

An exploration of testosterone levels in patients with bipolar disorder

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Background

Testosterone influences well-being, mood and cognition and may play a role in the pathophysiology of bipolar disorder.

Aim

To examine testosterone levels in patients with bipolar disorder compared with healthy controls.

Method

We examined baseline total testosterone levels and current depression scores in male and female patients with bipolar disorder and mild to moderate depression and healthy controls.

Results

A significant interaction between diagnosis and gender was observed ($F(2,97)=9.791$, $P=0.002$). Testosterone levels were significantly lower for male patients with bipolar disorder compared with male controls ($P=0.001$). Women with bipolar

disorder had significantly higher testosterone levels than female controls ($P=0.03$).

Conclusions

Disturbances in testosterone levels may represent an important neurobiological abnormality in bipolar disorder and may differ by gender. If these findings are confirmed, the use of gender appropriate treatment strategies for the normalisation of testosterone levels in bipolar disorder depression should be further explored.

Declaration of interest

None.

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Bipolar disorder is burdensome for the individual and for society; it is associated with significant functional impairment, high comorbidity, lower quality of life and higher rates of suicide.¹ Pharmacotherapy with mood stabilisers and antipsychotics may not lead to sustained remission and more than two-thirds of those treated experience a recurrence within 5 years.² Given such poor treatment outcomes, novel approaches to improve therapeutic interventions are an important objective of bipolar disorder research. Mounting, albeit inconsistent, evidence suggests that testosterone may play a role in the pathophysiology of mood disorders.³ However, the effects of testosterone are complex: the hormonal disorder polycystic ovarian syndrome is characterised by chronically increased testosterone levels and is associated with significantly increased depression,⁴ but paradoxically, amelioration of depression has been found following testosterone administration in males⁵ and females;^{6–8} low testosterone levels have been reported in certain subgroups of men with depression,⁹ androgen-induced hypomania has been reported;¹⁰ and high testosterone levels may predict suicidal behaviour in women with bipolar disorder.³ Further evidence clarifying the relationship between testosterone and bipolar disorder might pave the way for exploring the use of pharmacological strategies that optimise testosterone levels in patients with bipolar disorder. We therefore assessed testosterone levels in bipolar disorder and healthy controls and sought to explore whether this was different between males and females and whether there was a relationship between testosterone, mood and cognition.

Method

Participants and study setting

Participants in this study were 49 patients (male: $n=30$; female: $n=19$) with a diagnosis of bipolar disorder ($n=27$ bipolar disorder I; $n=22$ bipolar disorder II) and a current depressive episode (confirmed with the Structured Clinical Interview for DSM-IV¹¹),

who were 37 years old, and 37 education-matched healthy controls (male: $n=23$; female: $n=14$). Here we report baseline data collected as part of a study examining the effects of a glucocorticoid receptor antagonist in bipolar disorder depression.¹² Patient medication was unchanged for 4 weeks before participation. After a complete description of the study, written informed consent was obtained from all participants. The study was carried out at Newcastle University in the north east of England and was approved by Newcastle and North Tyneside Local Research Ethics Committee.

Neuroendocrine assessment

Blood samples were taken at 15.00 h. The blood was spun at 3000 rpm for 10 min in a refrigerated centrifuge, then separated and stored at -80°C until assayed for total testosterone. Testosterone was measured using the Roche Testosterone II assay on the Roche Modular Analytics E 170 analyser. Internal quality control involved material being assayed twice a day. The Clinical Biochemistry team at Newcastle Hospitals participates in the UK National External Quality Assessment Scheme (NEQAS) Steroid External Quality Assessment (EQA) Scheme.

Mood symptoms

The following mood measures were administered: the Hamilton Rating Scale for Depression (HRSD),¹³ the Montgomery and Åsberg Depression Rating Scale (MADRS)¹⁴ and the Beck Depression Inventory (BDI).¹⁵

Statistical analyses

Data were analysed using SPSS software (version 22 for Windows). Baseline demographic, neuroendocrine and mood data were compared between patients with bipolar disorder and controls. Due to the normal distribution of the data, quantitative characteristics are reported using means and standard deviations. We report summaries for the characteristics and the results of comparisons using independent-samples t -tests. Differences between gender (male *v.* female) and diagnosis (control *v.* patient)

Table 1 Demographic and clinical features of patients with bipolar disorder compared with healthy controls

