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Adiponectin levels in patients with bipolar disorder: A systematic review and meta-analysis

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ABSTRACT

Bipolar disorder (BD) is associated with high prevalence rates of obesity-related conditions and subclinical inflammation. Adiponectin is produced by adipose tissue and exerts anti-inflammatory activities. We aimed to perform a systematic review and meta-analysis of studies investigating adiponectin levels in BD patients and healthy controls. Electronic databases were searched from their inception until 15th Jan 2019. Random-effects models with the Hedges' g as the effect size (ES) estimate were used. We included 11 studies, representing 477 patients and 380 controls. Pooled data analysis revealed no significant differences in adiponectin levels between BD patients and controls (ES = 0.28, 95%CI: -0.34 – 0.90, p = 0.372). The levels of adiponectin were significantly higher during euthymia (ES = 1.09, 95%CI: 0.03–2.16, p = 0.044). The levels of adiponectin in depressed patients were lower, but this result did not reach statistical significance (ES = -0.90, 95%CI: -1.85 – 0.05, p = 0.063). Due to low number of studies, the subgroup analysis of manic patients was not performed; however, a severity of manic symptoms was not associated with the ES estimates. Longer illness duration and a higher percentage of BD type I (BD-I) patients were associated with higher ES estimates. A higher severity of depressive symptoms was associated with lower ES estimates. Heterogeneity was significant in all analyses. Results of the Egger's test were insignificant, showing no publication bias. Our results indicate that adiponectin might be a state marker of BD as it appears to be elevated in euthymia and decreased in depression. Illness progression and a diagnosis of BD-I might contribute to higher adiponectin levels.

1. Introduction

Bipolar disorder (BD) is a complex mental disorder with multidimensional psychopathology and lifetime prevalence rates estimated at 2–4% (Ketter, 2010). Several lines of evidence demonstrate high prevalence of cardiovascular risk factors and metabolic dysregulations that largely contribute to reduced life expectancy in patients with BD (Crump et al., 2013; Vancampfort et al., 2016, 2013). This phenomenon is associated with side effects of pharmacological treatment and poor life style characteristics (Fagiolini et al., 2008, 2005; McIntyre et al., 2010).

Metabolic dysregulations observed in BD, including obesity, type 2 diabetes and metabolic syndrome are also associated with unfavourable course of illness in terms of a higher number of depressive and manic episodes, more hospitalizations, suicidality, lower probability of recovery and poor response to lithium (Brietzke et al., 2011). A meta-analysis of longitudinal studies (Luppino et al., 2010) revealed a positive correlation between the probability of developing depressive mood and the body mass index (BMI). Obesity and overweight are also highly prevalent in drug-naïve patients with BD, suggesting that metabolic dysregulations might be closely related to the pathophysiology of BD (Maina et al., 2008). In addition, both BD and obesity are associated with subclinical inflammation (SayuriYamagata et al., 2017).

One of possible explanations for these associations are related to biological functions of adipose tissue that is now believed to serve as an endocrine organ, secreting over 600 bioactive compounds, called the adipokines (Platzer et al., 2018). Adipokines, represented by adiponectin and leptin, play an important role in various metabolic and immunological processes. Leptin regulates energy expenditure by signalling satiety to the brain and acts as a pro-inflammatory hormone. It

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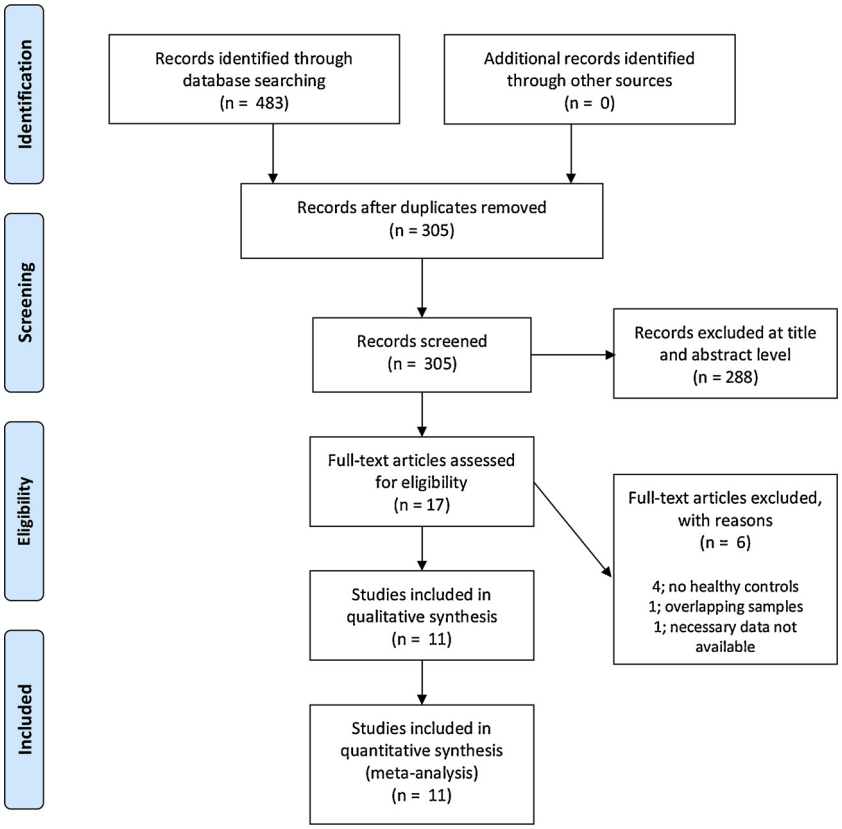

