

## *Supplementary Material*

### 1 Supplementary Data

**Supplementary Table 1.** Correlation between Insulin-like growth factor (IGF) proteins and inflammatory markers with age in all groups.

**Supplementary Table 2.** Insulin-like growth factor (IGF) and inflammatory markers differences in male and female in all groups.

**Supplementary Table 3.** Correlation among Insulin-like growth factor (IGF) proteins in all groups.

**Supplementary Table 4.** Correlation among inflammatory markers in all groups.

**Supplementary Table 5.** Correlation between differences and percentage reductions after pharmacological treatment in the levels of Insulin-like growth factor (IGF) proteins and inflammatory markers with the Young Mania Rating Scale (YMRS) differences and percentage reductions.

### 2 Supplementary Figures and Tables

Proteins	Groups	Age (years)		Proteins	Groups	Age (years)	
		r	p			r	p
IGF-2 (ng/ml)	All	0.151	0.352	IGFBP-1 (ng/ml)	All	0.227	0.159
	HC	0.374 <sup>s</sup>	0.104		HC	0.444	0.051
	BD	0.035	0.885		BD	0.031	0.898
	BD0	0.144	0.692		BD0	0.498	0.143
	BD1	-0.036	0.922		BD1	0.039	0.915
IGFBP-3 (ng/ml)	All	-0.153 <sup>s</sup>	0.347	IGFBP-5 (ng/ml)	All	-0.146	0.370
	HC	0.124	0.603		HC	-0.083	0.727
	BD	-0.170	0.473		BD	-0.040	0.868
	BD0	-0.472	0.168		BD0	-0.352	0.319
	BD1	-0.271	0.450		BD1	-0.083	0.821
IGFBP-7 (ng/ml)	All	<b>0.319</b>	<b>0.045</b>	MCP-1 (pg/ml)	All	0.227 <sup>s</sup>	0.159
	HC	<b>0.506<sup>s</sup></b>	<b>0.023</b>		HC	0.427 <sup>s</sup>	0.061
	BD	0.135 <sup>s</sup>	0.570		BD	0.114 <sup>s</sup>	0.632
	BD0	-0.232 <sup>s</sup>	0.519		BD0	0.323 <sup>s</sup>	0.362
	BD1	-0.208	0.565		BD1	0.176	0.627
MIP-1 $\beta$ (pg/ml)	All	<b>0.316</b>	<b>0.047</b>	TNF- $\alpha$ (pg/ml)	All	0.011 <sup>s</sup>	0.945
	HC	0.018	0.942		HC	0.082 <sup>s</sup>	0.730
	BD	<b>0.470</b>	<b>0.036</b>		BD	-0.040	0.867
	BD0	0.320	0.368		BD0	-0.159	0.661
	BD1	0.451 <sup>s</sup>	0.191		BD1	-0.591	0.072

**Supplementary Table 1.** Pearson's correlation coefficient was the main coefficient employed. r: coefficient values range from -1 to 1. <sup>s</sup> Spearman's correlation coefficient was used when at least one of both distributions did not adjust to a normal distribution (Shapiro-Wilk test; p-value < 0.05). All (n = 40): HC + BD groups; HC

(n = 20): healthy control; BD (n = 20): bipolar disorder; BD0 (n = 10): bipolar disorder time 0 (before treatment at hospital admission in longitudinal subgroup); BD1 (n = 10): bipolar disorder time 1 (after treatment at hospital admission in longitudinal subgroup); IGF: Insulin-like growth factor; IGFBP: Insulin-like growth factor binding protein; MCP-1: Monocyte chemoattractant protein 1; MIP-1 $\beta$ : Macrophage inflammatory protein 1 beta; TNF- $\alpha$ : Tumor necrosis factor alpha. p-value < 0.05 indicates statistical significance.

