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Common biological mechanisms between bipolar disorder and type 2 diabetes: Focus on inflammation

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ABSTRACT

Introduction: Bipolar disorder (BD) patients present a 3–5 fold greater risk of developing type 2 diabetes (T2D) compared to general population. The underlying mechanisms for the increased prevalence of T2D in BD population are poorly understood.
Objectives: The purpose of this review is to critically review evidence suggesting that inflammation may have an important role in the development of both BD and T2D.
Results: The literature covered in this review suggests that inflammatory dysregulation take place among many BD patients. Such dysregulated and low grade chronic inflammatory process may also increase the prevalence of T2D in BD population. Current evidence supports the hypothesis of dysregulated inflammatory processes as a critical upstream event in BD as well as in T2D.
Conclusions: Inflammation may be a factor for the development of T2D in BD population. The identification of inflammatory markers common to these two medical conditions will enable researchers and clinicians to better understand the etiology of BD and develop treatments that simultaneously target all aspects of this multi-system condition.

Contents

Abbreviations: ACE, angiotensin converting enzyme; AGEs and RAGE, advanced glycation products (AGEs) and receptor for AGEs; BCL2A1, B-cell lymphoma 2A1; BD, bipolar disorder; BMI, body mass index; C3, C4 and C6, complement factors 3, 4 and 6; CCL2, chemokine ligand 2; CCL11, ligand 11; CCR-2, chemokine receptor-2; COX-1 and COX-2, cyclooxygenase-1 and cyclooxygenase-2; CRP, C-reactive protein; DPP-4, dipeptidyl peptidase-4; EMP1, epithelial membrane protein 1; FSTL1, follistatin-like 1 cytokine; GFAP, glial fibrillary acidic protein; GM-CSF, granulocyte monocyte-colony stimulating factor; Hb_{A1C}, glycosylated hemoglobin; IFNα, interferon alpha-isoform; IFNγ, interferon gamma-isoform; IKKβ, kinase of the IKK family, phosphorylates inhibitors of NF-kappa-B; IKKβ, kinase of the IKK family, phosphorylates inhibitors of NF-kappa-B; IL-1, interleukin-1; IL-1β, interleukin-1 β-isoform; JNK, c-Jun N-terminal kinase; MAPK-6, mitogen-activated protein kinase 6; NF-κB, nuclear factor-kappa B; NLRP3 inflammasome, NAIP, CIITA, HET-E, TP-1 (NACHT), leucine rich repeats (LRR) and pyrin (PYD) domains-containing protein 3; NSAIDs, nonsteroidal anti-inflammatory drugs; PAI-1, plasminogen activator inhibitor-1; PGE2, prostaglandin E2; PLA_2, phospholipase A2; PPARγ-R, peroxisome proliferator-activated receptor gamma; PTX3, pentraxin 3; PUFA, polyunsaturated fatty acids; sIL-2R, soluble interleukin-2 receptor; sIL-6R, soluble interleukin-6 receptor; T2D, type 2 diabetes; TCF7L2, transcription factor 7-like 2; TGF-β, transforming growth factor β-isoform; TLR-4, toll-like receptor 4; TLR-2, toll-like receptor 2; TNF-α, tumor necrosis factor α-isoform; sTNFR1, soluble tumor necrosis factor receptor 1; VEGF, vascular endothelial growth factor.

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1. Introduction

Bipolar disorder (BD) and type 2 diabetes (T2D) are two highly disabling and apparently unrelated human disorders. However, both conditions share high comorbidity (Cassidy et al., 1999; Regenold et al., 2002; Ruzickova et al., 2003) as BD patients are at 3–5 times higher risk of developing T2D than general population (Calkin et al., 2013; Cassidy et al., 1999; Lilliker, 1980; Regenold et al., 2002). BD is conceptualized as a multi-system disorder with manic-depressive symptoms, cognitive impairment, and structural/functional brain abnormalities (Coffman et al., 1990; Swayze et al., 1990) coupled with increased risk for disturbances in glucose homeostasis, insulin resistance, higher body mass index and abnormal lipid profile with cognitive, autonomic, and sleep disturbances (for reviews, see: Calkin et al., 2013; Leboyer et al., 2012; Teixeira et al., 2013). Additionally, treatments of BD patients with mood stabilizers like lithium and valproic acid can exacerbate risk factors for T2D such as weight gain and craving for fast food fats (Chengappa et al., 2002; Dinesen et al., 1984; Martin et al., 2009). Evidences also support that, among BD patients, the comorbidity with metabolic disorders like T2D is associated with increased frequency of episodes, hospitalizations, severity of illness and suicidality as well as poor response to mood stabilizers (B. Kim et al., 2009; Calkin et al., 2009; Chengappa et al., 2002; Dinesen et al., 1984; Gomes et al., 2010; Martin et al., 2009; Ruzickova et al., 2003), as well as accelerated brain aging (Fotuhi et al., 2012).

Based on this evidence, several pathophysiological mechanisms involved in the development of BD have been proposed (Belmaker and Agam, 2005; Cousins et al., 2009; Fornito et al., 2009). However, there is no definitive understanding with regard to the biological basis of BD origin and progression. Thus, diagnosis of BD still heavily relies on traditional methods like behavioral observations, patient questionnaire and family reports.

In contrast, T2D has hallmark clinical features such as hyperglycemia that is routinely tested in laboratories for diagnosis and disease management (Lindmark et al., 2006; Manickam et al., 2013). T2D is a heterogeneous disorder that was previously referred to as 'mature onset' or 'non-insulin dependent diabetes mellitus (NIDDM)' and represents about 90% of global diabetes patients. It is a by-product of interactions between genetic susceptibility and environmental factors with characteristic decrease in response to insulin by target tissues — also called as insulin resistance. Considering the high rates of comorbidity between BD and T2D and the associated financial, emotional and healthcare burden on patients and family, there is an immediate need to search for common biological foundations for their co-existence. Some shared postulations among BD and T2D pathology are: genetic alterations (Kawamoto et al., 2004; Ross, 2011), elevated stress response and allostatic overload (i.e. inefficient homeostatic response) (Brietzke et al., 2011), neurochemical alterations (Hajek et al., 2013), lifestyle (Calkin et al., 2013; Morriss and Mohammed, 2005), BD medications (Castilla-Puentes, 2007), inflammation (Donath and Shoelson, 2011) and oxidative stress (de Sousa et al., 2014; Gohel and Chacko, 2013). This review aims at highlighting the importance of BD and T2D comorbidity and postulates 'inflammation' as a common malefactor for their coexistence.

2. Inflammation in bipolar disorder and type 2 diabetes

2.1. Inflammation and bipolar disorder

Balanced and acute inflammatory response is an evolutionary conserved and protective mechanism of the mammalian body to defend against various insults like stress, injury or infection and to clear localized deposition of unwanted metabolites and dead/damaged cells. However, inflammation as a body's protective response can go awry accompanied by constellation of pathologies if it has to fight for an extended periods as in chronic inflammatory conditions. As discussed in detail below, dysregulated and low grade chronic inflammatory responses are among the most consistently observed findings in BD patients (Goldstein et al., 2009; Kapczinski et al., 2011; Padmos et al., 2008).

Immune cells-derived cytokines are the major components involved in regulation of inflammatory processes. Cytokines are gaining widespread acknowledgement for their potential utility as prognostic and diagnostic markers in diverse human ailments (Dinarello et al., 2010). Multiple lines of evidence from clinical (Brietzke et al., 2009; Cunha et al., 2008; Dickerson et al., 2007), in vitro (Kim et al., 2007; Knijff et al., 2007) and genetic findings (Drexhage et al., 2010a; Padmos et al., 2008) also point to changes in cytokine levels in BD (Table 1). Based on their physiological properties, individual cytokines can be classified as anti-inflammatory (ex. IL-4, 10, 13, IFNα and TGF-β) and pro-inflammatory (ex. IL-1β, IL-2, 6, 8, 12, 18, TNF-α, IFNγ, VEGF and GM-CSF) in nature. Hypothetically, pro-inflammatory cytokines worsen the disease outcome, whereas anti-inflammatory cytokines work as counteractive mechanisms against pro-inflammatory responses. Additionally, immune system produces natural antagonists to neutralize pro-inflammatory cytokines mediated biological responses (Drexhage et al., 2010b). Cytokines require solubilized or cell surface receptors to exert their physiological and/or pathophysiological effects. Inflammatory cytokines could potentially activate neuronal apoptotic pathways, decrease serum neurotrophins levels and neuronal repair with changes in mood states as in BD. A significant progress has been made in recent past characterizing mood specific alterations in inflammatory markers in BD population. In general, meta-analysis demonstrated consistently elevated sIL-2R, sIL-6R, TNF-α, sTNFR1, IL-4 and no differences in IL-6, IL-1β, IL-1RA, IL-8, sTNFR2, IL-5, IL-10 and IFNγ during mania when compared with healthy control participants (Munkholm et al., 2013). Further, pro-inflammatory cytokines like IL-6, IL-8, CRP, and TNF-α seem to be elevated during depressive episodes (Brietzke et al., 2009; O'Brien et al., 2006; Ortiz-Dominguez et al., 2007), IL-2, sIL-2R, IL-4, IL-6, IL-8, TNF-α, and sTNFR1 during manic episodes (Barbosa et al., 2011; Brietzke et al., 2009; Hope et al., 2011; Kim et al., 2007; Maes et al., 1995; O'Brien et al., 2006; Ortiz-Dominguez et al., 2007; Tsai et al., 2001), and IL-4 and sTNFR1 (Barbosa et al., 2011; Tsai et al., 2012) during euthymia in BD patients (Brietzke et al., 2009) compared to healthy controls.

Production of pro- and anti-inflammatory cytokines by inflammatory cells is influenced by prostaglandins and leukotrienes derived from polyunsaturated fatty acid (PUFA) like arachidonic acid. Membrane phospholipids release arachidonic acid in response to triggers like tissue

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Table 1
Common pro- and anti-inflammatory cytokines in bipolar disorder and type 2 diabetes.