Fig. 1. Selection of studies (Moher et al., 2009).

is also involved in the regulation of sleep-wake cycle, sexual behaviour and reproductive functions. A recent meta-analysis did not reveal any significant differences between BD patients at various mood states and healthy controls (Fernandes et al., 2016). However, the authors observed a stronger association between leptin levels and both BMI and age in BD patients compared to healthy controls. In turn, adiponectin regulates energy expenditure, improves insulin sensitivity and fatty acid oxidation and is considered as an anti-inflammatory factor (Berg et al., 2002; Qi et al., 2004). Certain adiponectin isoforms might cross the blood-brain barrier and interact with the receptors located in several brain regions, including the hypothalamus, brainstem, cortical neurons and endothelial cells (Thundyil et al., 2012). Administration of exogenous adiponectin produces antidepressant-like effects in normal-weight and obese mice (Liu et al., 2012). In the same study, lower adiponectin levels were found in a chronic social defeat model of depression. As similar to several antidepressants (Warner-Schmidt and Duman, 2006), adiponectin might stimulate hippocampal neurogenesis (Zhang et al., 2011). Decreased blood levels of adiponectin have been found in obesity-related diseases (Nigro et al., 2014) and major depressive disorder (Cao et al., 2018).

Studies investigating blood levels of adiponectin have provided mixed findings and have not been subjected to quantitative synthesis. Therefore, in this study we aimed to perform a systematic review of adiponectin levels in patients with BD at various mood states.

2. Material and methods

2.1. Search strategy

Search strategy followed the PRISMA guidelines (Moher et al., 2009). Two authors (F.S and B.S.) independently performed an online search for relevant publications in the following databases: the Medline, the ERIC, the CINAHL Complete, as well as the Academic Search Complete and Health Source: Nursing/Academic Edition. Discrepancies were resolved by a consensus method, involving discussions with another author (B.M.). The following combination of keywords was used: "bipolar" or "psychosis" or "mania" or "manic" or "depress*" and "adiponectin". The search strategy was complemented by reviewing reference lists of eligible publications. The following exclusion criteria were established: 1) publications written in non-English language; 2) non-original articles (reviews, meta-analyses, commentaries and editorials); 3) studies without a group of healthy controls and 4) animal model studies. After considering exclusion criteria, search results were compared and studies investigating plasma or serum levels of adiponectin in patients with BD and healthy controls were included in further analysis. Our systematic review covered publication records from database inception until 15th Jan 2019.

2.2. Data analysis

We extracted the following data from eligible publications (mean and SD or the number of cases): 1) age; 2) sex; 3) BMI; 4) cigarette smoking status; 5) illness duration; 6) score of the Young Mania Rating Scale (YMRS); 7) score of the Hamilton Depression Rating Scale (HDRS); 8) mood state; 9) type of BD and 10) the levels of adiponectin. Corresponding authors of eligible studies were contacted in case of a lack of necessary data to perform meta-analysis. In case of one study (Vianna-Sulzbach et al., 2015), mean levels of adiponectin were extracted using the GetData Graph Digitizer 2.26. The Newcastle-Ottawa Scale (NOS) was used for quality assessment (Wells et al., 2000).

Differences in mean levels of adiponectin between BD patients and healthy controls were included as principal summary measures. Random-effects models were used to pool data due to anticipated heterogeneity. The effect size (ES) estimates were calculated as Hedges' g. Assessment of heterogeneity was performed using the Cochran Q test and the I^2 estimates. A sensitivity analysis was conducted by excluding

studies one at a time to verify if any single study accounted for heterogeneity. The Egger's test was used to evaluate publication bias. Additionally, funnel plot of asymmetry was inspected. Subgroup analyses were performed to examine the levels of adiponectin in patients with BD at various mood states (euthymia, mania and depression). Meta-regression was performed to test the effects of age, sex, BMI, cigarette smoking status, illness duration, scores of YMRS and HDRS on the ES estimates. Results were considered statistically significant if the p-value was < 0.05. Statistical analysis was performed using the STATISTICA software, version 12.5.

3. Results

Out of 483 records identified, 11 studies met our eligibility criteria and were included in systematic review and meta-analysis (Barbosa et al., 2012; Bond et al., 2017; Elmslie et al., 2009; Hung et al., 2007; Mansur et al., 2017, 2016; Platzer et al., 2018; Soeiro-de-Souza et al., 2014; Syk et al., 2019; Tunçel et al., 2018; Vianna-Sulzbach et al., 2015) (Fig. 1). Data regarding the largest sample of non-overlapping participants were obtained from the corresponding author of two studies (Mansur et al., 2017, 2016).

