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## Decreased Serum Hepatocyte Growth Factor (HGF) in Individuals with Bipolar Disorder Normalizes after Zinc and Anti-oxidant Therapy

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### Abstract

**Aim:** To assess serum HGF concentration in individuals with bipolar disorder and investigate the efficacy of zinc therapy on these levels.

**Subjects and methods:** Serum from 35 individuals diagnosed with bipolar disorder and 19 age and gender similar controls were tested for HGF concentration using ELISAs, and copper and zinc plasma levels using inductively-coupled plasma-mass spectrometry.

**Results:** HGF serum levels of individuals with bipolar disorder were significantly lower than age and gender similar controls ( $P = 0.0021$ ). HGF serum concentration was significantly lower in Bipolar patients pre-therapy ( $P = 0.0009$ ) and HGF levels normalized post-therapy. Zinc levels in these same individuals also normalized ( $P = 0.0046$ ) and patient's perceived severity of Bipolar symptoms significantly decreased after therapy ( $P = 0.0003$ ). We also found a significant direct correlation between Zinc and HGF serum concentration in the bipolar patients ( $P = 0.04$ ).

**Discussion:** These results suggest an association between low HGF levels and bipolar disorder and also demonstrate that zinc therapy may be associated with the normalization of HGF levels and decrease in severity of disease.

**Keywords:** bipolar disorder, hepatocyte growth factor, HGF

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## Introduction

Bipolar Disorder is characterized by episodes of mania and depression that are frequently acute, debilitating, and may be associated with gross social dysfunction and an elevated suicide rate.<sup>1-4</sup>

Recent findings indicate that the pathologic process of this disorder is involved in complex interactions between multiple susceptibility genes and environmental factors.<sup>5,6</sup>

More than two-thirds of people with bipolar disorder have at least one close relative with the disorder or with unipolar major depression, indicating that the disease has a genetic component. The monozygotic concordance rate for the disorder is 40%–70% and dizygotic twins have a 10%–23% concordance rate.<sup>7,8</sup>

There is also a correlation between DGKH (diacylglycerol kinase eta) and bipolar disorder. DGKH is a key protein in the lithium-sensitive phosphatidyl inositol pathway,<sup>9</sup> and more recently a link between environmental stress and schizophrenia and possibly bipolar disorder has been revealed.<sup>10</sup>

Recent advances in genetics, molecular and cellular biology, molecular neuroscience, and imaging technology have provided a variety of new and sophisticated approaches to evaluate the complex features of this disease. Important among these advances, high density DNA expression microarray technology has recently been widely adapted by scientists in the search for susceptibility genes for bipolar disorder,<sup>11-13</sup> and has helped reveal gene candidates coding for proteins related to mitochondrial function and apoptosis, glutamate receptors, markers of GABAergic neurons, molecular chaperones, and oligodendrocyte proteins are differentially expressed in postmortem brain tissue, peripheral blood cells, and olfactory neuroepithelium between control and bipolar disorder subjects.<sup>14-16</sup>

There is also an emerging body of data suggesting that oxidative stress may be associated with the pathophysiology of Bipolar Disorder,<sup>17-19</sup> including increased levels of glutamate found in the brains of patients with mood disorders.<sup>20</sup>

Hepatocyte growth factor (HGF), an 82 kDa, 674 amino acid residue heterodimeric glycoprotein, was originally isolated from rat platelets.<sup>21,22</sup> This growth factor has also been called scatter factor,

hepatopoietin A, and mammary growth factor.<sup>23</sup> It is one of a small family of factors lacking significant homology with other known growth factors, but including an HGF-like factor known as macrophage stimulating protein (MSP).<sup>24-27</sup> HGF has mitogenic, morphogenic, and motogenic effects on hepatocytes, as well as endothelial, mesenchymal and hematopoietic cell types,<sup>26,28,29</sup> and demonstrates noticeable species cross-reactivity.<sup>30</sup>