	Bipolar disorder	Type 2 diabetes
Pro-inflammatory cytokines		
IL-1	Gray matter deficits in BD were related to variability in IL-1 cluster (Papiol et al., 2008).	IL-1R blocker decrease inflammatory markers and improves glycemia and insulin secretion by pancreatic β cells (Carstensen et al., 2010; Larsen et al., 2007).
	Increase in cerebrospinal fluid (CSF) IL-1β levels is associated with recent manic/hypomanic episodes (Soderlund et al., 2011).	
	Increased IL-1β protein and mRNA levels in frontal cortex of post-mortem BD patient brains (Rao et al., 2010).	
IL-2	Decreased serum IL-2 levels in BD (Ortiz-Dominguez et al., 2007).	Increased sIL-2R in T2D patients (Pereira et al., 2006); Anti-inflammatory omega-3 fatty acid supplementation lowers serum IL-2 levels (Malekshahi et al., 2012).
IL-6	Increased IL-6 production in BD patients (Kim et al., 2007; Knijff et al., 2007).	Obese people experience higher serum IL-6 levels (Bal et al., 2010).
	Changes in depressive symptoms associated with changes in IL-6 (Lee et al., 2013).	IL-6 contributes to whole body insulin resistance and hyperglycemia and T2D patients (Daniele et al., in press).
	Lithium treatment reduces IL-6 levels (Knijff et al., 2007).	
IL-8	No significant differences between BD patients and healthy controls (Modabbernia et al., 2013).	Increased aqueous humor IL-8 levels (Dong et al., 2013) and higher IL-8 expression (Giulietti et al., 2007) in T2D patients.
TNF-α	Elevated during BD episodes (O'Brien et al., 2006; Ortiz-Dominguez et al., 2007).	Increased TNFα expression (Clausell et al., 1999).
		Increased TNFα plasma levels (Lechleitner et al., 2002).
Anti-inflammatory cytokines		
IL-4	Conflicting reports in mania: decreased during mania (Kim et al., 2007); higher in mania (Brietzke et al., 2009; Ortiz-Dominguez et al., 2007).	Polymorphisms in IL-4 may participate in risk for diabetes (Bid et al., 2008; Ho et al., 2010).
	Lowered during depressive phase (Ortiz-Dominguez et al., 2007).	
IL-10	No significant differences between BD patients and healthy controls (Munkholm et al., 2013).	IL-10 promoter polymorphisms are consistently associated with T2D (Mtiraoui et al., 2009). IL-10 levels increased in T2D patients (Al-Shukaili et al., 2013).

damage which is catalyzed by enzyme phospholipase A2 (PLA_2). This enzyme is a common target for steroidal anti-inflammatory drugs (Vadas, 1982). Evidences suggest disturbances in biotransformation of membrane phospholipids in BD patients (Kato et al., 1991; Soares and Mallinger, 1997). Horrobin and Bennett (1999) theorized that healthy individuals have some basal level of PLA_2 activity. In contrast, BD patients during manic episodes experience rapid surge in PLA_2 activity with resultant rise in production of inflammatory prostaglandin precursors like arachidonic acid, dihomogammalinoleic acid and eicosapentaenoic acid. This is followed by dramatic depletion of PUFAs and prostaglandins below basal level during depressive episodes (Abdulla and Hamadah, 1975). Interestingly, mood stabilizer like lithium blocks in vivo PLA_2 activity in the brain (Chang and Jones, 1998; Chang et al., 1996) and prevents excessive production of inflammatory prostaglandins (Horrobin and Lieb, 1981).

Post-mortem studies with BD patient brains further substantiate the role of inflammation in BD. While Rao et al. (2010) found elevated IL-1 and its receptor concentrations in the frontal cortex, McNamara et al. (2008) reported significantly decreased levels of arachidonic acid in the orbitofrontal cortex of BD patients — a common precursor for inflammatory mediators like prostaglandins and leukotrienes. Moreover, altered brain lipid concentrations (Igarashi et al., 2010) and overactive arachidonic acid pathways with elevated cortical prostaglandin E synthase and cyclooxygenase (COX) activity (Kim et al., 2011) were observed in BD patients. Apart from cytokines, acute phase inflammatory proteins CRP, amyloid A, and haptoglobin, as well as elevated levels of complement factors such as C3, C4 and C6 (Kapczinski et al., 2011), chemokines CCL11 (Barbosa et al., 2013), inflammatory pathway enzymes such as cyclooxygenase and prostaglandin-E synthase (Kim et al., 2011), in addition to increased monocyte count (Cassidy et al., 2002) were observed in BD patients.

Furthermore, genetic evidence suggests that BD patients show differences in the expression pattern and/or polymorphisms in genes for inflammatory and apoptosis markers like IL-6, TNF-α, chemokine ligand 2, MAPK-6, PTX3, EMP1 and BCL2A1 (Altamura et al., 2010; Czerski et al., 2008; Padmos et al., 2008), not only during acute mood states but also in euthymia (Herberth et al., 2011). On the other hand, there are studies suggesting no correlation between inflammatory marker gene and BD (Meira-Lima et al., 2005; Middle et al., 2000). Recently Stertz et al. (2013) reviewed the putative relevance of microglial activation in the characterization of BD is an inflammatory disorder. Microglial activation, as an innate immune response, may lead to release of proinflammatory TNF-α and IL-1β cytokines. Microglial activation may team up with systemic toxicity to contribute to synaptic pruning in BD.

Interestingly, it is still unclear whether inflammatory markers contribute to BD development or patients with BD are actually more vulnerable to dysregulated inflammatory responses. Alternatively, BD illness and dysregulated inflammatory mechanisms may be mutually predisposing. Multiple pathogenic mechanisms have been proposed in order to explain the possible relationship between mood disorders and inflammation. Some of them include: the macrophage hypothesis (Liu et al., 2004), TNF-α induced decrease in muscarinic M_2 receptor expression (Barnes et al., 1997; Haddad et al., 1996), gamma aminobutyric acid (GABA) neurogenesis (Laeng et al., 2004) and IL-6 induced tryptophan 2,3-dioxygenase activation and tryptophan breakdown in mania (Myint et al., 2007). However, the complexity of link between inflammatory markers and BD pathology seems to be distant from a direct cause-and-effect relationship. There are several challenges to overcome before considering inflammatory proteins as signatory markers for BD diagnosis and to evaluate efficacy of interventions. Because of overlapping nature of mood disorders like BD, schizophrenia and major depressive disorder, search for BD specific inflammatory marker(s) is an uphill task. Since changes in inflammatory proteins may be non-specific and elevated in many medical disorders, this may pose additional challenges in identifying specific inflammatory proteins as biomarkers for BD.

2.2. Bipolar disorder — type 2 diabetes comorbidity and role of inflammation

Even though the management of comorbid T2D in BD patients represents an important challenge in terms of healthcare, T2D is relatively less studied in comparison to other medical comorbidities of BD (Carney and Jones, 2006; Fagiolini et al., 2002; Kupfer, 2005). Since BD symptoms appear at an early age before appearance of symptoms for T2D, in general BD patients are on increased risk for development of T2D than the other way around. However, this association does not seem to be coincidental and has been acknowledged for more than 130 years. Pioneer British psychiatrist Henry Maudsley (1868) in his book '*The pathology of mind*' quoted that "diabetes is a disease which often shows itself in families in which insanity prevails". Other authors, such as Raphael and Parsons (1921), later provided experimental evidence for this notion. Among the leading theories addressing the origin and progression of T2D, the role of inflammation has been instrumental to our current understanding of this endocrine metabolic disorder. Inflammation seems to be crucial mechanism for β-cell dysfunction, insulin resistance and hyperglycemia. Several studies have reported

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increased systemic levels of inflammatory markers viz. cytokines IL-1β, IL-6, IL-1RA, chemokines and CRP (Carstensen et al., 2010; Herder et al., 2009; Pickup et al., 1997; Pradhan et al., 2001; Spranger et al., 2003) in T2D patients and/or in prediabetics. A list of the most common pro- and anti-inflammatory cytokines involved in the pathophysiology of T2D (as well as BD) is displayed in Table 1. Of notice, acute phase protein CRP is regarded as the best epidemiological marker for T2D (Pickup et al., 1997; Spranger et al., 2003).

Among the various T2D-associated inflammatory markers, IL-1β seems to hold unique significance in T2D pathogenesis because of its deleterious effects on pancreatic β-cells (Dinarello et al., 2010) and its role on the activation of other cytokines on IL-1R activation (Dinarello, 2000; Larsen et al., 2007). IL-1β is produced by adipocytes as well as pancreatic β-cells. Thus, IL-1β induced expression of antagonist for IL-1Rs in prediabetics may represent body's defense against unpleasant IL-1β response (Meier et al., 2002). Further, T2D associated hyperglycemia contributes to IL-1β production and aggravates pancreatic β-cell toxicity in response to high blood glucose (Maedler et al., 2002). Alternatively, amyloid polypeptide from pancreatic islets in T2D patients promotes IL-1β production via protein complex NLRP3 inflammasome mediated breakdown of pro-IL-1β (Masters et al., 2010). Evidence demonstrates elevations in IL-1β in T2D levels (Maedler et al., 2002). A 13-week double-blind parallel-group clinical trial using recombinant human IL-1R antagonist, anakinra helped to reduce levels of glycated Hb_{A1C}, IL-6 and CRP and pro-insulin to insulin ratio compared to T2D patients that were on placebo treatment (Larsen et al., 2007). Thus, elevated IL-1β levels may aggravate T2D associated hyperglycemia. Pharmacological interventions attenuating IL-1β mediated signaling may offer new vistas for the management of T2D.

Persistent hyperglycemia promotes production and accumulation of advanced glycation products (AGEs) (Goh and Cooper, 2008; Sourris and Forbes, 2009) which, via specific receptors (RAGEs), can induce the expression of inflammatory genes (Kim et al., 2009b; Ng et al., 2013) and chronic inflammatory pathways such as NF-κB, MAPK and adhesion molecules (Sparvero et al., 2009). Studies have also demonstrated the role of AGEs in neurological and associated disorders. AGEs could induce accumulation of abnormally folded proteins which may serve as a major pathogenic mechanism or an adjunctive etiological factor in neurological disorders (Sensi et al., 1991). In consonance with this assumption, a recent study addressed the role of soluble receptors for AGEs as a contributing mechanism for increased cardiovascular risk in schizophrenics and major depressive disorder (MDD) patients (Emanuele et al., 2011). Additionally, dietary AGEs along with endogenous AGEs have been shown to aggravate diabetes-associated organ toxicity (Vlassara and Palace, 2002), possibly including the brain. Moreover, reductions in the intake of dietary AGEs has been shown to lower inflammatory TNF-α levels (Luevano-Contreras et al., 2013). Thus, hyperglycemia associated AGEs may be an important predecessor for dysregulations of the inflammatory cascade, bringing about increased vulnerability of BD patients for T2D comorbidity. Further, parallel to BD, abnormalities in arachidonic acid pathway and PUFA metabolism are reported in diabetes (Horrobin, 1997). Impairments in metabolism of dietary essential fatty acids viz. α-linolenic acid and linoleic acid and significantly decreased membrane PUFAs are reported in diabetes. While dietary PUFAs are considered as 'good fats', saturated- and trans-fats are generally labeled as 'bad fats'. In diabetics, cells experience compromised ability to absorb PUFAs.