General characteristics of included studies were shown in Table 1. Of those studies, one study reported separate data for mania (Tunçel et al., 2018), five for depression (Hung et al., 2007; Mansur et al., 2017, 2016; Platzer et al., 2018; Soeiro-de-Souza et al., 2014) and six for euthymia (Barbosa et al., 2012; Mansur et al., 2017; Mansur et al., 2018; Platzer et al., 2018; Tunçel et al., 2018; Vianna-Sulzbach et al., 2015). One study reported the levels of adiponectin in the same group of patients in mania and euthymia (Tunçel et al., 2018). In three studies (Bond et al., 2017; Elmslie et al., 2009; Syk et al., 2018), the levels of adiponectin for patients at various mood states were not reported. Eligible studies included 477 patients with BD (mean age: 35.3 years) and 380 healthy controls (mean age: 34.8 years). Sample size of patients varied from 15 (Hung et al., 2007) to 120 (Platzer et al., 2018), while the sample size of healthy controls was between 14 (Hung et al., 2007) to 68 (Platzer et al., 2018). The majority of studies determined adiponectin levels in plasma, while only two studies were based on serum adiponectin levels (Bond et al., 2017; Vianna-Sulzbach et al., 2015). Almost all studies used the enzyme-linked immunosorbent assays (ELISA) to measure the levels of adiponectin, except for two studies that had been based on radioimmunoassay (Elmslie et al., 2009) and the Luminex xMAP technology (Bond et al., 2017). The NOS score ranged between 3 (Platzer et al., 2018) and 6 (Elmslie et al., 2009; Mansur et al., 2016).

Pooled data analysis, regardless of mood state, revealed no significant differences between BD patients and healthy controls (ES = 0.28, 95%CI: -0.34 – 0.90, p = 0.372). Subgroup analysis was presented in Fig. 2, showing significantly higher levels of adiponectin in euthymic BD patients (237 BD patients and 176 healthy controls, ES = 1.09, 95%CI: 0.03–2.16, p = 0.044). The levels of adiponectin were lower in depressed BD patients but this result did not reach statistical significance (108 BD patients and 133 healthy controls, ES = 0.90, 95%CI: -1.85 – 0.05, p = 0.063) compared to healthy controls. Only one study reported adiponectin levels in manic patients (30 BD patients and 30 healthy controls), showing no significant differences between this subgroup of patients and healthy controls (Tunçel et al., 2018). Heterogeneity was high in the pooled analysis [Q = 148.5, p (Q) < 0.001, I^2 = 93.9%] and subgroup analyses of euthymic and depressed patients [euthymia: Q = 99.0, p(Q) < 0.001, I^2 = 96.0%; depression: 31.2, p(Q) < 0.001, I^2 = 90.4%]. No single study thoroughly explained heterogeneity in the pooled analysis as well as subgroup analyses of depressed and manic patients after excluding one study at a time (sensitivity analysis).

Meta-regression analysis of adiponectin levels revealed that mean differences in age, the percentage of males, BMI and the percentage of smokers as well as the YMRS score and the NOS score were not

Table 1
General characteristics of studies included in systematic review and meta-analysis.

Study	Patients				Healthy controls			Matching	Assay	Serum/plasma	Medications	NOS
	N	Age	%males	Mood state	N	Age	%males					
Platzer et al. (2018)	120	42.2 ± 11.7	52.5	Depression and euthymia	68	36.9 ± 15.6	44.1	Age, BMI and sex	ELISA	Plasma	Li, AEs, SGAs, ADs and BZDs	3
Syk et al. (2019)	31	21.5 ± 2.3	16.1	NK	57	22.7 ± 2.5	22.8	BMI	ELISA	Plasma	NK	5
Tunçel et al. (2018)	30	34.4 ± 10.3	36.7	Mania and euthymia (the same patients)	30	35.0 ± 11.3	36.7	Age and sex	ELISA	Plasma	Li, FGAs, SGAs and valproate	5
Bond et al. (2017)	53	23.1 ± 4.6	45.3	Mania, euthymia and depression	22	25.0 ± 5.2	40.9	Age and sex	Luminex xMAP	Serum	MSs, SGAs, ADs and drug-free	5
Mansur et al. (2016) Mansur et al. (2017)	86	43.5 ± 10.0	NK	Depression and euthymia	21	38.6 ± 13.7	NK	Age, sex and BMI	ELISA	Plasma	Li, SGAs, FGAs, ADs and AEs	6
Vianna-Sulzbach et al. (2015)	34	44.9 ± 14.8	50.0	Euthymia	48	46.4 ± 11.2	37.5	Age, sex, BMI and years of education	ELISA	Serum	NK	4
Soeiro-de-Souza et al. (2014)	25	28.5 ± 5.7	24.0	Depression	23	27.1 ± 6.6	56.5	Age, BMI and cigarette smoking	ELISA	Plasma	Li and drug-free	5
Barbosa et al. (2012)	30	49.0 ± 10.9	23.3	Euthymia	30	47.1 ± 7.4	40.0	Age, BMI and sex	ELISA	Plasma	Li, AEs, FGAs and SGAs	5
Elmslie et al. (2009)	53	42.0 ± 11.0	18.3	NK	60	44.0 ± 12.0	16.7	Age, BMI, sex and ethnicity	RIA	Plasma	SGAs and valproate	6
Hung et al. (2007)	15	23.8 ± 0.7	100	depression	14	23.8 ± 0.6	100	Age, BMI and sex	ELISA	Plasma	NK	5

Abbreviations: ADs – antidepressants, AEs – antiepileptics, BMI – body mass index, ELISA – enzyme-linked immunosorbent assay FGAs – first-generation antipsychotics, Li – lithium, MSs – mood stabilizers, NK – not known, NOS – the Newcastle-Ottawa Scale, RIA – radioimmunoassay, SGAs – second-generation antipsychotics.

