinsulinaemia in subsequent remission.

Limitations: Treatments were not standardized and data were obtained for only two specific time points throughout a manic episode.

Conclusions: Hyperinsulinaemia is common amongst medicated bipolar patients in the subsequent remission of acute mania, regardless of the types of mood stabilizers or antipsychotics used. Throughout manic episodes, co-prescribing beta-blocker and bodyweight gain are risk factors for hyperinsulinaemia.

**Keywords:** Hyperinsulinaemia, insulin resistance, bipolar disorder, β- blocker, bodyweight gain, mania

## 1. Introduction

The prevalence of obesity, metabolic syndrome and its sequels (cardiovascular diseases and diabetes mellitus) is elevated in patients with bipolar disorder, particularly in those receiving the novel psychopharmacological therapy (Fagiolini et al., 2005; McIntyre et al., 2005; Tsai et al. 2005 ). Hyperinsulinaemia is closely linked to overall and central obesity, impaired glucose regulation, and metabolic syndrome (Reaven, 1988; Coazo-Cavell and Jensen, 2004), and indeed, it has been suggested that bipolar disorder populations may represent an at-risk group for glucose metabolic abnormalities (McIntyre et al., 2005).

β-adrenoceptor antagonists (beta-blockers), such as propranolol, are useful as a means of alleviating the acute extra-pyramidal effects induced by antipsychotics, as well as the problematic tremors associated with lithium and valproate (Holloman and Marder, 1997). The adverse effects of beta-blockers on lipid and carbohydrate metabolism are already well documented (Kaplan, 1992) and beta-blockers have been widely used in psychiatric patients. However, the effect of beta-blocker on insulin level of bipolar patients remains unknown.

The measurement of fasting insulin has been recommended, in epidemiological studies, as a surrogate estimate of insulin resistance (Balkau and Charles, 1999). Inflammation is closely associated with obesity and insulin insensitivity (Grimble

2002). It has been suggested that state-dependent activation of inflammatory response systems may exist in bipolar patients during manic episodes (Tsai et al., 1999; 2001). Thus, it is hypothesized that hyperinsulinaemia may exist in bipolar disorder, particularly during acute mania episodes. To our knowledge, no study has yet attempted to evaluate the alternation of fasting insulin levels amongst bipolar individuals during manic episodes. This study aims to determine the alternation of fasting insulin during manic episode, and to investigate the relationship hyperinsulinaemia and the clinical characteristics of bipolar patients as well as use of beta-blockers, particularly propranolol.

## 2. Methods

### *Subjects*

Patients aged ≤45 years, meeting the DSM-IV diagnostic criteria for bipolar I disorder, with Young Mania Rating Scale (YMRS) (Young et al.,1978 ) manic scores of ≥26, were invited to participate in the study. These patients were rated and diagnosed by two senior psychiatrists using the Chinese version of the Structured Clinical Interview for DSM–III–R, patient edition (Spitzer et al., 1990). Written informed consent was required from all subjects agreeing to participate in the study.

Patients were screened by physical examination, with complete blood counts (with differentials), serum enzyme and metabolite screening, and thyroid function tests

also being carried out. Exclusion criteria included the presence of any severe physical illness, any history of alcohol/substance abuse, any prior history of lipid lowering treatment and the presence of any endocrinological state. Patients with mixed episodes, or comorbidty with other Axis I psychiatric disorders, were also excluded. Follow-up blood samples of the same manic patients were collected whilst in subsequent remission (YMRS scores $\leq$12, and Hamilton Depression Rating Scale [HAMD-21] $\leq$8).

Treatments with lithium, valproate, benzodiazepine, and beta-blocker (propranolol), were openly assigned by patient reference after extensive review, by the treating clinicians, of the relative merits and liabilities of each of these agents. Dosing for both mood stabilizers was determined clinically, based upon effectiveness and tolerability. Use of antipsychotics (mainly typical antipsychotics) as adjuncts to mood stabilizing was permitted when clinically indicated.