Obesity – a common risk factor for T2D (Wellen and Hotamisligil, 2005) – is known to elevate circulating levels of inflammatory prostaglandin (PGE2) (Fain, 2010; Fain et al., 2002). Further, increased ratio of PUFAs over saturated fatty acids (SFAs) was reported in plasma of juvenile overweight individuals (Klein-Platat et al., 2005). Likewise, PGE2 mediated enhanced inflammatory response was reported in mice (Ivanov and Romanovsky, 2004). In addition, obesity may be associated with increased expression of inflammatory genes and release of inflammatory proteins by fat cells such as IL-6, IL-8, ACE, TGFβ1, TNF-α, IL-1β and PAI-1 (Fain, 2010). Using four different rodent models for T2D and obesity, Hotamisligil et al. (1993) suggested that the release of inflammatory markers such as TNF by fat cells is a crucial mechanism for insulin resistance in T2D and obesity. Interestingly, pharmacological antagonism of TNF-mediated response using anti-TNF antibodies such as infliximab and etanarcept has been reported to improve insulin sensitivity and normalize blood glucose concentration (Stanley et al., 2011; Yazdani-Biuki et al., 2004). Moreover, macrophage cells are great source of inflammatory proteins (Ehses et al., 2007; Weisberg et al., 2003), and obesity is associated with macrophageal M2 to M1 phenotypic changes. Accumulation of M1 macrophages with fat cells can increase insulin resistance — a hallmark feature of T2D (Lumeng et al., 2007). Feuerer et al. (2009) suggested that high abundance of CD4(+) Foxp3(+) T regulatory (T(reg)) cells in the abdominal fat of lean mice seems to play a role in helping neutralize the macrophageal and conventional T-cell associated inflammatory response and insulin resistance. In contrast, obese rodents experience dramatic reduction in the regulatory T cell number in abdominal fat, which t may explain their high propensity for inflammation and insulin resistance.

Apart from conventionally tested cytokines, a recent study suggested increases in the serum levels of novel proinflammatory cytokine Follistatin-like 1 (FSTL1) among obese subjects and *ob*/*ob* mice, which may contribute to insulin resistance (Fan et al., 2013). Various labs also investigated the association of inflammatory pathways like NF-κB, IKKβ, and JNK with insulin resistance (Arkan et al., 2005; Cai et al., 2005; Shoelson et al., 2007). Thus, T2D associated obesity may serve as a major contributor to the dysregulation of inflammatory processes in T2D patients.

2.3. Influence of medications for bipolar disorder and type 2 diabetes on inflammation

2.3.1. Bipolar disorder medications and inflammation

An evolving line of evidence suggests that mood stabilizers used for the management of BD may interfere with inflammatory markers signaling (Table 2). However, mood stabilizer-induced effect on systemic levels of inflammatory markers could be marker-specific. For instance, remission of elevated blood IL-6 levels in manic BD patients was observed with mood stabilizer treatment with no apparent effect on TNF-α (Kim et al., 2007). Further, the effect of mood stabilizers on inflammatory markers is more pronounced in drug responders versus poor responders (Guloksuz et al., 2012). One of the potential mechanisms for the positive effect of BD medications on inflammatory marker levels could be attributed to their anti-inflammatory potential (Bosetti et al., 2002, 2003; Lee et al., 2008; Maes et al., 2000; Rapaport and Manji, 2001). Mood stabilizers like lithium and valproate are reported for their ability to reduce breakdown of arachidonic acid into inflammatory eicosanoids like prostaglandins E2 (PGE2) by their specific inhibitory action on cyclooxygenase (COX-2 and/or COX-1) in the brain of rats (Bosetti et al., 2002, 2003).

2.3.2. Type 2 diabetes medications and inflammation

Scientific evidence clearly demonstrates the beneficial effects of antidiabetic medications against inflammatory responses (Table 3). Agonists of the peroxisome proliferator-activated receptor γ-isoform (PPARγ-R), also known as insulin sensitizers, are clinically proven for their application in the management of T2D. A wide range of evidence supports their systemic and central anti-inflammatory potential (Cuzzocrea et al., 2004; Morgenweck et al., 2010). PPARγ-R agonists' anti-inflammatory effect could be attributed to their ability to thwart NF-κB transcriptional activity (Remels et al., 2009), suppression of macrophage activation, differentiation induced pro-inflammatory genes expression (Abdelrahman et al., 2005) and/or attenuation of IL-1R antagonist activity (Halvorsen et al., 2010). In addition to their peripheral anti-inflammatory effects, PPARγ agonists may act via their receptors in the CNS (Moreno et al., 2004; Morgenweck et al., 2010).

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Table 2
Effect of bipolar disorder medications on inflammation.

Medication	Findings	References
Lithium	Long-term lithium treatment prevents telomerase shortening in BD patients.	Martinsson et al. (2013)
	Poor lithium responders BD (euthymic) patients show elevated TNF-α level.	Guloksuz et al. (2012)
Valproic acid	Valproate-induced lymphocyte toxicity in vitro is associated with its metabolite induced release of high pro-inflammatory cytokine level.	Neuman et al. (2013)
	Elevated uric acid and total homocysteine (tHcy) levels in epileptic patients.	Chuang et al. (2012)
Carbamazepine	Elevated hsCRP level and disturbances in tHcy epileptic patients.	Chuang et al. (2012)
Atypical antipsychotics	Compromised anti-inflammatory capacity as evidenced by decrease in serum IL-1RA and endogenous anticytokine Clara Cell protein (CC16) levels in treatment-resistant schizophrenics.	Maes et al. (2000)
	Atypical antipsychotics (olanzapine, quetiapine, risperidone, paliperidone, clozapine) significantly increase TNF-α concentrations in BD patients and potentially contribute to atypical antipsychotics associated metabolic syndrome.	Prossin et al. (2013)
Antidepressants	Anti-inflammatory effect via inhibition of microglial TNF-α production.	Tynan et al. (2012)

Apart from conventional antidiabetic medications like PPARγ agonists and sulfonylureas, new generation antidiabetics such as glucagon-like-peptide-1 (GLP-1) receptor agonists (e.g. liraglutide) and dipeptidyl peptidase-4 (DPP-4) inhibitors (e.g. sitagliptin) also have anti-inflammatory properties. One group reported anti-inflammatory effects of liraglutide against intracerebral hemorrhage induced inflammation (Hou et al., 2012). Likewise, sitagliptin showed anti-inflammatory effects at cellular and molecular levels as evidenced by significant reductions in the expression and/or plasma levels of TNFα, CD26, CRP, IL-6, toll-like receptors for endotoxins (TLR-2, TLR-4), chemokine receptor (CCR-2), proinflammatory c-Jun N-terminal kinase-1 and IKKβ with sitagliptin treatment (Makdissi et al., 2012; Rizzo et al., 2012; Satoh-Asahara et al., 2013). DPP-4 inhibitors and GLP-1 agonists readily cross blood brain barrier and are reported for their neuroprotective effects and improved learning behavior in preclinical studies. Moreover, a population-based cohort study hinted for the potential role of sulfonylureas and metformin in the treatment of unipolar and bipolar disorders (Wahlqvist et al., 2012).

2.4. Anti-inflammatory medications in bipolar disorder and type 2 diabetes

A recent review addressed the possible role of non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin in spectrum of mental illnesses (Berk et al., 2013). NSAIDs via their ability to inhibit COX-1 and COX-2 enzymes significantly affect the local and systemic milieu of inflammatory mediators like prostaglandins and thromboxanes (Vane and Botting, 2003). A recent pharmacoepidemiological study suggested that concomitant aspirin treatment significantly reduced the risk of clinical deterioration among patients on lithium treatment (Stolk et al., 2010). Interestingly, the effects observed were independent of the duration of the aspirin treatment. A six-week add-on therapy with COX-2 inhibitor celecoxib in a small sample of BD patients (n = 28) who were on lithium or atypical antipsychotic treatment suggested significant improvement in their depressive symptoms (Nery et al., 2008). These findings point to a faster onset of the antidepressant effect of mood stabilizers when they are combined with anti-inflammatory medications among BD patients. Moreover, it has been suggested that 6-week mood stabilizer treatment helps to bring IL-6 back to basal levels in manic BD patients (Kim et al., 2007). Add-on anti-inflammatory medications seems to bring about improvements in mood (particularly in depression), with rapid onset of action (Table 4). However, pharmacokinetic interactions between lithium and anti-inflammatory drugs with increased risk for lithium toxicity are documented (Table 4). In view of the narrow therapeutic window of lithium and the putative role of inflammation in BD, clinical studies evaluating the efficacy of anti-inflammatory agents, either alone or as an add-on therapy in a larger BD population may lead to important advancements in evaluating the efficacy and safety of such combinations in the management of BD. Several clinical studies also reported the benefits of inhibiting inflammatory NF-κB and IKKβ pathways employing anti-inflammatory drugs, with improvements in insulin sensitivity and decrease in fasting blood glucose and CRP levels (Fleischman et al., 2008; Goldfine et al., 2008, 2010). In view of the plethora of evidences supporting the role inflammation in the T2D pathophysiology, this classic metabolic disorder is also been acknowledged as an autoinflammatory disease (Donath and Shoelson, 2011).

3. Inflammation as a unifying mechanism for bipolar disorder — type 2 diabetes comorbidity

The putative role of dysregulated inflammatory response as a critical upstream event for BD and T2D comorbidity is illustrated in Fig. 1. Mood stabilizers used for BD treatment are known to interfere with energy homeostasis augmenting obesity and increasing the risk for T2D (Castilla-Puentes, 2007). A recent study suggested a strong inclination of prescribers toward co-prescription of antidiabetics and mood stabilizers (Svendal et al., 2012). Further, a population-based cohort study suggested that T2D serves as a precursor for affective disorders and the combination of antidiabetic medications (e.g. sulfonylurea and metformin) seems to significantly reduce the risk for the development of unipolar and bipolar affective disorders in T2D patients (Wahlqvist et al., 2012). Clinical and preclinical evidence also suggests that medications used for the management of BD (Martinsson et al., 2013) and T2D (Corzo and Griffin, 2013) interfere with inflammatory responses. Mood stabilizers such as lithium (Baptista et al., 1995), valproic acid (Masuccio et al., 2010; Verrotti et al., 2011), atypical antipsychotics (McIntyre and Konarski, 2005) and antidepressants (Fava, 2000) are known for body

Table 3
Effect of type 2 diabetes medications on inflammation.