Demographic and clinical features ^a	Male patients (n=30)	Male controls (n=23)	Female patients (n=19)	Female controls (n=14)
	Mean (s.d.)			
Age, years	47 (10.0)	42 (15.4)	47 (9.1)	48 (10.7)
HDRS	18 (4.6)	0.1 (0.3)	21 (4.6)	0.1 (0.4)
MADRS	26 (8.7)	0.5 (0.9)	28 (8.5)	0.4 (0.7)
BDI	27 (10.5)	0.9 (1.5)	30 (11.3)	0.9 (1.2)
Testosterone level, nmol/L	11.3 (3.8)	15.5 (4.2)	1.4 (0.4)	1.2 (0.2)

BDI, Beck Depression Inventory; HDRS, Hamilton Rating Scale for Depression; MADRS, Montgomery and Åsberg Depression Rating Scale.
a. Missing mood measure data on n=2 male patients and n=3 female patients; n=2–7 male controls and n=3–7 female controls.

in terms of testosterone levels were examined using as two-way analysis of variance (ANOVA). All cited *P*-values are two-tailed, with a significance level set at *P*=0.05.

Results

Demographic and clinical features of male and female patients with bipolar disorder compared with healthy male and female controls are outlined in Table 1.

A two-way ANOVA revealed a statistically significant interaction between gender and diagnosis on baseline testosterone level, $F(2,97)=9.791$, $P=0.002$. These results together with the independent-samples *t*-test indicated that male participants with bipolar disorder had reduced testosterone levels compared with male controls, $t(51)=3.777$, $P=0.001$, whereas female participants with bipolar disorder had higher testosterone levels compared with female controls, $t(31)=-2.252$, $P=0.03$.

No significant correlations were observed between total testosterone levels and depression severity on the HRSD, MADRS or the BDI in patients. We found no relationship between testosterone and neuropsychological performance.

Discussion

To our knowledge, this is one of the first studies to directly investigate differences in testosterone levels in participants with current depression with bipolar disorder compared with healthy matched controls. Testosterone levels were found to be significantly lower in male patients with bipolar disorder depression compared with male controls, whereas female participants with bipolar disorder depression had significantly higher testosterone levels than female controls.

These findings support earlier work showing low testosterone in males with depression.⁸ In a recent study examining whether testosterone predicted suicide attempts in females with bipolar disorder followed up prospectively for up to 2.5 years,³ the authors reported that higher baseline testosterone levels predicted suicide attempts during the follow-up period. Although the present study was not a follow-up study and we did not investigate links with suicide, we do report a consistent finding of abnormal testosterone levels being significant also for females with bipolar disorder with current depression.

To explore this finding further with a view to establishing new treatments for bipolar disorder, further research is necessary to confirm the role of testosterone in bipolar disorder and to understand why this divergence in testosterone levels occurs in males and in females with the illness. Important clinical questions to explore in this field of research from both a biological and psychological perspective are: (a) whether reduced anabolic or androgenic effects caused by low levels of testosterone reduce

feelings of masculinity and therefore self-satisfaction and self-worth in males; (b) whether an increase in the anabolic or androgenic effects of testosterone reduce feelings of femininity, lowering self-satisfaction and self-worth in females; (c) whether testosterone could be a useful biomarker for bipolar disorder; (d) whether testosterone could be a useful biomarker for depression *per se*; and (e) whether testosterone levels are stable in the course of bipolar disorder depression or could they reflect a worsening of bipolar disorder symptoms, including signifying risk of suicide in females with bipolar disorder.³ Additionally, a systematic review of the effects of testosterone treatments would be important before testosterone normalisation treatments are recommended.

Strengths and limitations

The study was relatively small and exploratory. We enrolled only participants with bipolar disorder with current depression into the study, therefore our findings may only relate to participants in this particular phase of the illness. The strength of the study was that the sample was clinically well characterised.

Implications

Pharmacological interventions for bipolar disorder depression can be effective, yet many patients fail to respond to treatment. The findings presented herein build on an existing literature that draws attention to the role of testosterone in bipolar disorder and has significant implications for clinical interventions. Expanding treatment methods by incorporating hormonal monitoring may reflect an important shift in addressing the treatment of bipolar disorder using a more holistic approach. These preliminary findings should be examined further to establish the consequences of altered sex hormone levels in bipolar disorder depression.

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