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# FURTHER EVIDENCE OF ACCELERATED AGING IN BIPOLAR DISORDER: FOCUS ON GDF-15

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**Abstract**

BACKGROUND: Bipolar disorder (BD) is a mood disorder associated with cardiovascular and metabolic diseases and premature aging. Growth differentiation factor 15 (GDF-15) has emerged as a biomarker for cardiovascular risk and aging. Our aim was to compare plasma levels of GDF-15 between BD patients and controls, and to evaluate whether they were associated with clinical parameters. METHODS: Forty-six patients with type I BD (23 in euthymia and 23 in mania) and 33 healthy controls were recruited for this study. Plasma levels of GDF-15 were measured by immunoassay. RESULTS: The levels of GDF-15 were significantly higher (p < 0.001) in patients with BD in comparison with controls. In patients, GDF-15 levels correlated with age (rho = 0.434; p = 0.003) and illness duration (rho = 0.502; p = 0.001). CONCLUSION: Our findings corroborate the view that BD is an illness associated with accelerated aging.

## 1. Introduction

Bipolar disorder (BD) is a chronic and often severe mood disorder characterized by alternating episodes of depression and mania. BD affects 3-5% of adolescents and adults [1–3]. BD is associated with substantial morbidity and mortality [4; 5], resulting not only from psychiatric symptoms, but also from a wide variety of comorbid medical problems including cardiovascular diseases (CVD), diabetes mellitus, obesity and thyroid diseases [6; 7].

As a leading cause of death in BD, CVD occur five times more frequently in adults with BD than in the general population [8; 9]. Moreover, BD patients manifest CVD up to 17 years earlier than adults without BD [10; 11]. The standardized mortality ratio for CVD is high for BD patients across all age groups, but is more pronounced in adults younger than 40 years-old [12]. Similarly, metabolic complications including diabetes are significantly more frequent in patients with BD than in the general population. Therefore, early prevention and management of CVD and metabolic syndromes in BD is of paramount importance.

The progressive nature of BD has received much attention in the last decade [13–15], leading to the concept of "neuroprogression" and staging models of BD [14; 16]. However, the neurobiological evidence supporting these hypotheses is still limited. Despite great efforts, biomarkers to monitor illness progression remain elusive and so far no biomarker has been clearly linked to morbidity and mortality in BD[17]. Therefore, candidate biomarkers for molecular staging of BD need to be explored.

Recently, a divergent member of the transforming growth factor-beta family, growth differentiation factor 15 (GDF-15), also known as macrophage inhibitory cytokine 1 (MIC-1), has emerged as a relevant biomarker for CVD and diabetes [18; 19]. GDF-15 has also been investigated for its role in the aging process, including age-related changes in the brain structure and cognitive decline. The association of this molecule with aging and longevity was highlighted by animal studies in which overexpression of GDF-15 resulted in the prolongation of lifespan [20]. As BD has been associated with accelerated aging [21; 22], we hypothesized that GDF-15 is a potential biomarker of BD progression. Accordingly, the aims of this study were: i) to compare the plasma levels of GDF-15 between patients with BD and controls; ii) to evaluate whether circulating levels of GDF-15 levels were associated with clinical parameters, especially illness course.

## 2. Methods

### 2.1 Subjects and clinical evaluation

Forty-six patients with type I BD diagnosed according to the DSM-IV-TR criteria were enrolled in this study. Of these, 23 were euthymic and 23 were manic. In addition, this study included a control group consisting of 33 age- and gender-matched healthy subjects recruited from the local community. All subjects were evaluated by an experienced

psychiatrist through the Mini-International Neuropsychiatric Interview [23].

Patients who met the following criteria were included: 1) aged 18-65 years; 2) DSM-IV-TR diagnosis criteria of type I BD; 3) at least one year of BD diagnosis. For each patient, the Young Mania Rating Scale (YMRS) [24] and the Hamilton Rating Scale for Depression (HRSD) [25] were used to assess the severity of manic and depressive symptoms, respectively. All patients were under treatment with mood stabilizers and/or antipsychotics.

The control group included only participants who did not have a psychiatric disorder (evaluated through Mini-International Neuropsychiatric Interview) or family history of major psychiatry disorders, suicide attempts, or completed suicides.