Proteins	Groups	Gender (F/M)		p
		F	M	
IGF-2 (ng/ml)	All	124.35 $\pm$ 54.81	125.43 $\pm$ 62.28	0.954
	HC	121.85 $\pm$ 47.12	107.21 $\pm$ 55.35	0.532
	BD	126.86 $\pm$ 64.09	143.65 $\pm$ 66.24	0.572
	BD0	170.83 $\pm$ 55.89	155.11 $\pm$ 48.59	0.648
	BD1	163.01 $\pm$ 57.76	174.80 $\pm$ 49.91	0.739
IGFBP-1 (ng/ml)	All	7.49 $\pm$ 4.55	9.59 $\pm$ 4.07	0.052 <sup>1</sup>
	HC	6.38 $\pm$ 3.59	9.96 $\pm$ 5.31	0.089 <sup>1</sup>
	BD	8.61 $\pm$ 5.30	9.23 $\pm$ 2.54	0.742
	BD0	7.01 $\pm$ 4.54	6.91 $\pm$ 2.15	0.964
	BD1	10.68 $\pm$ 6.49	9.56 $\pm$ 2.44	0.728
IGFBP-3 (ng/ml)	All	389.28 $\pm$ 134.18	349.15 $\pm$ 121.64	0.328
	HC	504.06 $\pm$ 79.12	444.59 $\pm$ 77.81	0.107
	BD	274.50 $\pm$ 49.75	253.71 $\pm$ 70.28	0.455
	BD0	268.83 $\pm$ 42.90	231.03 $\pm$ 28.29	0.139
	BD1	286.39 $\pm$ 34.76	229.26 $\pm$ 13.08	<b>0.008<sup>1</sup></b>
IGFBP-5 (ng/ml)	All	60.98 $\pm$ 28.69	54.82 $\pm$ 28.55	0.501
	HC	85.36 $\pm$ 13.04	79.55 $\pm$ 16.48	0.684 <sup>1</sup>
	BD	36.59 $\pm$ 15.69	30.10 $\pm$ 9.52	0.278
	BD0	42.39 $\pm$ 5.35	37.23 $\pm$ 4.81	0.147
	BD1	48.60 $\pm$ 6.08	37.59 $\pm$ 5.42	<b>0.016</b>
IGFBP-7 (ng/ml)	All	121.63 $\pm$ 126.08	91.66 $\pm$ 66.00	0.678 <sup>1</sup>
	HC	75.56 $\pm$ 28.29	64.62 $\pm$ 29.92	0.412
	BD	167.71 $\pm$ 167.46	118.71 $\pm$ 81.72	0.853 <sup>1</sup>
	BD0	133.94 $\pm$ 49.30	175.78 $\pm$ 121.94	0.841 <sup>1</sup>
	BD1	274.66 $\pm$ 180.78	135.51 $\pm$ 70.93	0.310 <sup>1</sup>
MCP-1 (pg/ml)	All	87.22 $\pm$ 43.11	94.43 $\pm$ 70.98	0.968 <sup>1</sup>
	HC	65.72 $\pm$ 22.31	78.91 $\pm$ 31.06	0.209
	BD	108.72 $\pm$ 48.98	109.95 $\pm$ 95.58	0.481 <sup>1</sup>
	BD0	115.07 $\pm$ 42.34	82.22 $\pm$ 20.15	0.310 <sup>1</sup>
	BD1	67.44 $\pm$ 32.06	90.38 $\pm$ 47.74	0.310 <sup>1</sup>
MIP-1 $\beta$ (pg/ml)	All	62.89 $\pm$ 34.59	61.22 $\pm$ 90.13	0.068 <sup>1</sup>
	HC	48.69 $\pm$ 26.14	38.49 $\pm$ 20.98	0.348
	BD	77.10 $\pm$ 37.34	83.95 $\pm$ 124.74	0.123 <sup>1</sup>
	BD0	83.61 $\pm$ 31.27	44.80 $\pm$ 51.73	0.189
	BD1	71.95 $\pm$ 71.52	34.58 $\pm$ 29.76	0.312
TNF- $\alpha$ (pg/ml)	All	33.84 $\pm$ 12.45	48.23 $\pm$ 26.98	0.072 <sup>1</sup>
	HC	32.58 $\pm$ 12.52	39.43 $\pm$ 21.21	0.391

BD	35.10 ± 12.92	57.03 ± 30.25	0.063 <sup>1</sup>
BD0	126.86 ± 64.10	143.65 ± 66.25	0.573
BD1	27.91 ± 9.22	41.95 ± 32.86	0.690 <sup>1</sup>