Medication	Findings	References
Metformin	Decrease in advanced oxidation protein products and restoration of CRP in T2D patients.	Chakraborty et al. (2011)
	Reduction in CRP level in T2D patients.	Carter et al. (2005)
	Significantly decreased IL-6, ICAM-1, and TNF-α level in T2D patients.	Fidan et al. (2011)
PPARγ agonists	Significantly decreased IL-6, and TNF-α level in T2D patients.	Fidan et al. (2011)
	Significantly reduced CRP levels.	Md Isa et al. (2006)
DPP-4 inhibitors	Significant reduction in cytokines IL-6 and IL-18 in T2D patients.	Rizzo et al. (2012)
	Significantly decreased serum amyloid A-LDL (SAA-LDL), CRP, and TNF-α level in T2D patients' post-3-month sitagliptin treatment.	Satoh-Asahara et al. (2013)
GLP-1 analogues	Reduced CRP level and systemic inflammation in T2D patients with long-term exenatide treatment.	Chiquette et al. (2012), Wu et al. (2011)

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Table 4
Effect of anti-inflammatory medications on bipolar disorder.

Medication	Findings	Reference(s)
Aspirin	Significantly decreased risk of clinical deterioration in lithium treated patients with low dose aspirin treatment.	Stolk et al. (2010)
Infliximab	Infliximab may help to improve depressive symptoms in patients with elevated basal level of inflammatory biomarkers such as TNFα.	Raison et al. (2013)
Celecoxib	Rapid onset of antidepressant effect in BD patients treated with celecoxib as an adjunct treatment to mood stabilizer or atypic.al antipsychotics.	Nery et al. (2008)
	Elevated systemic lithium levels.	Slordal et al. (2003)
Rofecoxib	Increased risk of lithium toxicity.	Ratz Bravo et al. (2004)
Flurbiprofen	Elevated systemic lithium levels with concomitant furbiprofen treatment.	Hughes et al. (1997)
Ibuprofen	Increased serum lithium levels in BD patients.	Ragheb (1987)
Ketorolac	Elevated systemic lithium levels.	Langlois and Paquette (1994)
Mefenamic acid	Acute lithium toxicity that may be because of inhibition of prostaglandin activity.	Shelley (1987)
Sulindac	Does not affect serum lithium level and is safe in lithium users.	Ragheb and Powell (1986)
Indomethacin	Potentially fatal risk of lithium toxicity.	Herschberg and Sierles (1983)

weight gain, fat deposition and obesity with increased risk for T2D. Fat cells are known for their ability to secrete gamut of inflammatory proteins such as TNFα and IL-6. Both, mood stabilizers (e.g. lithium, valproic acid) and antidiabetics (e.g. insulin, pioglitazone) medications — are reported to block inflammatory GSK3β pathway (Gould et al., 2004; Ponce-Lopez et al., 2011). Additionally, Toledo and Inestrosa (2010) reported that both lithium and rosiglitazone inhibit inflammatory response in a double transgenic mouse model for Alzheimer's disease. Lithium and rosiglitazone, via activation of wnt canonical pathway, significantly reduce soma size of inflammatory astrocytes, their glial fibrillary acidic protein (GFAP) intensity — a marker for microglial and astroglial activation and number of CD11b marked microglial cells in the cortex and hippocampus, indicating their anti-inflammatory response. Interestingly, a recent genome-wide association study suggested polymorphism (rs12772424) in the TCF7L2 gene that encodes for wnt pathway transcription factor TCF/LF as a common genetic risk for BD, T2D and increased body mass index (BMI) (Winham et al., 2013). Intrigued with these reports, it is tempting to speculate that dysregulated wnt signaling may be a common contributor for increased inflammatory response in BD and T2D.

4. Challenges in projecting inflammatory proteins as biomarkers

Biomarkers should ideally help predicting the risk of development of a disease and its chances of progression, as well as its response to certain treatments. Unfortunately biomarkers research for BD is still in infancy. Currently, there are no available clinical laboratory tests that can help in the diagnosis of BD or to evaluate the response to pharmacological and behavioral interventions. Given the gamut of theories proposed as pathophysiological mechanisms for BD and T2D, the quest for a single unifying pathway leading to their high comorbidity is challenging. Learning whether routine laboratory screening of inflammatory biomarkers in

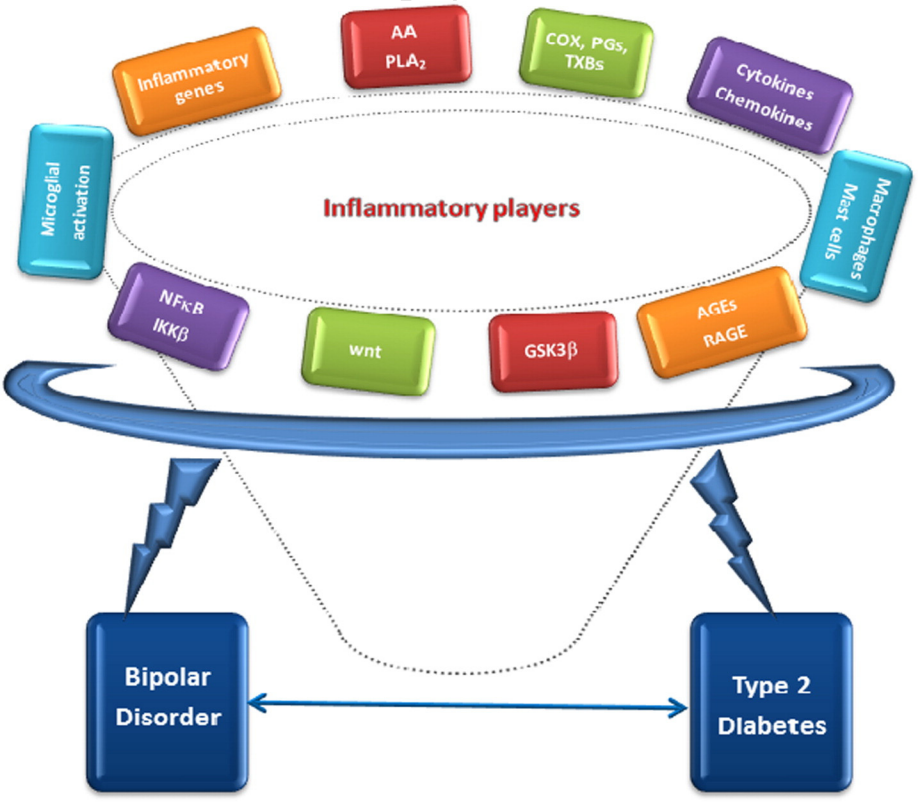

Fig. 1. Dysregulated inflammatory response as a critical upstream event for bipolar disorder and type 2 diabetes comorbidity. Abbreviations: (1) AA: arachidonic acid; (2) PLA_2: phospholipase A_2; (3) COX: cyclooxygenase; (4) PGs: prostaglandins; (5) TXBs: thromboxanes; (6) AGEs: advanced glycation products; (7) RAGE: receptor for AGEs; (8) GSK3β: glycogen synthase kinase-3β; (9) NFκB: nuclear factor kappa-light-chain-enhancer of activated B cells; (10) IKKb: inhibitor of nuclear factor kappa-B kinase subunit beta.

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BD population will be cost effective and reliable represents an area of high interest. The reliability of inflammatory markers in estimating BD prognosis will also depend on whether changes are BD-specific or shared with other psychiatric disorders like schizophrenia and major depressive disorder (MDD). Laboratory measures of inflammatory biomarkers could potentially be affected by unrelated medical conditions like microbial infections, chronic inflammatory diseases (e.g. rheumatoid arthritis), mechanical injuries, gender, age, and ethnicity among others. Environmental influences such as socio-economic status, childhood abuse, dietary practices, irregular sleep habits, sedentary lifestyle, medication history, severity and/or duration of disease may pose as potential confounding factors, as they may also influence the laboratory measures of inflammatory biomarkers. Moreover, inconsistencies in the replication of findings between laboratory measurements, differences in assay methods, length of specimen storage period and storage temperature, freeze–thaw cycles prior to laboratory analysis, quality of antibodies for inflammatory marker assay represent additional challenges (Kapczinski et al., 2011; Kupka et al., 2002; Ortiz-Dominguez et al., 2007).

5. Conclusions

In view of the limitations of the behavioral and symptom-based diagnosis of BD, there is a need for biomarkers aiming at making its identification more reliable. Definitive markers will help clinicians plan better treatment strategies and refine their clinical practices with more definitive diagnosis, early intervention, personalized treatment and improved BD patient compliance. Although the exact mechanisms are not yet fully understood, there is a clear evidence for (1) higher prevalence of T2D in BD patients and (2) dysregulated inflammatory processes in BD as well as in T2DM. However, there is paucity of data studying inflammation as a common mediator for the comorbidity of BD with T2D. Although several inflammatory proteins pose as potential candidates, there are no systematic studies till date that convincingly points to specific inflammatory proteins as biomarkers for BD, T2D, or both. Further, it is debatable whether inflammation serves as a precursor for BD or BD brings about dysregulation of inflammatory response. While literature must be interpreted with care, apparently BD and inflammation share bidirectional relationships and inflammation may be a factor for the development of T2D in BD population. Further, co-morbid T2D makes disease management more difficult in BD population. Additionally, co-morbidity of BD and T2D is relatively less studied, and hitherto, there are not adequate published reports to examine if certain BD subtype patients are more vulnerable than other subtypes for the development of T2D. Molecular profiling of physiological specimens from BD patients with or without T2D for inflammatory markers will help improve our understanding about their absolute contribution to this high comorbidity. Since the strength of the 'BD–inflammation–T2D' association may significantly heighten the risk of treatment failure, there is a need for novel therapeutics that can simultaneously target all aspects of these multi-system conditions. Coordinated pharmacological interventions managing mental health, inflammation and glucose homeostasis coupled with behavioral and weight reduction approaches may help lessen disease burden. Inflammatory markers for BD may bring researcher and clinicians one step closer to understanding its underlying mechanisms, with consequent improvements in its management.