Subjects with dementia, infectious or autoimmune diseases, or who had used steroids, anti-inflammatory drugs, or antibiotics in the four weeks prior to the clinical evaluation were excluded from this research protocol. All subjects provided written informed consent before admission to the study. The Research Ethics Committee of the *Universidade Federal de Minas Gerais*, Brazil approved this study.

## 2.2 Sample collection and preparation

Plasma GDF-15 levels were measured in both groups. Peripheral venous blood samples were drawn by venipuncture in tubes containing heparin. Participants were in the fasting state and the blood was obtained on the same day of clinical assessment. The blood samples were centrifuged at 1,800 g for 10 min at 4°C for plasma separation. The Luminex® technique was applied to measure the plasma concentration of GDF-15 (Merck Millipore, Darmstadt, Germany). This assessment was performed blind to the clinical diagnosis.

## 2.3 Data analysis

The chi-square test was used to test for the difference of sex proportion between groups. The Shapiro-Wilk normality test was used to check whether the continuous variables follow a Gaussian distribution. Two groups (patients with BD *vs*. controls) were compared using the Mann–Whitney U test since data were

determined to not follow a normal distribution. Spearman's correlation analyses were performed to assess the correlation between GDF-15 levels and demographic and clinical variables in patients.

All data were analyzed using the SPSS for Window software (SPSS Inc.; Chicago, IL, USA). Two-tailed significance levels were set at 0.05.

## 3. Results

A total of 46 patients (17 males and 29 females) and 33 age- and gender-matched healthy controls (9 males and 24 females) were included in this study. Of 46 patients, 23 were euthymic and 23 were manic. The median age [interquartile range] of patients and controls were 50.5 [42.0 – 58.0] and 48.0 [38.5 – 54.0], respectively. There were no significant differences in sex and median age between patients with BD and controls as tested by Chi-square (p = 0.36) and Mann-Whitney test (p = 0.18), respectively. The median BD length [interquartile range] was 22.0 [13 - 32.25] years.

GDF-15 levels were significantly higher in BD patients (median [interquartile range] = 0.490 [0.398 – 0.875] pg/mL) than controls (0.275 [0.183 – 0.348] pg/mL) (Figure 1). There was no significant difference in GDF-15 levels between euthymic and manic patients.

A positive correlation was observed between age and GDF-15 plasma levels in

patients, rho = 0.434, p = 0.003, indicating that an increase in age was moderately associated with an increase in GDF-15 levels in patients. There was also a moderate positive correlation between illness length and GDF-15 levels, rho = 0.502, p = 0.001. There was no correlation between YMRS or HRSD scores and GDF-15 levels.

## 4. Discussion

In the current study, we showed that patients with BD presented increased plasma levels of GDF-15 when compared with controls. To our knowledge, this was the first controlled cross-sectional study that specifically evaluated GDF-15 levels in a cohort of BD patients. Our results were consistent with two recent proteomic studies showing that GDF-15 was one of the proteins that could distinguish BD patients from healthy controls [26; 27]. We also found that the older the patients with BD, the higher the GDF-15 levels. In addition, higher GDF-15 levels were associated with longer disease duration.

GDF-15 is primarily involved in inflammatory, apoptotic, and stress responses. It plays important roles in the development and progression of a wide variety of chronic conditions, such as coronary artery disease, atherosclerosis, obesity, insulin resistance, diabetes, and cognitive impairment [18; 19]. As shown in a cohort study of 984 patients, GDF-
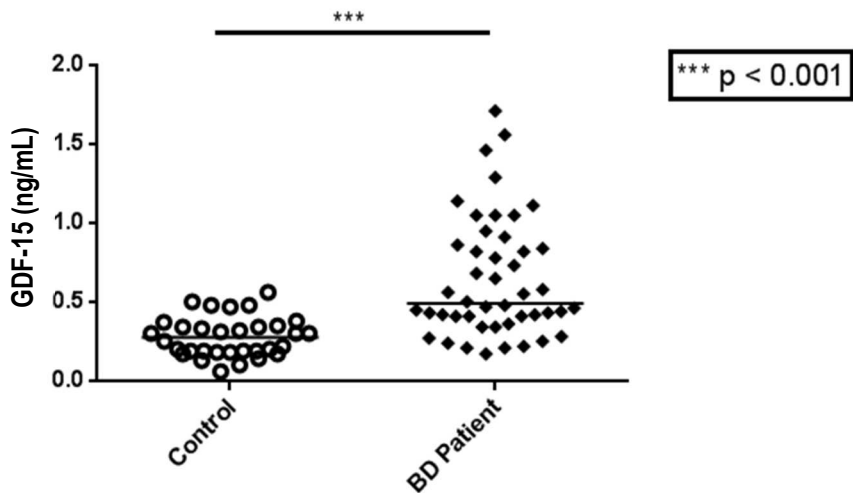