**Supplementary Table 2.** Parametric Student's T test was the main statistical test employed. <sup>1</sup> Non-parametric Mann-Whitney's test was used if at least one of both distributions did not adjust to a normal distribution (Shapiro-Wilk test; p-value < 0.05). F: Female. M: Male. All (F/M; 20/20): HC + BD; HC (F/M; 10/10): healthy control; BD (F/M; 10/10): bipolar disorder; BD0 (F/M; 5/5): bipolar disorder time 0 (before treatment at hospital admission in longitudinal subgroup); BD1 (F/M; 5/5): bipolar disorder time 1 (after treatment at hospital admission in longitudinal subgroup); IGF: Insulin-like growth factor; IGFBP: Insulin-like growth factor binding protein. MCP-1: Monocyte chemoattractant protein 1; MIP-1 $\beta$ : Macrophage inflammatory protein 1 beta; TNF- $\alpha$ : Tumor necrosis factor alpha. p-value < 0.05 indicates statistical significance.

IGF Protein	Groups	IGFBP-1 (ng/ml)		IGFBP-3 (ng/ml)		IGFBP-5 (ng/ml)		IGFBP-7 (ng/ml)	
		r	p	r	p	r	p	r	p
IGF-2 (ng/ml)	All	0.172	0.287	0.067 <sup>S</sup>	0.681	0.003	0.984	<b>0.814<sup>S</sup></b>	<b>&lt;0.0001</b>
	HC	0.136 <sup>S</sup>	0.567	0.414 <sup>S</sup>	0.070	0.317 <sup>S</sup>	0.173	<b>0.836<sup>S</sup></b>	<b>&lt;0.0001</b>
	BD	0.244	0.300	0.157	0.509	0.262	0.264	<b>0.767<sup>S</sup></b>	<b>&lt;0.0001</b>
	BD0	0.087	0.812	0.052	0.886	0.159	0.662	<b>0.903<sup>S</sup></b>	<b>&lt;0.0001</b>
	BD1	-0.082	0.823	0.153	0.673	-0.071	0.846	<b>0.737</b>	<b>0.015</b>
IGFBP-1 (ng/ml)	All			-0.214 <sup>S</sup>	0.184	-0.093	0.570	<b>0.322<sup>S</sup></b>	<b>0.043</b>
	HC			-0.329	0.157	-0.338	0.146	0.227	0.335
	BD			-0.090	0.704	0.367	0.112	0.355 <sup>S</sup>	0.125
	BD0			-0.521	0.122	-0.460	0.181	0.139 <sup>S</sup>	0.701
	BD1			0.088	0.810	0.283	0.428	-0.061	0.867
IGFBP-3 (ng/ml)	All					<b>0.810<sup>S</sup></b>	<b>&lt;0.0001</b>	0.021 <sup>S</sup>	0.898
	HC					<b>0.653</b>	<b>0.002</b>	<b>0.459</b>	<b>0.042</b>
	BD					-0.082	0.732	0.385 <sup>S</sup>	0.094
	BD0					<b>0.953</b>	<b>&lt;0.0001</b>	0.042 <sup>S</sup>	0.907
	BD1					<b>0.811</b>	<b>0.004</b>	<b>0.652</b>	<b>0.041</b>
IGFBP-5 (ng/ml)	All							-0.047 <sup>S</sup>	0.773
	HC							0.360	0.119
	BD							0.371 <sup>S</sup>	0.107
	BD0							0.152 <sup>S</sup>	0.676
	BD1							0.418	0.229

**Supplementary Table 3.** Pearson's correlation coefficient was the main coefficient employed. r: coefficient values range from -1 to 1. <sup>S</sup> Spearman's correlation coefficient was used when at least one of both distributions did not adjust to a normal distribution (Shapiro-Wilk test; p-value < 0.05). All (n = 40): HC + BD groups; HC (n = 20): healthy control; BD (n = 20): bipolar disorder; BD0 (n = 10): bipolar disorder time 0 (before treatment at hospital admission in longitudinal subgroup); BD1 (n = 10): bipolar disorder time 1 (after treatment at hospital admission in longitudinal subgroup); IGF: Insulin-like growth factor; IGFBP: Insulin-like growth factor binding protein. p-value < 0.05 indicates statistical significance.