***Assays***

Following an overnight fasting from 2400 hours of the preceding night, heparinized blood was drawn by venous puncture. Plasma was collected and frozen at $-80^{o}$C until use.

Serum total cholesterol was measured by the esterase-oxidase method, whilst triglycerides were measured using an enzymatic procedure. Plasma levels of leptin and

insulin were measured in duplicate, under the immunoradiometric assay principle, using commercial kits obtained from Diagnostic Systems Laboratories, Inc. (TX, USA). Assays of insulin and leptin in bipolar individuals, during both acute mania and remission, were carried out simultaneously, and in the same run. The respective intra- and inter-assay coefficients of variation (CV) were <7% for leptin, and <12 % for insulin.

The reference range for normal fasting insulin was 2.1-30.8 μIU/mL, with hyperinsulinaemia being defined by the top quartile cut-off for fasting insulin, specified by gender, in the non-diabetic background Taiwanese population: ≥8.7 μIU/mL (52.45 pmol/L) for men, and ≥11.3 μIU/mL ( 67.84 pmol/L) for women (Chien et al., 1999).

*Statistical Analysis*

Differences in the continuous variables between acute mania and subsequent remission in bipolar individuals were assessed by means of paired-*t* test. Two-group comparisons were undertaken using the Chi-square test or Fisher's exact test for the categorical variables, and the *t*-test for the continuous variables. Multivariate logistic regression analysis was performed using SPSS Base 10.0 software package. The stepwise selection method with a selected acceptance level of 0.05 was chosen.

**3. Results**

The participants in this study comprised of 20 female and 22 male manic patients, with a mean age of 33.1 ± 8.5 years. Fourteen patients (33.3 %) in acute mania, and 30 patients (71.4 %) in subsequent remission, met the Taiwanese criterion for hyperinsulinaemia. In acute mania, comparable mean plasma insulin levels were recorded from the measurement of the 13 patients receiving propranolol (11.33 ± 20.89 μIU/mL) and the 29 patients not receiving propranolol (11.06 ± 10.77 μIU/mL).The 30 patients with hyperinsulinaemia in subsequent remission comprised of 15 out of 16 patients (93.8 %) taking propranolol, and 15 out of 26 patients (57.7 %) free of propranolol.

Ten patients in acute mania (23.8%) and 26 patients (61.9 %) in subsequent remission had a plasma insulin level greater than 15 mIU/mL; moreover, 20 remitted patients (47.6 %) whose fasting insulin levels were abnormally elevated (>30 μIU/mL). In subsequent remission, 26 patients (61.9 %) had fasting insulin levels greater than 15 μIU/mL, including 20 patients (47.6 %) whose fasting insulin levels were abnormally elevated (>30 μIU/mL). The mean time interval from acute measurement to remission was 46.3 ± 55.3 days, ranging between 12 and 116 days. The plasma insulin and leptin levels, bodyweight and BMI were all significantly elevated in subsequent remission (Table 1).

<Table 1 is inserted here>

There were no differences, in acute mania, between the baseline measurements of plasma insulin levels amongst the 9 drug-free patients (10.47 ± 8.54, μIU/mL), the 20 medicated patients not receiving propranolol (11.32 ± 11.83, μIU/mL), and the 23 propranolol-treated patients (11.33 ± 20.90, μIU/mL). The elevation of plasma leptin levels from the acute to follow-up measurements (Δleptin) (endline values minus baseline values) had a significantly positive correlation with the increase in BMI (Δ BMI), (Pearson's product-moment correlations: $r = 0.32$, $p < 0.05$) and the increase in bodyweight (ΔBW) ($r = 0.27$, $p = 0.067$). However, the Δinsulin had no correlation with Δleptin, ΔBMI or ΔBW.