HGF regulates cell growth, cell motility, and morphogenesis by activating a tyrosine kinase signaling cascade after binding to the proto-oncogenic c-Met receptor (translated by the MET gene). HGF is secreted by mesenchymal cells and, although it was first considered to exert biological effects only on specific target cells, it has since been demonstrated to mediate inflammatory responses to tissue injury, and regulate cell growth, cell motility, and morphogenesis in a wide variety of cells. Its ability to stimulate branching morphogenesis, cell migration, survival and proliferation gives it a central role in angiogenesis, tissue regeneration, as well as tumorigenesis.<sup>31-37</sup>

Signaling by HGF has also been found to have anti-inflammatory, antifibrotic, and pro-regenerative activity on various types of tissue. But it seems to be particularly active in the nervous system, where it has been found to have neurotrophic and angiogenic activity on CNS neurons, promote both the survival of neurons and the regeneration of injured nerves, and function as a target-derived axonal chemoattractant, guiding axons to their target. As a result, it plays significant roles in the development of the CNS.<sup>38</sup>

Zinc is well known as one of the most important trace elements in the body. Dietary zinc deficiency is associated with a variety of physiological defects including anorexia, skin lesion, and growth retardation.<sup>39</sup> Mechanistic studies demonstrated that zinc deficiency affects a large number of hepatic genes involved in multiple cellular functions. In particular, zinc deficiency has been shown to down-regulate hepatic gene expression of metallothionein (MT), insulin-like growth factor I (IGF-I), insulin-like growth factor binding protein 1 (IGFBP1), cyclin D1, and HGF, which are involved in cell proliferation.<sup>40-42</sup>

Genes involved in GABAergic neurotransmission (43.44) and decreased levels of serum GABA<sup>45</sup> have been associated with Bipolar Disorder. HGF has been



shown to modulate GABAergic activity<sup>46</sup> and enhance NMDA currents in the hippocampus.<sup>47</sup>

Because of the potential association between HGF, GABA and neurological development and differentiation, and its association with the etiology of neurological diseases, and because zinc deficiency may down regulate HGF synthesis, we tested patients with Bipolar Disease for serum concentration of HGF and then compared those levels with zinc and copper levels as well as perceived severity of disease, before and after zinc therapy.

## Materials and Methods

### Elisa to measure serum HGF (Elisa Kit, R&D Systems, Minneapolis, Minn.)

All reagents and specimens were equilibrated to room temperature before the assay was performed. A 1:51 dilution of the patient samples was prepared by mixing 10  $\mu$ l of the patient's sera with 0.5 ml of Serum Diluent. One hundred microliters of calibrators (20–200 Eu/ml antibodies), positive and negative control serums, serum diluent alone, and diluted patient samples were added to the appropriate microwells of a microculture plate (each well contained affinity purified polyclonal IgG to HGF). Wells were incubated for 60 minutes ( $\pm 5$  min) at room temperature, then washed 4x with wash buffer. One hundred microliters of pre-diluter anti-human IgG conjugated with HRP was added to all microwells, incubated for 30 minutes ( $\pm 5$  min) at room temperature, then wash 4x with wash buffer. One hundred microliters of enzyme substrate was added to each microwell. After approximately 30 minutes at room temperature, the reaction was stopped by adding 50  $\mu$ l of 1M sulfuric acid, then the wells were read at 405 nm with an ELISA reader (BioRad Laboratories, Inc., Hercules, CA, USA).

### Copper and zinc serum concentration

Assay to establish copper and zinc plasma concentration was performed by LabCorp, Inc. (Naperville, IL 60563) using inductively-coupled plasma-mass spectrometry.

### Serums

All serums, experimental and control serums were treated in an identical fashion—frozen at  $-70^{\circ}\text{C}$  immediately after collection and cell/serum

separation, then stored at  $-70^{\circ}\text{C}$  until thawed for use in ELISAs.

## Subjects

### Experimental and controls

Serum from individuals with diagnosed (psychiatric interview using DSM criteria) Bipolar Disorder ( $n = 35$ ; 18 male; mean age  $34 \pm 12$  years) and controls ( $n = 19$ ; 10 male mean age  $41 \pm 14$  years) was obtained from patients at the Health Research Institute/Pfeiffer Treatment Center. Most of these individuals were previously diagnosed with Bipolar Disorder, then all were assessed using the modified Mood Disorder Questionnaire, before presenting at the Pfeiffer Treatment Center, Warrenville, IL.\*

All patients in this study received zinc and B-6 therapy.