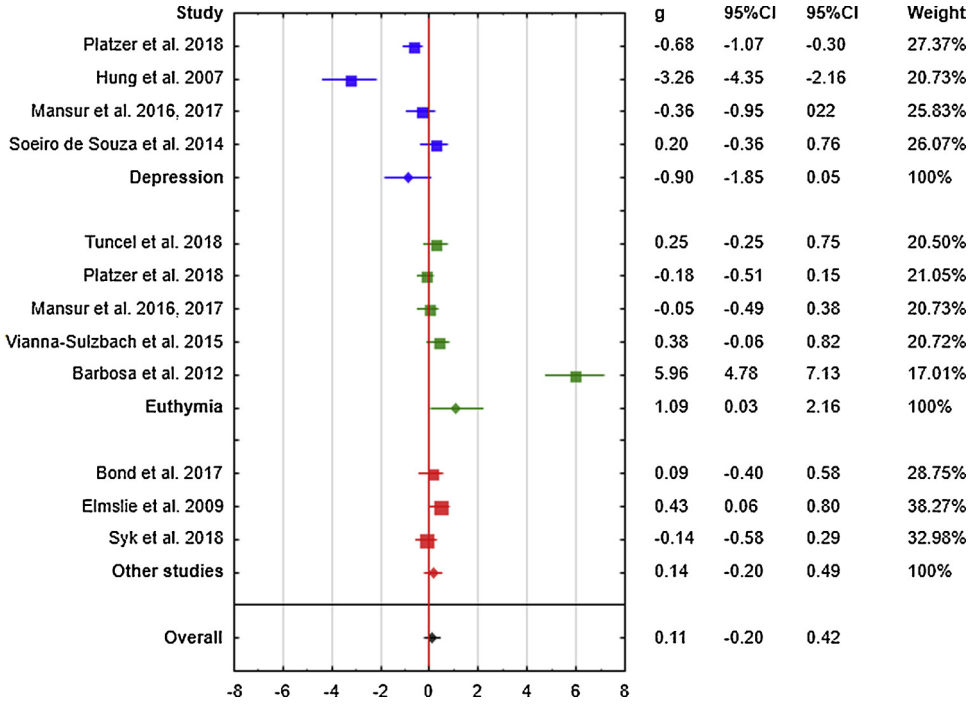

Fig. 2. Subgroup analysis of adiponectin levels taking into account mood states. Other studies represent those that did not provide adiponectin levels for patients at specific mood states.

Table 2
Meta-regression of adiponectine levels.

Moderator	N	β	95%CI	p	Adj. R^2
Mean difference in age	10	0.07	−0.22 – 0.35	0.644	
Mean difference in % of males	9	−0.03	−0.07 – 0.02	0.230	
Mean difference in BMI	10	0.007	−0.41 – 0.41	0.997	
Mean difference in % of smokers	5	−0.02	−0.05 – −0.01	0.159	38.6%
Patients with BD type I (%)	8	0.03	0.029 – 0.07	**0.032**	
HDRS score	5	−0.17	−0.28 – −0.07	**0.001**	17.2%
YMRS score	7	−0.01	−0.09 – 0.06	0.740	
Illness duration	6	0.19	0.02 – 0.37	**0.026**	
NOS score	10	0.13	−0.67 – 0.93	0.743	

Significant effects were marked with bold characters ($p < 0.05$).
Mean difference was calculated by subtracting the mean or percentage of cases in controls from the mean or percentage of cases in the group of BD patients.

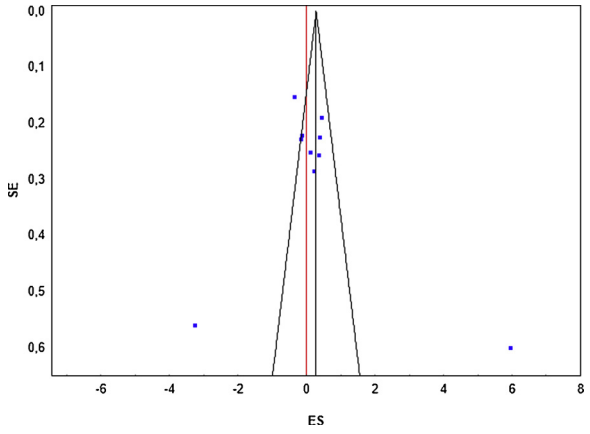

Fig. 3. Funnel plot of asymmetry illustrating a lack of publication bias.

associated with the ES estimates (Table 2). However, a higher percentage of patients with BD type I (BD-I), longer illness duration and lower HDRS scores were related to higher ES estimates. Results of the Egger's test were insignificant (β = 3.53, 95%CI = -5.58 – 12.63, t = 0.89, p = 0.398) (funnel plot of asymmetry was presented in Fig. 3).

4. Discussion

In this study, we found significantly higher levels of adiponectin in euthymic BD patients. A higher severity of depressive symptoms was related to lower adiponectin levels. The levels of adiponectin were also lower in depressed patients but this result did not reach statistical significance. We also found that longer illness duration and BD-I might be associated with higher adiponectin levels. Importantly, differences in adiponectin levels between BD patients and healthy controls were not associated with differences in age, sex, BMI and cigarette smoking in meta-regression analysis. There is weak evidence of unaltered adiponectin levels in manic BD patients based on one study (Tunçel et al., 2018).