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References

Abdelrahman M, Sivarajah A, Thiemermann C. Beneficial effects of PPAR-gamma ligands in ischemia–reperfusion injury, inflammation and shock. Cardiovasc Res 2005;65:772–81.

Abdulla YH, Hamadah K. Effect of ADP on PGE1 formation in blood platelets from patients with depression, mania and schizophrenia. Br J Psychiatry 1975;127:591–5.

Al-Shukaili A, Al-Ghafri S, Al-Marhoobi S, Al-Abri S, Al-Lawati J, Al-Maskari M. Analysis of inflammatory mediators in type 2 diabetes patients. Int J Endocrinol 2013;2013:976810.

Altamura AC, Mundo E, Cattaneo E, Pozzoli S, Dell'osso B, Gennarelli M, et al. The MCP-1 gene (SCYA2) and mood disorders: preliminary results of a case–control association study. Neuroimmunomodulation 2010;17:126–31.

Arkan MC, Hevener AL, Greten FR, Maeda S, Li ZW, Long JM, et al. IKK-beta links inflammation to obesity-induced insulin resistance. Nat Med 2005;11:191–8.

Bal Y, Adas M, Helvaci A. Evaluation of the relationship between insulin resistance and plasma tumor necrosis factor-alpha, interleukin-6 and C-reactive protein levels in obese women. Bratisl Lek Listy 2010;111:200–4.

Baptista T, Teneud L, Contreras Q, Alastre T, Burguera JL, de Burguera M, et al. Lithium and body weight gain. Pharmacopsychiatry 1995;28:35–44. Q5

Barbosa IG, Huguet RB, Mendonca VA, Sousa LP, Neves FS, Bauer ME, et al. Increased plasma levels of soluble TNF receptor I in patients with bipolar disorder. Eur Arch Psychiatry Clin Neurosci 2011;261:139–43.

Barbosa IG, Rocha NP, Bauer ME, de Miranda AS, Huguet RB, Reis HJ, et al. Chemokines in bipolar disorder: trait or state? Eur Arch Psychiatry Clin Neurosci 2013;263:159–65.

Barnes PJ, Haddad EB, Rousell J. Regulation of muscarinic M2 receptors. Life Sci 1997;60:1015–21.

Belmaker RH, Agam G. Bipolar disorder: neurochemistry and drug mechanisms. Discov Med 2005;5:191–8.

Berk M, Dean O, Drexhage H, McNeil JJ, Moylan S, O'Neil A, et al. Aspirin: a review of its neurobiological properties and therapeutic potential for mental illness. BMC Med 2013;11:74.

Bid HK, Konwar R, Agrawal CG, Banerjee M. Association of IL-4 and IL-1RN (receptor antagonist) gene variants and the risk of type 2 diabetes mellitus: a study in the north Indian population. Indian J Med Sci 2008;62:259–66.

Bosetti F, Rintala J, Seemann R, Rosenberger TA, Contreras MA, Rapoport SI, et al. Chronic lithium downregulates cyclooxygenase-2 activity and prostaglandin E(2) concentration in rat brain. Mol Psychiatry 2002;7:845–50.

Bosetti F, Weerasinghe GR, Rosenberger TA, Rapoport SI. Valproic acid down-regulates the conversion of arachidonic acid to eicosanoids via cyclooxygenase-1 and -2 in rat brain. J Neurochem 2003;85:690–6.

Brietzke E, Stertz L, Fernandes BS, Kauer-Sant'Anna M, Mascarenhas M, Escosteguy VA, et al. Comparison of cytokine levels in depressed, manic and euthymic patients with bipolar disorder. J Affect Disord 2009;116:214–7.

Brietzke E, Kapczinski F, Grassi-Oliveira R, Grande I, Vieta E, McIntyre RS. Insulin dysfunction and allostatic load in bipolar disorder. Expert Rev Neurother 2011;11:1017–28.

Cai D, Yuan M, Frantz DF, Melendez PA, Hansen L, Lee J, et al. Local and systemic insulin resistance resulting from hepatic activation of IKK-beta and NF-kappaB. Nat Med 2005;11:183–90.

Calkin C, van de Velde C, Ruzickova M, Slaney C, Garnham J, Hajek T, et al. Can body mass index help predict outcome in patients with bipolar disorder? Bipolar Disord 2009;11:650–6. Q6

Calkin CV, Gardner DM, Ransom T, Alda M. The relationship between bipolar disorder and type 2 diabetes: more than just co-morbid disorders. Ann Med 2013;45:171–81.

Carney CP, Jones LE. Medical comorbidity in women and men with bipolar disorders: a population-based controlled study. Psychosom Med 2006;68:684–91.

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Carstensen M, Herder C, Kivimaki M, Jokela M, Roden M, Shipley MJ, et al. Accelerated increase in serum interleukin-1 receptor antagonist starts 6 years before diagnosis of type 2 diabetes: Whitehall II prospective cohort study. Diabetes 2010;59:1222–7.

Carter AM, Bennett CE, Bostock JA, Grant PJ. Metformin reduces C-reactive protein but not complement factor C3 in overweight patients with Type 2 diabetes mellitus. Diabet Med 2005;22:1282–4.

Cassidy F, Ahearn E, Carroll BJ. Elevated frequency of diabetes mellitus in hospitalized manic-depressive patients. Am J Psychiatry 1999;156:1417–20.

Cassidy F, Wilson WH, Carroll BJ. Leukocytosis and hypoalbuminemia in mixed bipolar states: evidence for immune activation. Acta Psychiatr Scand 2002;105:60–4.

Castilla-Puentes R. Effects of psychotropics on glycosylated hemoglobin (HbA1c) in a cohort of bipolar patients. Bipolar Disord 2007;9:772–8.

Chakraborty A, Chowdhury S, Bhattacharyya M. Effect of metformin on oxidative stress, nitrosative stress and inflammatory biomarkers in type 2 diabetes patients. Diabetes Res Clin Pract 2011;93:56–62.

Chang MC, Jones CR. Chronic lithium treatment decreases brain phospholipase A2 activity. Neurochem Res 1998;23:887–92.

Chang MC, Grange E, Rabin O, Bell JM, Allen DD, Rapoport SI. Lithium decreases turnover of arachidonate in several brain phospholipids. Neurosci Lett 1996;220:171–4.

Chengappa KN, Chalasani L, Brar JS, Parepally H, Houck P, Levine J. Changes in body weight and body mass index among psychiatric patients receiving lithium, valproate, or topiramate: an open-label, nonrandomized chart review. Clin Ther 2002;24:1576–84.

Chiquette E, Toth PP, Ramirez G, Cobble M, Chilton R. Treatment with exenatide once weekly or twice daily for 30 weeks is associated with changes in several cardiovascular risk markers. Vasc Health Risk Manag 2012;8:621–9.

Chuang YC, Chuang HY, Lin TK, Chang CC, Lu CH, Chang WN, et al. Effects of long-term antiepileptic drug monotherapy on vascular risk factors and atherosclerosis. Epilepsia 2012;53:120–8.

Clausell N, Kalil P, Biolo A, Molossi S, Azevedo M. Increased expression of tumor necrosis factor-alpha in diabetic macrovasculopathy. Cardiovasc Pathol 1999;8:145–51.

Coffman JA, Bornstein RA, Olson SC, Schwarzkopf SB, Nasrallah HA. Cognitive impairment and cerebral structure by MRI in bipolar disorder. Biol Psychiatry 1990;27:1188–96.

Corzo C, Griffin PR. Targeting the peroxisome proliferator-activated receptor-gamma to counter the inflammatory milieu in obesity. Diabetes Metab J 2013;37:395–403.

Cousins DA, Butts K, Young AH. The role of dopamine in bipolar disorder. Bipolar Disord 2009;11:787–806.

Cunha AB, Andreazza AC, Gomes FA, Frey BN, da Silveira LE, Goncalves CA, et al. Investigation of serum high-sensitive C-reactive protein levels across all mood states in bipolar disorder. Eur Arch Psychiatry Clin Neurosci 2008;258:300–4.

Cuzzocrea S, Pisano B, Dugo L, Ianaro A, Maffia P, Patel NS, et al. Rosiglitazone, a ligand of the peroxisome proliferator-activated receptor-gamma, reduces acute inflammation. Eur J Pharmacol 2004;483:79–93.

Czerski PM, Rybakowski F, Kapelski P, Rybakowski JK, Dmitrzak-Weglarz M, Leszczynska-Rodziewicz A, et al. Association of tumor necrosis factor −308G/A promoter polymorphism with schizophrenia and bipolar affective disorder in a Polish population. Neuropsychobiology 2008;57:88–94.

Daniele G, Guardado MR, Winnier D, Fiorentino TV, Pengou Z, Cornell J, et al. The inflammatory status score including IL-6, TNF-alpha, osteopontin, fractalkine, MCP-1 and adiponectin underlies whole-body insulin resistance and hyperglycemia in type 2 diabetes mellitus. Acta Diabetol 2014. (In press).

de Sousa RT, Zarate Jr CA, Zanetti MV, Costa AC, Talib LL, Gattaz WF, et al. Oxidative stress in early stage Bipolar Disorder and the association with response to lithium. J Psychiatr Res 2014;50:36–41.

Dickerson F, Stallings C, Origoni A, Boronow J, Yolken R. Elevated serum levels of C-reactive protein are associated with mania symptoms in outpatients with bipolar disorder. Prog Neuropsychopharmacol Biol Psychiatry 2007;31:952–5.

Dinarello CA. The role of the interleukin-1-receptor antagonist in blocking inflammation mediated by interleukin-1. N Engl J Med 2000;343:732–4.

Dinarello CA, Donath MY, Mandrup-Poulsen T. Role of IL-1beta in type 2 diabetes. Curr Opin Endocrinol Diabetes Obes 2010;17:314–21.

Dinesen H, Gram L, Andersen T, Dam M. Weight gain during treatment with valproate. Acta Neurol Scand 1984;70:65–9.

Donath MY, Shoelson SE. Type 2 diabetes as an inflammatory disease. Nat Rev Immunol 2011;11:98–107.

Dong N, Xu B, Wang B, Chu L. Study of 27 aqueous humor cytokines in patients with type 2 diabetes with or without retinopathy. Mol Vis 2013;19:1734–46.

Drexhage RC, Knijff EM, Padmos RC, Heul-Nieuwenhuijzen L, Beumer W, Versnel MA, et al. The mononuclear phagocyte system and its cytokine inflammatory networks in schizophrenia and bipolar disorder. Expert Rev Neurother 2010a;10:59–76.