Each of the patients had taken at least one mood stabilizer throughout the acute episode, including lithium (n = 14), valproate (n = 19) and lithium plus valproate (n = 9). Eleven patients had openly received atypical antipsychotics, with mean 360.6 ± 340.8 CPZ equivalent (mg chlorpromazine/day) adjunctive to either lithium or valproate, whose mean plasma level of insulin in remission (41.06 ± 48.63 μIU/mL) was lower than 49.88 ± 53.20 μIU/mL of those (n=31) free of atypical antipsychotics, including 10 patients taking mood stabilizer alone and 21 patients receiving concomitant typical antipsychotics ($t = 1.05$, df = 40, ns).

Amongst the 23 patients who had not received propranolol throughout their acute episode, the mean plasma insulin level (26.18± 30.69 μIU/mL) and BMI

(24.7± 4.2 kg/m$^2$) in subsequent remission were also significantly elevated in comparison with their values in acute mania. ( insulin:11.15± 9.84 μIU/mL, t=2.52, df=22, p< 0.025; BMI:23.9± 4.1 kg/m$^2$, t=3.91, df=22, p=0.001).

A comparison between hyperinsulinaemic and non-hyperinsulinaemic groups was shown in Table 2, and there was also no difference in dosage of lithium or valporate in acute mania, duration of medication, YMRS and HDRS scores, and fasting glucose serum levels, cholesterol, triglycerides and thyoxine in acute mania (data not shown).

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Based upon the univariate associations identified in the preceding analyses, the multivariate logistic regression revealed that the use of proparnolol in remission (adjusted OR = 10.04; 95% CI = 1.03-97.96), along with the increase in BMI (adjusted OR = 1.35; 95% CI = 1.01-1.80), yielded the best explanatory models for hyperinsulinaemia in subsequent remission (goodness of fit: $\chi^2$ = 11.53, df = 2, $p$ = 0.003).

## 4. **Discussion**

Racial differences may be present in the clustering of insulin resistance syndrome (Saad et al., 1991); furthermore, there is currently no universally-accepted criterion for hyperinsulinaemia in the fasting state. Yet, even so, the present findings demonstrate that hyperinsulinaemia, as defined by the criteria for both Taiwanese (Chien et al., 1999) and Western (>15 μIU/mL) (Ferrannini and Balkau, 2002) populations, was present in an alarmingly high proportion of medicated bipolar patients, particularly in the subsequent remission of acute mania.

Although acute manic patients of various medication statuses had comparable plasma insulin levels, hyperinsulinaemia was found to be very common amongst bipolar patients in subsequent remission, regardless of the types of mood stabilizers or antipsychotics being used. Our analyses indicate that, in all patients, bodyweight gain may account for the presence of hyperinsulinaemia throughout the acute mania. Whilst a number of mechanisms have been proposed for lithium- or valproate-induced weight gain (Keck and McElroy 2004), this is an issue which remains uncertain in bipolar patients. Taken together, we suggest that it is the weight gain itself, rather than the direct effects of mood stabilizers or antipsychotics, which leads to hyperinsulinaemia throughout bipolar manic episode.

Our findings are consistent with the proposition that elevated plasma leptin levels have a positive relationship with a medication-induced increase in bodyweight and

BMI (McIntyre et al., 2005). It is, however, noted that a rapid and significant elevation in plasma insulin level is not accompanied by any proportional increments in plasma leptin, bodyweight gain or BMI. This uncoupling process may indicate that regulation of insulin through other mechanisms, with the exception of bodyweight gain, may exist in bipolar patients throughout the acute episode.

It is clear that the administration of propranolol, the classic beta-blocker, in one-third of our patients may contribute to the extreme elevation of plasma insulin levels in subsequent remission. However, it is also apparent that patients in acute mania had comparable insulin levels, irrespective of whether or not they were taking propranolol. The available evidence indicates that beta-blocker treatment is often associated with a 0.5 kg to 3.5 kg increase in body weight after six to twelve months of treatment (Sharma et al., 2001). With a mean 46-day interval between the two measurements, it is unlikely that propranolol-induced bodyweight gain is associated with an elevation in insulin level. Therefore, it is surmised that medicated bipolar patients tend to be overweight and use of propranolol exacerbating insulin resistance prior to weight gain may play a role for hyperinsulinaemia in propranolol-treated patients.