Our findings suggest that adiponectin might be a state marker of BD and are in agreement with previous meta-analyses, showing decreased adiponectin levels in patients with unipolar depression (Cao et al., 2018; Carvalho et al., 2014). Dynamic changes of adiponectin levels across mood states might be explained by various mechanisms related to anti-inflammatory activities of adiponectin. On the basis of a meta-analysis, Rowland et al. (2018) found increased levels of inflammatory markers – interleukin(IL)-6 and C-reactive protein (CRP) in euthymic and manic BD patients, but not in those during a depressive episode. These results might suggest that changes in adiponectin levels appear as a response to inflammatory processes that are particularly active during euthymia. Indeed, adiponectin inhibits tumour necrosis factor-α (TNF-α) signalling pathway, NF-κB activation and phagocytic activity of macrophages as well as stimulates the production of anti-inflammatory cytokines represented by IL-10 and IL-1 receptor antagonist (Soczynska et al., 2011). Adiponectin has also been found to exert anti-depressive effects in a social defeat mouse model of depression (Liu et al., 2012). Notably, we did not find significant changes of adiponectin levels in

manic patients; however, there was only one study conducted in this group of patients (Tunçel et al., 2018). A severity of manic symptoms was not associated with the ES estimates (data from seven studies). It is also important to note that various mechanisms might underlie adiponectin responses to inflammatory states. In contrast to obesity-related conditions that are accompanied by low adiponectin levels; autoimmune diseases, including rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease or type 1 diabetes are associated with elevated adiponectin levels (Fantuzzi, 2008). In light of these observations, it has been proposed that elevated levels of adiponectin in these conditions might occur as a result of inflammation-induced catabolic responses, which are not present in case of obesity-related inflammation (Fantuzzi, 2008). This differential regulation of adiponectin responses in various inflammation-related conditions is particularly relevant to BD, which is associated with high prevalence rates of metabolic syndrome together with its single components and autoimmune diseases (Rosenblat and Mcintyre, 2015).

Our meta-analysis demonstrated a positive correlation between the ES estimates of differences in adiponectin levels and illness duration. These findings imply that a higher adiponectin level might be the marker of illness progression and point to the staging concept of BD (Berk et al., 2017; Kapczinski et al., 2014). The staging model of BD is supported by a number of biological dysregulations that exacerbate with illness progression and include oxidative stress, a deficiency of neurotrophins and inflammation. For instance, it has been reported that the levels of pro-inflammatory cytokines - IL-6 and TNF-α are elevated in both early and late stage BD, while the levels of anti-inflammatory cytokine IL-10 are increased only in late stage BD (Kauer-Sant'Anna et al., 2009). In this study (Kauer-Sant'Anna et al., 2009), the levels of TNF-α showed a significant increase in late stage BD. The association between BD-I and higher adiponectin levels may also be explained by the results from studies addressing inflammatory responses in BD patients. Indeed, previous studies reported elevated levels of IL-8, soluble IL-2 and TNF-α receptors in BD-I patients compared to those with BD type II (BD-II) (Bai et al., 2014; Wang et al., 2016).

There are several limitations of this meta-analysis that need to be discussed. Firstly, there was a limited number of studies that were found to be eligible, especially in case of those reporting adiponectin levels in manic patients. However, a severity of manic symptoms was not associated with the ES estimates in meta-regression analysis of seven studies. Heterogeneity was also high and factors explaining this observation were not identified. At this point, it is important to note that our findings in euthymic patients might be much affected by a single outlier (Barbosa et al., 2012). It should be noted that both longer illness duration and a higher percentage of BD-I patients were associated with higher ES estimates in meta-regression. In the study by Barbosa et al. (2012), all patients had a diagnosis of BD-I and illness duration was the longest compared to other studies included in our meta-analysis (mean: 25.54 years). In this study, there were also significantly higher rates of hypothyroidism and dyslipidaemia in the group of patients compared to controls. In some studies, thyroid hormones have been associated with adiponectin levels (Altinova et al., 2006; Cabanelas et al., 2010; Iglesias and Diez, 2007). However, detailed information regarding somatic comorbidities was not provided in other studies of euthymic BD patients. Additionally, we were unable to control for a number of potential confounding factors. As mentioned above, several somatic comorbidities might impact adiponectin levels and thus conclusions regarding intrinsic mechanisms of adiponectin alterations in BD cannot be established. We were also unable to examine the effects of various types of plasma in meta-regression analysis since this information was not provided in studies included in our meta-analysis. Furthermore, the vast majority of patients in studies included in our meta-analysis were not drug-free. Indeed, it should be noted that a number of medications used in the treatment of BD, including mood stabilizers, antidepressants and antipsychotics might impact adiponectin levels (Bartoli et al., 2015; Omata et al., 2012). These medications might also influence immune-inflammatory processes. For instance, it has been found that antidepressants may decrease the levels of IL-6 and TNF-α (Hannestad et al., 2011). Furthermore, there is evidence that lithium may normalize cytokine responses (van den Ameele et al., 2016). Similarly, antipsychotics have been found to decrease the levels of IL-1β and interferon-γ (Romeo et al., 2018). Another limitation is that we were not able to control for the effects of any other inflammatory markers to investigate potential mechanisms of changes in adiponectin levels across various mood states. Finally, studies included in our meta-analysis did not control for several factors that might impact adiponectin levels, including physical activity, dietary habits, subclinical infections or the gut dysbiosis.

In summary, results of our meta-analysis indicate elevated levels of adiponectin in euthymic BD patients and the association with depressive symptoms. More studies are needed to conclude regarding adiponectin alterations in mania. Adiponectin levels might be higher in patients with BD-I and those at late stage of illness. Dynamic changes of adiponectin levels across various mood states might reflect immune-inflammatory alterations previously reported in BD patients. Future studies should investigate the mechanisms underlying adiponectin alterations in BD, taking into account the impact of comorbid obesity-related conditions and autoimmune diseases.

Conflict of interest

None to declare.