Figure 1: GDF-15 levels were significantly higher in BD patients than controls

15 levels were elevated in the early subclinical stage of CVD and predicted adverse outcomes and mortality in these patients [28]. GDF-15 is also associated with the prognosis of type 2 diabetes mellitus [29]. Altogether, these observations supported GDF-15 as a potential diagnostic and prognostic biomarker for CVD [30], obesity [30] and diabetes [31], conditions that are frequently comorbid with BD.

In addition to its involvement in CVD, GDF-15 was also associated with non-cardiovascular mortality [32]. Increased circulating levels of GDF-15 predicted all-cause mortality in the general population independent of multiple genetic and environmental risk factors for mortality including age, body mass index, smoking history, serum IL-6 and CRP levels, and telomere length [32]. It was hypothesized that the association between serum GDF-15 levels and all-cause mortality is related to the aging process, and accumulating evidence has supported GDF-15 as a biomarker of aging [33; 34]. In a prospective study of Uppsala seniors, plasma GDF-15 levels were also strong predictors of mortality in elderly community-dwelling individuals [35]. At the molecular level, GDF-15 influences several cellular processes implicated in aging, such as apoptosis [36], mitochondrial dysfunction [37], endoplasmic reticulum stress [38] and inflammatory response [39]. Furthermore, the expression of GDF-15 increases with age [35; 40] and is induced by many age-related stressors [40; 41]. Accordingly, there was evidence that GDF-15 levels may reflect the load of environmental toxicity [32], contributing to and/or indexing the mortality.

BD has been considered a condition of accelerated aging as a wide range of aging processes – low-grade inflammation, excessive oxidative stress, altered neurotrophic factors, mitochondrial dysfunction, and premature cellular senescence - occur in these patients [42–44]. The neuroprogression model of BD proposes that the cumulative exposure to environmental stresses and/or repeated mood episodes play a major role in the progression from early to late illness stages [16; 45–47]. We found a moderate positive correlation of GDF-15 with age and illness duration in the subjects with BD, the latter being an important parameter of illness staging. As GDF-15 circulating levels are associated with pathological aging and can be influenced by environmental factors [32], these results suggest that GDF-15 may be regarded as a candidate biomarker of neuroprogression and/or a biomarker to estimate the cumulative burden from environmental stresses and repeated mood episodes during the course of BD. The levels of GDF-15 did not show a significant difference between patients in euthymia and those in manic state, further suggesting that GDF-15 can be regarded as a marker of disease stage instead of disease state.

The role of GDF-15 in the central nervous system was largely investigated in animal models. Only a very limited studies have investigated its involvement in cognitive aging and dementia [33]. Higher concentrations of serum GDF-15 were associated with decreased grey matter volumes and white matter integrity, which were shown to mediate worse cognitive function [48; 49]. Brain structural changes in BD include enlargement of the third and lateral ventricles [50], decreased gray matter [51], and reduced volumes in certain the prefrontal cortex regions [50; 52]. It remains to be determined whether the changes in GDF-15 levels are associated with these brain structural changes in patients with BD.

Limitations of the study include the small sample size and the cross-sectional design. With larger sample size and improved statistical power in the future, we may assess the levels of GDF-15 in distinct mood states in these patients. We did not have a comparison of the levels of GDF-15 with other biomarkers implicated in BD physiopathology.

In summary, we showed that GDF-15 levels were increased in the plasma of BD patients and the levels were closely associated with illness duration, a major parameter for the staging of BD. Future investigations are needed to establish whether GDF-15 can be regarded as a biological marker for prognostic evaluation of BD. As demonstrated in animal studies [53], it is also possible that therapeutic interventions that modify GDF-15 levels might decrease mortality risk and increase longevity in BD patients.

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