Our study is limited somewhat by its failure to control for individual variations which are known to effect insulin levels (such as smoking), the permission for

concomitant medication, and the fact that data were obtained for only two specific time points throughout a manic episode. Although the side-effect of insulin resistance amongst bipolar patients treated with atypical antipsychotics was not observed in this study, we nevertheless await further empirical confirmation before drawing any conclusions from this.

Although the direction of the cause-and-effect relationship between hyperinsulinaemia and bodyweight gain remains unclear, our data provide some evidence to support that bipolar patients are at high risk of developing hyperinsulinaemia. Our findings therefore suggest that by controlling body weight, and co-prescribing beta-blocker with greater caution, a reduction can be achieved in the overall risk of hyperinsulinaemia.

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**Table 1.Comparison of insulin, leptin, body weight and body mass index between acute mania and subsequent remission of bipolar patients (N=42)**

| Variables | Acute Mania | | Subsequent Remission | | *t* | *p* |
|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | | |
| Insulin, μIU/mL | 11.14 | 14.39 | 48.27 | 51.39 | 3.71 | <0.001 |
| Leptin, ng/mL | 15.02 | 15.01 | 20.81 | 17.14 | 2.86 | <0.01 |
| Body weight, kg | 64.60 | 12.87 | 67.10 | 12.84 | 3.62 | <0.001 |
| Body mass index, $kg/m^2$ | 23.97 | 4.06 | 24.91 | 4.09 | 3.63 | <0.001 |

**Table 2.Comparison in continuous variables between bipolar patients with and without hyperinsulinaemia in subsequent remission**

| Variables | Patients with hyperinsulinaemia (N=30) | Patients without hyperinsulinaemia (N=12) | *t* | *p* |
|---|---|---|---|---|
| | Mean (SD) | Mean (SD) | | |
| Age | 32.9(8.4) | 33.7(9.2) | 0.27 | ns |
| Age at onset | 23.1(7.2) | 25.8 (6.5) | 1.13 | ns |
| No. of lifetime affective episodes | 4.9 (4.0) | 5.2 (4.2) | 0.16 | ns |
| Dosage of lithium, mg | 555.2 (611.0) | 350.0 (418.9) | -1.23 | ns |
| Dosage of valporate, mg | 646.7 (635.0) | 600.0 (668.8) | -0.21 | ns |
| Insulin level in acute mania, μIU/mL | 12.27 (15.96) | 8.32 (9.39) | -0.80 | ns |
| Insulin level in remission, μIU/mL | 57.06 (44.59) | 5.31(3.73) | -6.30 | 0.000 |
| BMI in acute mania | 24.5 (4.3) | 23.6 (3.9) | -0.59 | ns |
| BMI in remission, $kg/m^2$ | 25.7（4.2) | 22.5 (2.9) | 2.27 | <0.025 |
| Fasting leptin level in acute mania, ng/mL | 14.1(12.9) | 17.3(19.8) | 0.61 | ns |
| Fasting leptin level in remission, ng/mL | 23.59 ( 18.68) | 13.89±10.02 | 2.18 | <0.05 |

**Table 3.Comparison in categorical variables between bipolar patients with and without hyperinsulinaemia in subsequent remission**

| Categorical variables | Patients with hyperinsulinaemia (N=30) | | Patients without hyperinsulinaemia (N=12) | | *p** |
|---|---|---|---|---|---|
| | N. | % | N | % | |
| Male | 19 | 63.3 | 3 | 25.0 | <0.05 |
| Prior history of depressive episode | 6 | 20.0 | 5 | 41.6 | ns |
| Smoking | 11 | 36.6 | 0 | 0 | <0.025 |
| Use of propranolol | | | | | |
| in acute mania | 12 | 40.0 | 1 | 8.3 | 0.067 |
| in subsequent remission | 15 | 50.0 | 1 | 8.3 | < 0.025 |

* Fisher's exact test