Drexhage RC, Heul-Nieuwenhuijsen L, Padmos RC, van Beveren N, Cohen D, Versnel MA, et al. Inflammatory gene expression in monocytes of patients with schizophrenia: overlap and difference with bipolar disorder. A study in naturalistically treated patients. Int J Neuropsychopharmacol 2010b;13:1369–81.

Ehses JA, Perren A, Eppler E, Ribaux P, Pospisilik JA, Maor-Cahn R, et al. Increased number of islet-associated macrophages in type 2 diabetes. Diabetes 2007;56:2356–70.

Emanuele E, Martinelli V, Carlin MV, Fugazza E, Barale F, Politi P. Serum levels of soluble receptor for advanced glycation endproducts (sRAGE) in patients with different psychiatric disorders. Neurosci Lett 2011;487:99–102.

Fagiolini A, Frank E, Houck PR, Mallinger AG, Swartz HA, Buysse DJ, et al. Prevalence of obesity and weight change during treatment in patients with bipolar I disorder. J Clin Psychiatry 2002;63:528–33.

Fain JN. Release of inflammatory mediators by human adipose tissue is enhanced in obesity and primarily by the nonfat cells: a review. Mediators Inflamm 2010;2010:513948.

Fain JN, Kanu A, Bahouth SW, Cowan Jr GS, Hiler ML, Leffler CW. Comparison of PGE2, prostacyclin and leptin release by human adipocytes versus explants of adipose tissue in primary culture. Prostaglandins Leukot Essent Fatty Acids 2002;67:467–73.

Fan N, Sun H, Wang Y, Wang Y, Zhang L, Xia Z, et al. Follistatin-like 1: a potential mediator of inflammation in obesity. Mediators Inflamm 2013;2013:752519.

Fava M. Weight gain and antidepressants. J Clin Psychiatry 2000;61(Suppl. 11):37–41.

Feuerer M, Herrero L, Cipolletta D, Naaz A, Wong J, Nayer A, et al. Lean, but not obese, fat is enriched for a unique population of regulatory T cells that affect metabolic parameters. Nat Med 2009;15:930–9.

Fidan E, Onder EH, Yilmaz M, Yilmaz H, Kocak M, Karahan C, et al. The effects of rosiglitazone and metformin on inflammation and endothelial dysfunction in patients with type 2 diabetes mellitus. Acta Diabetol 2011;48:297–302.

Fleischman A, Shoelson SE, Bernier R, Goldfine AB. Salsalate improves glycemia and inflammatory parameters in obese young adults. Diabetes Care 2008;31:289–94.

Fornito A, Yucel M, Pantelis C. Reconciling neuroimaging and neuropathological findings in schizophrenia and bipolar disorder. Curr Opin Psychiatry 2009;22:312–9.

Fotuhi M, Do D, Jack C. Modifiable factors that alter the size of the hippocampus with ageing. Nat Rev Neurol 2012;8:189–202.

Giulietti A, van Etten E, Overbergh L, Stoffels K, Bouillon R, Mathieu C. Monocytes from type 2 diabetic patients have a pro-inflammatory profile. 1,25-dihydroxyvitamin D(3) works as anti-inflammatory. Diabetes Res Clin Pract 2007;77:47–57.

Goh SY, Cooper ME. Clinical review: the role of advanced glycation end products in progression and complications of diabetes. J Clin Endocrinol Metab 2008;93:1143–52.

Gohel MG, Chacko AN. Serum GGT activity and hsCRP level in patients with type 2 diabetes mellitus with good and poor glycemic control: an evidence linking oxidative stress, inflammation and glycemic control. J Diabetes Metab Disord 2013;12:56.

Goldfine AB, Silver R, Aldhahi W, Cai D, Tatro E, Lee J, et al. Use of salsalate to target inflammation in the treatment of insulin resistance and type 2 diabetes. Clin Transl Sci 2008;1:36–43.

Goldfine AB, Fonseca V, Jablonski KA, Pyle L, Staten MA, Shoelson SE. The effects of salsalate on glycemic control in patients with type 2 diabetes: a randomized trial. Ann Intern Med 2010;152:346–57.

Goldstein BI, Kemp DE, Soczynska JK, McIntyre RS. Inflammation and the phenomenology, pathophysiology, comorbidity, and treatment of bipolar disorder: a systematic review of the literature. J Clin Psychiatry 2009;70:1078–90.

Gomes FA, Sant'Anna M, Magalhaes PV, Jacka FN, Dodd S, Gama CS, et al. Obesity is associated with previous suicide attempts in bipolar disorder. Acta Neuropsychiatr. 2010;22:63–7.

Gould TD, Chen G, Manji HK. In vivo evidence in the brain for lithium inhibition of glycogen synthase kinase-3. Neuropsychopharmacology 2004;29:32–8.

Guloksuz S, Altinbas K, Aktas CE, Kenis G, Bilgic GS, Deniz G, et al. Evidence for an association between tumor necrosis factor-alpha levels and lithium response. J Affect Disord 2012;143:148–52.

Haddad EB, Rousell J, Lindsay MA, Barnes PJ. Synergy between tumor necrosis factor alpha and interleukin 1beta in inducing transcriptional down-regulation of muscarinic M2 receptor gene expression. Involvement of protein kinase A and ceramide pathways. J Biol Chem 1996;271:32586–92.

Hajek T, Calkin C, Blagdon R, Slaney C, Alda M. Type 2 diabetes mellitus: a potentially modifiable risk factor for neurochemical brain changes in bipolar disorders. Biol Psychiatry 2013.

Halvorsen B, Heggen E, Ueland T, Smith C, Sandberg WJ, Damas JK, et al. Treatment with the PPARgamma agonist rosiglitazone downregulates interleukin-1 receptor antagonist in individuals with metabolic syndrome. Eur J Endocrinol 2010;162:267–73.

Herberth M, Koethe D, Levin Y, Schwarz E, Krzyszton ND, Schoeffmann S, et al. Peripheral profiling analysis for bipolar disorder reveals markers associated with reduced cell survival. Proteomics 2011;11:94–105.

Herder C, Brunner EJ, Rathmann W, Strassburger K, Tabak AG, Schloot NC, et al. Elevated levels of the anti-inflammatory interleukin-1 receptor antagonist precede the onset of type 2 diabetes: the Whitehall II study. Diabetes Care 2009;32:421–3.

Herschberg SN, Sierles FS. Indomethacin-induced lithium toxicity. Am Fam Physician 1983;28:155–7.

Ho KT, Shiau MY, Chang YH, Chen CM, Yang SC, Huang CN. Association of interleukin-4 promoter polymorphisms in Taiwanese patients with type 2 diabetes mellitus. Metabolism 2010;59:1717–22.

Hope S, Dieset I, Agartz I, Steen NE, Ueland T, Melle I, et al. Affective symptoms are associated with markers of inflammation and immune activation in bipolar disorders but not in schizophrenia. J Psychiatr Res 2011;45:1608–16.

Horrobin DF. Essential fatty acids in the management of impaired nerve function in diabetes. Diabetes 1997;46(Suppl. 2):S90–3.

Horrobin DF, Bennett CN. Depression and bipolar disorder: relationships to impaired fatty acid and phospholipid metabolism and to diabetes, cardiovascular disease, immunological abnormalities, cancer, ageing and osteoporosis. Possible candidate genes. Prostaglandins Leukot Essent Fat Acids 1999;60:217–34.

Horrobin DF, Lieb J. A biochemical basis for the actions of lithium on behaviour and on immunity: relapsing and remitting disorders of inflammation and immunity such as multiple sclerosis or recurrent herpes as manic-depression of the immune system. Med Hypotheses 1981;7:891–905.

Hotamisligil GS, Shargill NS, Spiegelman BM. Adipose expression of tumor necrosis factor-alpha: direct role in obesity-linked insulin resistance. Science 1993;259:87–91.

Hou J, Manaenko A, Hakon J, Hansen-Schwartz J, Tang J, Zhang JH. Liraglutide, a long-acting GLP-1 mimetic, and its metabolite attenuate inflammation after intracerebral hemorrhage. J Cereb Blood Flow Metab 2012;32:2201–10.

Hughes BM, Small RE, Brink D, McKenzie ND. The effect of flurbiprofen on steady-state plasma lithium levels. Pharmacotherapy 1997;17:113–20.

Igarashi M, Ma K, Gao F, Kim HW, Greenstein D, Rapoport SI, et al. Brain lipid concentrations in bipolar disorder. J Psychiatr Res 2010;44:177–82.

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Ivanov AI, Romanovsky AA. Prostaglandin E2 as a mediator of fever: synthesis and catabolism. Front Biosci 2004;9:1977–93.

Kapczinski F, Dal-Pizzol F, Teixeira AL, Magalhaes PV, Kauer-Sant'Anna M, Klamt F, et al. Peripheral biomarkers and illness activity in bipolar disorder. J Psychiatr Res 2011; 45:156–61.

Kato T, Shioiri T, Takahashi S, Inubushi T. Measurement of brain phosphoinositide metabolism in bipolar patients using in vivo 31P-MRS. J Affect Disord 1991;22:185–90.

Kawamoto T, Horikawa Y, Tanaka T, Kabe N, Takeda J, Mikuni M. Genetic variations in the WFS1 gene in Japanese with type 2 diabetes and bipolar disorder. Mol Genet Metab 2004;82:238–45.

Kim YK, Jung HG, Myint AM, Kim H, Park SH. Imbalance between pro-inflammatory and anti-inflammatory cytokines in bipolar disorder. J Affect Disord 2007;104:91–5.

Kim B, Kim S, McIntyre RS, Park HJ, Kim SY, Joo YH. Correlates of metabolic abnormalities in bipolar I disorder at initiation of acute phase treatment. Psychiatry Investig 2009a; 6:78–84.

Kim OY, Jo SH, Jang Y, Chae JS, Kim JY, Hyun YJ, et al. G allele at RAGE SNP82 is associated with proinflammatory markers in obese subjects. Nutr Res 2009b;29:106–13.

Kim HW, Rapoport SI, Rao JS. Altered arachidonic acid cascade enzymes in postmortem brain from bipolar disorder patients. Mol Psychiatry 2011;16:419–28.

Klein-Platat C, Drai J, Oujaa M, Schlienger JL, Simon C. Plasma fatty acid composition is associated with the metabolic syndrome and low-grade inflammation in overweight adolescents. Am J Clin Nutr 2005;82:1178–84.