Authors contribution

BM – online search, extraction of data, quality assessment, data analysis, manuscript writing; FS – online search and manuscript writing, JK – manuscript writing, ML – manuscript writing, BS – online search and manuscript writing.

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References

Altinova, A.E., Toruner, F.B., Akturk, M., Bukan, N., Cakir, N., Ayvaz, G., Arslan, M., 2006. Adiponectin levels and cardiovascular risk factors in hypothyroidism and hyperthyroidism. Clin. Endocrinol. (Oxf.) 65, 530–535.

Bai, Y.M., Su, T.P., Tsai, S.J., Wen-Fei, C., Li, C.T., Pei-Chi, T., Mu-Hong, C., 2014. Comparison of inflammatory cytokine levels among type I/type II and manic/hypomanic/euthymic/depressive states of bipolar disorder. J. Affect. Disord. 166, 187–192.

Barbosa, I.G., Rocha, N.P., Miranda, A.Sde, Magalhães, P.Vda S., Huguet, R.B., Souza, L.Pde, Kapczinski, F., Teixeira, A.L., 2012. Increased levels of adipokines in bipolar disorder. J. Psychiatr. Res. 46, 389–393.

Bartoli, F., Lax, A., Crocamo, C., Clerici, M., Carrà, G., 2015. Plasma adiponectin levels in schizophrenia and role of second-generation antipsychotics: a meta-analysis. Psychoneuroendocrinology 56, 179–189.

Berg, A.H., Combs, T.P., Scherer, P.E., 2002. ACRP30/adiponectin: an adipokine regulating glucose and lipid metabolism. Trends Endocrinol. Metab. 13, 84–89.

Berk, M., Post, R., Ratheesh, A., Gliddon, E., Singh, A., Vieta, E., Carvalho, A.F., Ashton, M.M., Berk, L., Cotton, S.M., McGorry, P.D., Fernandes, B.S., Yatham, L.N., Dodd, S., 2017. Staging in bipolar disorder: from theoretical framework to clinical utility. World Psychiatry 16, 236–244.

Bond, D.J., Andreazza, A.C., Hughes, J., Dhanoa, T., Torres, I.J., Kozicky, J.M., Young, L.T., Lam, R.W., Yatham, L.N., 2017. A longitudinal study of the relationships between mood symptoms, body mass index, and serum adipokines in bipolar disorder.