Infl. Markers	Groups	MIP-1 $\beta$ (pg/ml)		TNF- $\alpha$ (pg/ml)	
		r	p	r	p

MCP-1 (pg/ml)	All	<b>0.496</b>	<b>0.001</b>	0.287	0.072
	HC	0.429	0.059	0.388	0.091
	BD	<b>0.556</b>	<b>0.011</b>	0.053	0.823
	BD0	<b>0.758</b>	<b>0.011</b>	0.042	0.907
	BD1	0.261	0.467	-0.255 <sup>P</sup>	0.478
MIP-1 $\beta$ (pg/ml)	All			0.013	0.935
	HC			-0.049 <sup>P</sup>	0.836
	BD			-0.056	0.813
	BD0			0.007 <sup>P</sup>	0.985
	BD1			-0.006	0.987

**Supplementary Table 4.** Spearman's correlation coefficient was the main coefficient employed. r: coefficient values range from -1 to 1. <sup>P</sup> Pearson's correlation coefficient was used when both distributions adjust to a normal distribution (Shapiro-Wilk test; p-value > 0.05). All (n = 40): HC + BD groups; HC (n = 20): healthy control; BD (n = 20): bipolar disorder; BD0 (n = 10): bipolar disorder time 0 (before treatment at hospital admission in longitudinal subgroup); BD1 (n = 10): bipolar disorder time 1 (after treatment at hospital admission in longitudinal subgroup); MCP-1: Monocyte chemoattractant protein 1; MIP-1 $\beta$ : Macrophage inflammatory protein 1 beta; TNF- $\alpha$ : Tumor necrosis factor alfa. p-value < 0.05 indicates statistical significance.

Proteins		YMRS (dif)		YMRS (% red)	
		r	p	r	p
IGF-2 (ng/ml)	Dif	<b>0.727</b>	<b>0.017</b>	0.254	0.478
	%red	<b>0.687</b>	<b>0.028</b>	0.282	0.430
IGFBP-1 (ng/ml)	Dif	0.589	0.073	0.302	0.397
	%red	0.588	0.074	0.190	0.599
IGFBP-3 (ng/ml)	Dif	0.379	0.281	0.424	0.222
	%red	0.309	0.384	0.392	0.263
IGFBP-5 (ng/ml)	Dif	-0.067 <sup>S</sup>	0.854	0.055 <sup>S</sup>	0.881
	%red	-0.122 <sup>S</sup>	0.738	0.105 <sup>S</sup>	0.777
IGFBP-7 (ng/ml)	Dif	0.187	0.605	0.001	0.999
	%red	0.309	0.386	0.209	0.562
MCP-1 (pg/ml)	Dif	0.419	0.228	0.390	0.265
	%red	0.480 <sup>S</sup>	0.160	0.139 <sup>S</sup>	0.701
MIP-1 $\beta$ (pg/ml)	Dif	0.305	0.391	-0.179	0.621
	%red	0.389 <sup>S</sup>	0.266	-0.006 <sup>S</sup>	0.987
TNF- $\alpha$ (pg/ml)	Dif	-0.065	0.859	-0.112	0.759
	%red	-0.193	0.593	-0.310	0.384

**Supplementary Table 5.** Pearson's correlation coefficient was the main coefficient employed. r: coefficient values range from -1 to 1. <sup>S</sup> Spearman's correlation coefficient was used when at least one of both distributions did not adjust to a normal distribution (Shapiro-Wilk test; p-value < 0.05). Dif: difference in values in BD patients after (BD1) and before (BD0) treatment (BD1-BD0). % red: percentage reduction in values in BD patients after (BD1) and before (BD0) patients ((BD1-BD0)/BD1\*100). IGF: Insulin-like growth factor; IGFBP: Insulin-like growth factor binding protein. MCP-1: Monocyte chemoattractant protein 1; MIP-1 $\beta$ : Macrophage

inflammatory protein 1 beta; TNF- $\alpha$ : Tumor necrosis factor alpha. YMRS: Young Manic Rating Scale. p-value < 0.05 indicates statistical significance.