Knijff EM, Breunis MN, Kupka RW, de Wit HJ, Ruwhof C, Akkerhuis GW, et al. An imbalance in the production of IL-1beta and IL-6 by monocytes of bipolar patients: restoration by lithium treatment. Bipolar Disord 2007;9:743–53.

Kupfer DJ. The increasing medical burden in bipolar disorder. JAMA 2005;293:2528–30.

Kupka RW, Breunis MN, Knijff E, Ruwhof C, Nolen WA, Drexhage HA. Immune activation, steroid resistancy and bipolar disorder. Bipolar Disord 2002;4(Suppl. 1):73–4.

Laeng P, Pitts RL, Lemire AL, Drabik CE, Weiner A, Tang H, et al. The mood stabilizer valproic acid stimulates GABA neurogenesis from rat forebrain stem cells. J Neurochem 2004;91:238–51.

Langlois R, Paquette D. Increased serum lithium levels due to ketorolac therapy. CMAJ 1994;150:1455–6.

Larsen CM, Faulenbach M, Vaag A, Volund A, Ehses JA, Seifert B, et al. Interleukin-1-receptor antagonist in type 2 diabetes mellitus. N Engl J Med 2007;356:1517–26.

Leboyer M, Soreca I, Scott J, Frye M, Henry C, Tamouza R, et al. Can bipolar disorder be viewed as a multi-system inflammatory disease? J Affect Disord 2012;141:1–10.

Lechleitner M, Herold M, Dzien-Bischinger C, Hoppichler F, Dzien A. Tumour necrosis factor-alpha plasma levels in elderly patients with Type 2 diabetes mellitus-observations over 2 years. Diabet Med 2002;19:949–53.

Lee HJ, Ertley RN, Rapoport SI, Bazinet RP, Rao JS. Chronic administration of lamotrigine downregulates COX-2 mRNA and protein in rat frontal cortex. Neurochem Res 2008;33:861–6.

Lee SY, Chen SL, Chang YH, Chen PS, Huang SY, Tzeng NS, et al. Inflammation's association with metabolic profiles before and after a twelve-week clinical trial in drug-naive patients with bipolar II disorder. PLoS One 2013;8:e66847.

Lilliker SL. Prevalence of diabetes in a manic-depressive population. Compr Psychiatry 1980;21:270–5.

Lindmark S, Buren J, Eriksson JW. Insulin resistance, endocrine function and adipokines in type 2 diabetes patients at different glycaemic levels: potential impact for glucotoxicity in vivo. Clin Endocrinol (Oxf) 2006;65:301–9.

Liu HC, Yang YY, Chou YM, Chen KP, Shen WW, Leu SJ. Immunologic variables in acute mania of bipolar disorder. J Neuroimmunol 2004;150:116–22.

Luevano-Contreras C, Garay-Sevilla ME, Wrobel K, Malacara JM, Wrobel K. Dietary advanced glycation end products restriction diminishes inflammation markers and oxidative stress in patients with type 2 diabetes mellitus. J Clin Biochem Nutr 2013; 52:22–6.

Lumeng CN, Bodzin JL, Saltiel AR. Obesity induces a phenotypic switch in adipose tissue macrophage polarization. J Clin Invest 2007;117:175–84.

Maedler K, Sergeev P, Ris F, Oberholzer J, Joller-Jemelka HI, Spinas GA, et al. Glucose-induced beta cell production of IL-1beta contributes to glucotoxicity in human pancreatic islets. J Clin Invest 2002;110:851–60.

Maes M, Bosmans E, Calabrese J, Smith R, Meltzer HY. Interleukin-2 and interleukin-6 in schizophrenia and mania: effects of neuroleptics and mood stabilizers. J Psychiatr Res 1995;29:141–52.

Maes M, Bocchio CL, Bignotti S, Battisa TG, Pioli R, Boin F, et al. Effects of atypical antipsychotics on the inflammatory response system in schizophrenic patients resistant to treatment with typical neuroleptics. Eur Neuropsychopharmacol 2000;10:119–24.

Makdissi A, Ghanim H, Vora M, Green K, Abuaysheh S, Chaudhuri A, et al. Sitagliptin exerts an antinflammatory action. J Clin Endocrinol Metab 2012;97:3333–41.

Malekshahi MA, Saedisomeolia A, Djalali M, Djazayery A, Pooya S, Sojoudi F. Efficacy of omega-3 fatty acid supplementation on serum levels of tumour necrosis factor-alpha, C-reactive protein and interleukin-2 in type 2 diabetes mellitus patients. Singapore Med J 2012;53:615–9.

Manickam B, Neagu V, Kukreja SC, Barengolts E. Relationship between glycated hemoglobin and circulating 25-hydroxyvitamin D concentration in African American and Caucasian American men. Endocr Pract 2013;19:73–80.

Martin CK, Han H, Anton SD, Greenway FL, Smith SR. Effect of valproic acid on body weight, food intake, physical activity and hormones: results of a randomized controlled trial. J Psychopharmacol 2009;23:814–25.

Martinsson L, Wei Y, Xu D, Melas PA, Mathe AA, Schalling M, et al. Long-term lithium treatment in bipolar disorder is associated with longer leukocyte telomeres. Transl Psychiatry 2013;3:e261.

Masters SL, Dunne A, Subramanian SL, Hull RL, Tannahill GM, Sharp FA, et al. Activation of the NLRP3 inflammasome by islet amyloid polypeptide provides a mechanism for enhanced IL-1beta in type 2 diabetes. Nat Immunol 2010;11:897–904.

Masuccio F, Verrotti A, Chiavaroli V, de Giorgis T, Giannini C, Chiarelli F, et al. Weight gain and insulin resistance in children treated with valproate: the influence of time. J Child Neurol 2010;25:941–7.

Maudsley H. The physiology and pathology of mind; 1868 [In. Macmillan].

McIntyre RS, Konarski JZ. Tolerability profiles of atypical antipsychotics in the treatment of bipolar disorder. J Clin Psychiatry 2005;66(Suppl. 3):28–36.

McNamara RK, Jandacek R, Rider T, Tso P, Stanford KE, Hahn CG, et al. Deficits in docosahexaenoic acid and associated elevations in the metabolism of arachidonic acid and saturated fatty acids in the postmortem orbitofrontal cortex of patients with bipolar disorder. Psychiatry Res 2008;160:285–99.

Md Isa SH, Najihah I, Nazaimoon WM, Kamarudin NA, Umar NA, Mat NH, et al. Improvement in C-reactive protein and advanced glycosylation end-products in poorly controlled diabetics is independent of glucose control. Diabetes Res Clin Pract 2006;72: 48–52.

Meier CA, Bobbioni E, Gabay C, Assimacopoulos-Jeannet F, Golay A, Dayer JM. IL-1 receptor antagonist serum levels are increased in human obesity: a possible link to the resistance to leptin? J Clin Endocrinol Metab 2002;87:1184–8.

Meira-Lima I, Michelon L, Cordeiro Q, Cho HJ, Vallada H. Allelic association analysis of the functional insertion/deletion polymorphism in the promoter region of the serotonin transporter gene in bipolar affective disorder. J Mol Neurosci 2005;27:219–24.

Middle F, Jones I, Robertson E, Lendon C, Craddock N. Tumour necrosis factor alpha and bipolar affective puerperal psychosis. Psychiatr Genet 2000;10:195–8.

Modabbernia A, Taslimi S, Brietzke E, Ashrafi M. Cytokine alterations in bipolar disorder: a meta-analysis of 30 studies. Biol Psychiatry 2013;74:15–25.

Moreno S, Farioli-Vecchioli S, Ceru MP. Immunolocalization of peroxisome proliferator-activated receptors and retinoid X receptors in the adult rat CNS. Neuroscience 2004;123:131–45.

Morgenweck J, Abdel-Aleem OS, McNamara KC, Donahue RR, Badr MZ, Taylor BK. Activation of peroxisome proliferator-activated receptor gamma in brain inhibits inflammatory pain, dorsal horn expression of Fos, and local edema. Neuropharmacology 2010; 58:337–45.

Morriss R, Mohammed FA. Metabolism, lifestyle and bipolar affective disorder. J Psychopharmacol 2005;19:94–101.

Mtiraoui N, Ezzidi I, Kacem M, Ben Hadj MM, Chaieb M, Haj Jilani AB, et al. Predictive value of interleukin-10 promoter genotypes and haplotypes in determining the susceptibility to nephropathy in type 2 diabetes patients. Diabetes Metab Res Rev 2009; 25:57–63.

Munkholm K, Brauner JV, Kessing LV, Vinberg M. Cytokines in bipolar disorder vs. healthy control subjects: a systematic review and meta-analysis. J Psychiatr Res 2013;47: 1119–33.

Myint AM, Kim YK, Verkerk R, Park SH, Scharpe S, Steinbusch HW, et al. Tryptophan breakdown pathway in bipolar mania. J Affect Disord 2007;102:65–72.

Nery FG, Monkul ES, Hatch JP, Fonseca M, Zunta-Soares GB, Frey BN, et al. Celecoxib as an adjunct in the treatment of depressive or mixed episodes of bipolar disorder: a double-blind, randomized, placebo-controlled study. Hum Psychopharmacol 2008; 23:87–94.

Neuman MG, Nanau RM, Shekh-Ahmad T, Yagen B, Bialer M. Valproic acid derivatives signal for apoptosis and repair in vitro. Clin Biochem 2013;46:1532–7.

Ng ZX, Kuppusamy UR, Iqbal T, Chua KH. Receptor for advanced glycation end-product (RAGE) gene polymorphism 2245G/A is associated with pro-inflammatory, oxidative-glycation markers and sRAGE in diabetic retinopathy. Gene 2013;521:227–33.

O'Brien SM, Scully P, Scott LV, Dinan TG. Cytokine profiles in bipolar affective disorder: focus on acutely ill patients. J Affect Disord 2006;90:263–7.

Ortiz-Dominguez A, Hernandez ME, Berlanga C, Gutierrez-Mora D, Moreno J, Heinze G, et al. Immune variations in bipolar disorder: phasic differences. Bipolar Disord 2007;9:596–602.

Padmos RC, Hillegers MH, Knijff EM, Vonk R, Bouvy A, Staal FJ, et al. A discriminating messenger RNA signature for bipolar disorder formed by an aberrant expression of inflammatory genes in monocytes. Arch Gen Psychiatry 2008;65:395–407.