J. Clin. Psychiatry 78, 441–448.
Brietzke, E., Kapczinski, F., Grassi-Oliveira, R., Grande, I., Vieta, E., McIntyre, R.S., 2011. Insulin dysfunction and allostatic load in bipolar disorder. Expert Rev. Neurother. 11, 1017–1028.
Cabanelas, A., Cordeiro, A., Santos Almeida, N.A., Monteiro de Paula, G.S., Coelho, V.M., Ortiga-Carvalho, T.M., Pazos-Moura, C.C., 2010. Effect of triiodothyronine on adiponectin expression and leptin release by white adipose tissue of normal rats. Horm. Metab. Res. 42, 254–260.
Cao, B., Chen, Y., Brietzke, E., Cha, D., Shaukat, A., Pan, Z., Park, C., Subramaniapillai, M., Zuckerman, H., Grant, K., Mansur, R.B., McIntyre, R.S., 2018. Leptin and adiponectin levels in major depressive disorder: a systematic review and meta-analysis. J. Affect. Disord. 238, 101–110.
Carvalho, A.F., Rocha, D.Q.C., McIntyre, R.S., Mesquita, L.M., Köhler, C.A., Hyphantis, T.N., Sales, P.M.G., Machado-Vieira, R., Berk, M., 2014. Adipokines as emerging depression biomarkers: a systematic review and meta-analysis. J. Psychiatr. Res. 59, 28–37.
Crump, C., Sundquist, K., Winkleby, M.A., Sundquist, J., 2013. Comorbidities and mortality in bipolar disorder: a Swedish national cohort study. JAMA Psychiatry 70, 931–939.
Elmslie, J.L., Porter, R.J., Joyce, P.R., Hunt, P.J., Shand, B.I., Scott, R.S., 2009. Comparison of insulin resistance, metabolic syndrome and adiponectin in overweight bipolar patients taking sodium valproate and controls. Aust. N. Z. J. Psychiatry 43, 53–60.
Fagiolini, A., Frank, E., Scott, J.A., Turkin, S., Kupfer, D.J., 2005. Metabolic syndrome in bipolar disorder: findings from the bipolar disorder center for Pennsylvanians. Bipolar Disord. 7, 424–430.
Fagiolini, A., Chengappa, K.N.R., Soreca, I., Chang, J., 2008. Bipolar disorder and the metabolic syndrome: causal factors, psychiatric outcomes and economic burden. CNS Drugs 22, 655–669.
Fantuzzi, G., 2008. Adiponectin and inflammation: consensus and controversy. J. Allergy Clin. Immunol. 121, 326–330.
Fernandes, B.S., Dash, S., Jacka, F., Dodd, S., Carvalho, A.F., Köhler, C.A., Steiner, J., da Graça Cantarelli, M., Nardin, P., Gonçalves, C.A., Berk, M., 2016. Leptin in bipolar disorder: a systematic review and meta-analysis. Eur. Psychiatry 35, 1–7.
Hannestad, J., DellaGiola, N., Bloch, M., 2011. The effect of antidepressant medication treatment on serum levels of inflammatory cytokines: a meta-analysis. Neuropsychopharmacology 36, 2452–2459.
Hung, Y.J., Hsieh, C.H., Chen, Y.J., Pei, D., Kuo, S.W., Shen, D.C., Sheu, W.H.H., Chen, Y.C., 2007. Insulin sensitivity, proinflammatory markers and adiponectin in young males with different subtypes of depressive disorder. Clin. Endocrinol. (Oxf.) 67, 784–789.
Iglesias, P., Diez, J.J., 2007. Influence of thyroid dysfunction on serum concentrations of adipocytokines. Cytokine 40, 61–70.
Kapczinski, F., Magalhães, P.V.S., Balanzá-Martinez, V., Dias, V.V., Frangou, S., Gama, C.S., Gonzalez-Pinto, A., Grande, I., Ha, K., Kauer-Sant'Anna, M., Kunz, M., Kupka, R., Leboyer, M., Lopez-Jaramillo, C., Post, R.M., Rybakowski, J.K., Scott, J., Strejilevitch, S., Tohen, M., Vazquez, G., Yatham, L., Vieta, E., Berk, M., 2014. Staging systems in bipolar disorder: an international society for bipolar disorders task force report. Acta Psychiatr. Scand. 130, 354–363.
Kauer-Sant'Anna, M., Kapczinski, F., Andreazza, A.C., Bond, D.J., Lam, R.W., Young, L.T., Yatham, L.N., 2009. Brain-derived neurotrophic factor and inflammatory markers in patients with early- vs. Late-stage bipolar disorder. Int. J. Neuropsychopharmacol. 12, 447–458.
Ketter, T.A., 2010. Diagnostic features, prevalence, and impact of bipolar disorder. J. Clin. Psychiatry 71, e14.
Liu, J., Guo, M., Zhang, D., Cheng, S.Y., Liu, M., Scherer, P.E., Liu, F., Lu, X.Y., 2012. Adiponectin is critical in determining susceptibility to depressive behaviors and has antidepressant-like activity. Proc. Natl. Acad. Sci. U. S. A. 109, 12248–12253.
Luppino, F.S., De Wit, L.M., Bouvy, P.F., Stijnen, T., Cuijpers, P., Penninx, B.W.J.H., Zitman, F.G., 2010. Overweight, obesity, and depression: a systematic review and meta-analysis of longitudinal studies. Arch. Gen. Psychiatry 67, 220–229.
Maina, G., Salvi, V., Vitalucci, A., D'Ambrosio, V., Bogetto, F., 2008. Prevalence and correlates of overweight in drug-naïve patients with bipolar disorder. J. Affect. Disord. 110, 149–155.
Mansur, R.B., Rizzo, L.B., Santos, C.M., Asevedo, E., Cunha, G.R., Noto, M.N., Pedrini, M., Zeni, M., Cordeiro, Q., McIntyre, R.S., Brietzke, E., 2016. Adipokines, metabolic dysfunction and illness course in bipolar disorder. J. Psychiatr. Res. 74, 63–69.
Mansur, R.B., Rizzo, L.B., Santos, C.M., Asevedo, E., Cunha, G.R., Noto, M.N., Pedrini, M., Zeni-Graiff, M., Cordeiro, Q., McIntyre, R.S., Brietzke, E., 2017. Plasma copeptin and metabolic dysfunction in individuals with bipolar disorder. Psychiatry Clin. Neurosci. 71, 624–636.
McIntyre, R.S., Danilewitz, M., Liauw, S.S., Kemp, D.E., Nguyen, H.T.T., Kahn, L.S., Kucyi, A., Soczynska, J.K., Woldeyohannes, H.O., Lachowski, A., Kim, B., Nathanson, J., Alsuwaidan, M., Taylor, V.H., 2010. Bipolar disorder and metabolic syndrome: an international perspective. J. Affect. Disord. 126, 366–387.
Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., Altman, D., Antes, G., Atkins, D., Barbour, V., Barrowman, N., Berlin, J.A., Clark, J., Clarke, M., Cook, D., D'Amico, R., Deeks, J.J., Devereaux, P.J., Dickersin, K., Egger, M., Ernst, E., Gøtzsche, P.C., Grimshaw, J., Guyatt, G., Higgins, J., Ioannidis, J.P.A., Kleijnen, J., Lang, T., Magrini, N., McNamee, D., Moja, L., Mulrow, C., Napoli, M., Oxman, A., Pham, B., Rennie, D., Sampson, M., Schulz, K.F., Shekelle, P.G., Tovey, D., Tugwell, P., 2009. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 6, e1000097.
Nigro, E., Scudiero, O., Monaco, M.L., Palmieri, A., Mazzarella, G., Costagliola, C., Bianco, A., Daniele, A., 2014. New insight into adiponectin role in obesity and obesity-related diseases. Biomed Res. Int. 658913.
Omata, N., Murata, T., Narita, K., Maruoka, N., Mitsuya, H., Mita, K., Nishimoto, T., Sato, M., Wada, Y., 2012. Effects of antidepressants and mood stabilizers on serum levels of adiponectin. Neuro Endocrinol. Lett. 33, 1–2.
Platzer, M., Fellendorf, F.T., Bengesser, S.A., Birner, A., Dalkner, N., Hamm, C., Hartleb, R., Queissner, R., Pilz, R., Rieger, A., Maget, A., Mangge, H., Zelzer, S., Reininghaus, B., Kapfhammer, H.P., Reininghaus, E.Z., 2018. Adiponectin is decreased in bipolar depression. World J. Biol. Psychiatry 20, 1–8.
Qi, Y., Takahashi, N., Hileman, S.M., Patel, H.R., Berg, A.H., Pajvani, U.B., Scherer, P.E., Ahima, R.S., 2004. Adiponectin acts in the brain to decrease body weight. Nat. Med. 10, 524–529.
Romeo, B., Brunet-Lecomte, M., Martelli, C., Benyamina, A., 2018. Kinetics of cytokine levels during antipsychotic treatment in schizophrenia: a meta-analysis. Int. J. Neuropsychopharmacol. 21, 828–836.
Rosenblat, J.D., Mcintyre, R.S., 2015. Are medical comorbid conditions of bipolar disorder due to immune dysfunction? Acta Psychiatr. Scand. 132, 180–191.
Rowland, T., Perry, B.I., Upthegrove, R., Barnes, N., Chatterjee, J., Gallacher, D., Marwaha, S., 2018. Neurotrophins, cytokines, oxidative stress mediators and mood state in bipolar disorder: systematic review and meta-analyses. Br. J. Psychiatry 213, 514–525.
SayuriYamagata, A., Brietzke, E., Rosenblat, J.D., Kakar, R., McIntyre, R.S., 2017. Medical comorbidity in bipolar disorder: the link with metabolic-inflammatory systems. J. Affect. Disord. 211, 99–106.
Soczynska, J.K., Kennedy, S.H., Woldeyohannes, H.O., Liauw, S.S., Alsuwaidan, M., Yim, C.Y., McIntyre, R.S., 2011. Mood disorders and obesity: understanding inflammation as a pathophysiological nexus. Neuromol. Med. 13, 93–116.
Soeiro-de-Souza, M.G., Gold, P.W., Brunoni, A.R., de Sousa, R.T., Zanetti, M.V., Carvalho, A.F., Gattaz, W.F., Machado-Vieira, R., Teixeira, A.Ô.L., 2014. Lithium decreases plasma adiponectin levels in bipolar depression. Neurosci. Lett. 564, 111–114.
Syk, M., Ellstrom, S., Mwinyi, J., Schioth, H.B., Ekselius, L., Ramklint, M., Cunningham, J.L., 2019. Plasma levels of leptin and adiponectin and depressive symptoms in young adults. Psychiatry Res. 272, 1–7.
Thundyil, J., Pavlovski, D., Sobey, C.G., Arumugam, T.V., 2012. Adiponectin receptor signalling in the brain. Br. J. Pharmacol. 165, 313–327.
Tunçel, Ö.K., Sarısoy, G., Bilgici, B., Pazvantoğlu, O., Çetin, E., Tunçel, E.K., 2018. Adipocytokines and ghrelin level of bipolar patients from manic episode to euthymic episode. Nord. J. Psychiatry 72, 150–156.
van den Ameele, S., van Diermen, L., Staels, W., Coppens, V., Dumont, G., Sabbe, B., Morrens, M., 2016. The effect of mood-stabilizing drugs on cytokine levels in bipolar disorder: a systematic review. J. Affect. Disord. 203, 364–373.
Vancampfort, D., Vansteelandt, K., Correll, C.U., Mitchell, A.J., De Herdt, A., Sienaert, P., Probst, M., De Hert, M., 2013. Metabolic syndrome and metabolic abnormalities in bipolar disorder: a meta-analysis of prevalence rates and moderators. Am. J. Psychiatry 170, 265–274.
Vancampfort, D., Correll, C.U., Galling, B., Probst, M., De Hert, M., Ward, P.B., Rosenbaum, S., Gaughran, F., Lally, J., Stubbs, B., 2016. Diabetes mellitus in people with schizophrenia, bipolar disorder and major depressive disorder: a systematic review and large scale meta-analysis. World Psychiatry 15, 166–174.
Vianna-Sulzbach, M., Rocha, N.P., Teixeira, A.L., Rosa, E.D., Goldani, A.A.S., Kauer-Sant'Anna, M., Gama, C.S., 2015. Right hippocampus size is negatively correlated with leptin serum levels in bipolar disorder. Psychiatry Res. 230, 719–721.
Wang, T.Y., Lee, S.Y., Chen, S.L., Chung, Y.L., Li, C.L., Chang, Y.H., Wang, L.J., Chen, P.S., Chen, S.H., Chu, C.H., Huang, S.Y., Tzeng, N.S., Hsieh, T.H., Chiu, Y.C., Lee, I.H., Chen, K.C., Yang, Y.K., Hong, J.S., Lu, R.B., 2016. The differential levels of inflammatory cytokines and bdnf among bipolar spectrum disorders. Int. J. Neuropsychopharmacol. 19 pyw012.
Warner-Schmidt, J.L., Duman, R.S., 2006. Hippocampal neurogenesis: opposing effects of stress and antidepressant treatment. Hippocampus 16, 239–249.
Wells, G., Shea, B., O'Connell, D., Peterson, J., Welch, V., Losos, M., Tugwell, P., 2000. Newcastle-Ottawa Scale Assess. Qual. Nonrandomised Stud. Meta-analyses. No Title [WWW Document]URL. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
Zhang, D., Guo, M., Zhang, W., Lu, X.Y., 2011. Adiponectin stimulates proliferation of adult hippocampal neural stem/progenitor cells through activation of p38 mitogen-activated protein kinase (p38MAPK)/glycogen synthase kinase 3β (GSK-3β)/β-catenin signaling cascade. J. Biol. Chem. 286, 44913–44920.