Papiol S, Molina V, Desco M, Rosa A, Reig S, Sanz J, et al. Gray matter deficits in bipolar disorder are associated with genetic variability at interleukin-1 beta gene (2q13). Genes Brain Behav 2008;7:796–801.

Pereira FO, Frode TS, Medeiros YS. Evaluation of tumour necrosis factor alpha, interleukin-2 soluble receptor, nitric oxide metabolites, and lipids as inflammatory markers in type 2 diabetes mellitus. Mediators Inflamm 2006;2006:39062.

Pickup JC, Mattock MB, Chusney GD, Burt D. NIDDM as a disease of the innate immune system: association of acute-phase reactants and interleukin-6 with metabolic syndrome X. Diabetologia 1997;40:1286–92.

Ponce-Lopez T, Liy-Salmeron G, Hong E, Meneses A. Lithium, phenserine, memantine and pioglitazone reverse memory deficit and restore phospho-GSK3beta decreased in hippocampus in intracerebroventricular streptozotocin induced memory deficit model. Brain Res 2011;1426:73–85.

Pradhan AD, Manson JE, Rifai N, Buring JE, Ridker PM. C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. JAMA 2001;286:327–34.

Prossin AR, Zalcman SS, Evans SJ, McInnis MG, Ellingrod VL. A pilot study investigating tumor necrosis factor-alpha as a potential intervening variable of atypical antipsychotic-associated metabolic syndrome in bipolar disorder. Ther Drug Monit 2013;35:194–202.

Ragheb M. Ibuprofen can increase serum lithium level in lithium-treated patients. J Clin Psychiatry 1987;48:161–3.

Ragheb MA, Powell AL. Failure of sulindac to increase serum lithium levels. J Clin Psychiatry 1986;47:33–4.

Raison CL, Rutherford RE, Woolwine BJ, Shuo C, Schettler P, Drake DF, et al. A randomized controlled trial of the tumor necrosis factor antagonist infliximab for treatment-resistant depression: the role of baseline inflammatory biomarkers. JAMA Psychiatry 2013;70:31–41.

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Rao JS, Harry GJ, Rapoport SI, Kim HW. Increased excitotoxicity and neuroinflammatory markers in postmortem frontal cortex from bipolar disorder patients. Mol Psychiatry 2010;15:384–92.

Rapaport MH, Manji HK. The effects of lithium on ex vivo cytokine production. Biol Psychiatry 2001;50:217–24.

Raphael T, Parsons JP. Blood sugar studies in dementia praecox and manic-depressive insanity. Archieves Neurol Psychiatry 1921;5:687–709.

Ratz Bravo AE, Egger SS, Crespo S, Probst WL, Krahenbuhl S. Lithium intoxication as a result of an interaction with rofecoxib. Ann Pharmacother 2004;38:1189–93.

Regenold WT, Thapar RK, Marano C, Gavirneni S, Kondapavuluru PV. Increased prevalence of type 2 diabetes mellitus among psychiatric inpatients with bipolar I affective and schizoaffective disorders independent of psychotropic drug use. J Affect Disord 2002;70:19–26.

Remels AH, Langen RC, Gosker HR, Russell AP, Spaapen F, Voncken JW, et al. PPARgamma inhibits NF-kappaB-dependent transcriptional activation in skeletal muscle. Am J Physiol Endocrinol Metab 2009;297:E174–83.

Rizzo MR, Barbieri M, Marfella R, Paolisso G. Reduction of oxidative stress and inflammation by blunting daily acute glucose fluctuations in patients with type 2 diabetes: role of dipeptidyl peptidase-IV inhibition. Diabetes Care 2012;35:2076–82.

Ross KA. Evidence for somatic gene conversion and deletion in bipolar disorder, Crohn's disease, coronary artery disease, hypertension, rheumatoid arthritis, type-1 diabetes, and type-2 diabetes. BMC Med 2011;9:12.

Ruzickova M, Slaney C, Garnham J, Alda M. Clinical features of bipolar disorder with and without comorbid diabetes mellitus. Can J Psychiatry 2003;48:458–61.

Satoh-Asahara N, Sasaki Y, Wada H, Tochiya M, Iguchi A, Nakagawachi R, et al. A dipeptidyl peptidase-4 inhibitor, sitagliptin, exerts anti-inflammatory effects in type 2 diabetic patients. Metabolism 2013;62:347–51.

Sensi M, Pricci F, Andreani D, Di MU. Advanced nonenzymatic glycation endproducts (AGE): their relevance to aging and the pathogenesis of late diabetic complications. Diabetes Res 1991;16:1–9.

Shelley RK. Lithium toxicity and mefenamic acid. A possible interaction and the role of prostaglandin inhibition. Br J Psychiatry 1987;151:847–8.

Shoelson SE, Herrero L, Naaz A. Obesity, inflammation, and insulin resistance. Gastroenterology 2007;132:2169–80.

Slordal L, Samstad S, Bathen J, Spigset O. A life-threatening interaction between lithium and celecoxib. Br J Clin Pharmacol 2003;55:413–4.

Soares JC, Mallinger AG. Intracellular phosphatidylinositol pathway abnormalities in bipolar disorder patients. Psychopharmacol Bull 1997;33:685–91.

Soderlund J, Olsson SK, Samuelsson M, Walther-Jallow L, Johansson C, Erhardt S, et al. Elevation of cerebrospinal fluid interleukin-1ss in bipolar disorder. J Psychiatry Neurosci 2011;36:114–8.

Sourris KC, Forbes JM. Interactions between advanced glycation end-products (AGE) and their receptors in the development and progression of diabetic nephropathy — are these receptors valid therapeutic targets. Curr Drug Targets 2009;10:42–50.

Sparvero LJ, Asafu-Adjei D, Kang R, Tang D, Amin N, Im J, et al. RAGE (Receptor for Advanced Glycation Endproducts), RAGE ligands, and their role in cancer and inflammation. J Transl Med 2009;7:17.

Spranger J, Kroke A, Mohlig M, Hoffmann K, Bergmann MM, Ristow M, et al. Inflammatory cytokines and the risk to develop type 2 diabetes: results of the prospective population-based European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam Study. Diabetes 2003;52:812–7.

Stanley TL, Zanni MV, Johnsen S, Rasheed S, Makimura H, Lee H, et al. TNF-alpha antagonism with etanercept decreases glucose and increases the proportion of high molecular weight adiponectin in obese subjects with features of the metabolic syndrome. J Clin Endocrinol Metab 2011;96:E146–50.

Stertz L, Magalhaes PV, Kapczinski F. Is bipolar disorder an inflammatory condition? The relevance of microglial activation. Curr Opin Psychiatry 2013;26:19–26.

Stolk P, Souverein PC, Wilting I, Leufkens HG, Klein DF, Rapoport SI, et al. Is aspirin useful in patients on lithium? A pharmacoepidemiological study related to bipolar disorder. Prostaglandins Leukot Essent Fatty Acids 2010;82:9–14.

Svendal G, Fasmer OB, Engeland A, Berk M, Lund A. Co-prescription of medication for bipolar disorder and diabetes mellitus: a nationwide population-based study with focus on gender differences. BMC Med 2012;10:148.

Swayze VW, Andreasen NC, Alliger RJ, Ehrhardt JC, Yuh WT. Structural brain abnormalities in bipolar affective disorder. Ventricular enlargement and focal signal hyperintensities. Arch Gen Psychiatry 1990;47:1054–9.

Teixeira AL, Barbosa IG, Machado-Vieira R, Rizzo LB, Wieck A, Bauer ME. Novel biomarkers for bipolar disorder. Expert Opin Med Diagn 2013;7:147–59.

Toledo EM, Inestrosa NC. Activation of Wnt signaling by lithium and rosiglitazone reduced spatial memory impairment and neurodegeneration in brains of an APPswe/PSEN1DeltaE9 mouse model of Alzheimer's disease. Mol Psychiatry 2010;15:272–85.

Tsai SY, Yang YY, Kuo CJ, Chen CC, Leu SJ. Effects of symptomatic severity on elevation of plasma soluble interleukin-2 receptor in bipolar mania. J Affect Disord 2001;64:185–93.

Tsai SY, Chung KH, Wu JY, Kuo CJ, Lee HC, Huang SH. Inflammatory markers and their relationships with leptin and insulin from acute mania to full remission in bipolar disorder. J Affect Disord 2012;136:110–6.

Tynan RJ, Weidenhofer J, Hinwood M, Cairns MJ, Day TA, Walker FR. A comparative examination of the anti-inflammatory effects of SSRI and SNRI antidepressants on LPS stimulated microglia. Brain Behav Immun 2012;26:469–79.

Vadas P. The efficacy of anti-inflammatory agents with respect to extracellular phospholipase A2 activity. Life Sci 1982;30:155–62.

Vane JR, Botting RM. The mechanism of action of aspirin. Thromb Res 2003;110:255–8.

Verrotti A, D'Egidio C, Mohn A, Coppola G, Chiarelli F. Weight gain following treatment with valproic acid: pathogenetic mechanisms and clinical implications. Obes Rev 2011;12:e32–43.

Vlassara H, Palace MR. Diabetes and advanced glycation endproducts. J Intern Med 2002;251:87–101.

Wahlqvist ML, Lee MS, Chuang SY, Hsu CC, Tsai HN, Yu SH, et al. Increased risk of affective disorders in type 2 diabetes is minimized by sulfonylurea and metformin combination: a population-based cohort study. BMC Med 2012;10:150.

Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel RL, Ferrante Jr AW. Obesity is associated with macrophage accumulation in adipose tissue. J Clin Invest 2003;112:1796–808.

Wellen KE, Hotamisligil GS. Inflammation, stress, and diabetes. J Clin Invest 2005;115:1111–9.

Winham SJ, Cuellar-Barboza AB, Oliveros A, McElroy SL, Crow S, Colby C, et al. Genome-wide association study of bipolar disorder accounting for effect of body mass index identifies a new risk allele in TCF7L2. Mol Psychiatry 2013. Q12

Wu JD, Xu XH, Zhu J, Ding B, Du TX, Gao G, et al. Effect of exenatide on inflammatory and oxidative stress markers in patients with type 2 diabetes mellitus. Diabetes Technol Ther 2011;13:143–8.

Yazdani-Biuki B, Stelzl H, Brezinschek HP, Hermann J, Mueller T, Krippl P, et al. Improvement of insulin sensitivity in insulin resistant subjects during prolonged treatment with the anti-TNF-alpha antibody infliximab. Eur J Clin Invest 2004;34:641–2.

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