Patients ( $n = 35$ ) for this study were chosen randomly as they presented to The Pfeiffer Treatment Center. At the time of the blood draw, six were taking anti-depressants, four were taking anti-epileptic drugs, eight were taking anti-psychotics, eight were taking lithium and nine presented not taking any associated drugs. We did not find any significant difference in HGF serum concentration in any of these groups (ANOVA;  $P = 0.995$ ;  $F = 0.157$ ). All patients presented after having mixed manic and depression episodes.

Patient consent was obtained from all patients involved in this study.

Controls were normal healthy volunteers, all employees of the Pfeiffer Treatment Center.

### Severity of disease

A modified questionnaire asking patients to rank the severity of the signs and symptoms of Bipolar Disease, found in the Mood Disorder Questionnaire,<sup>56</sup> was used to determine the overall severity. Patients were asked to rate on a scale of 0–5 (5 being the highest), behaviors such as; irritability and anger, lack of ability to focus/concentrate, obsessive behavior, trouble sleeping, paranoia, migraines, intrusive thoughts, anxiety, depression and panic. We evaluated the

\*The Pfeiffer Treatment Center is a comprehensive treatment and research center, specializing in the care of with neurological disorders, including Bipolar Disorders.



overall severity of Bipolar Disease by establishing the mean of all of the scores for each patient. The overall bipolar behavior assessment includes assessment of all the behaviors (above).

### Zinc and anti-oxidant therapy

Individuals in this study who presented to the Pfeiffer Treatment Center with Bipolar Disease were tested for zinc, copper and anti-oxidant levels. Based on deficiencies, they were then prescribed the appropriate dose of anti-oxidants. Pre-therapy patients represent those who were tested when they first presented and were not previously taking any zinc or anti-oxidants. Post-therapy patients received anti-oxidant therapy (One dose—Vitamin C (125 mg), E (50 IU), B6 (37.5 mg) as well as Magnesium (11 mg), and Manganese (3.75 mg) if warranted), and zinc supplementation (as zinc picolinate) (25 mg), for a minimum of 8 weeks. Pre and post therapy patients were different groups.

### Statistics

Inferential statistics were derived from unpaired t-test and odds ratios with 95% confidence intervals. ANOVA was used to assess variance between groups.

### Results

Serum from 35 individuals diagnosed with bipolar disorder and 19 age and gender similar controls were tested for HGF concentration using ELISAs, and copper and zinc plasma levels were established using inductively-coupled plasma-mass spectrometry (Labcorp, Naperville IL).

HGF serum levels of individuals with bipolar disorder were significantly lower than age and gender similar controls ( $P = 0.0018$ ) (Table 1). HGF serum

**Table 1.** HGF levels in bipolar disorder patients and controls.

	HGF bipolar	HGF controls
Mean	402.3	573.9
SD	204.5	142.8
SEM	34.6	32.8
N	35	19

**Notes:** The two-tailed  $P$  value equals 0.0021;  $t = 3.2457$ ;  $df = 52$ ; Standard error of difference = 52.859.

concentration before zinc therapy was significantly lower in Bipolar patients when compared to levels post-therapy ( $P = 0.0009$ ) and HGF levels normalized (increased to the level of controls) post-therapy (Table 2). We found a dose dependent correlation between zinc and HGF ( $P = 0.04$ ) (Fig. 1), and zinc levels in these same individuals also rose ( $P = 0.0046$ ) and normalized post-therapy (Table 3) (normal zinc is 90–150  $\mu\text{g}/\text{dL}$ ). Copper levels decreased post therapy, but not significantly ( $P = 0.59$ ). Patient's perceived severity of overall Bipolar symptoms decreased significantly post therapy ( $P = 0.0003$ ) (Table 4).

### Discussion

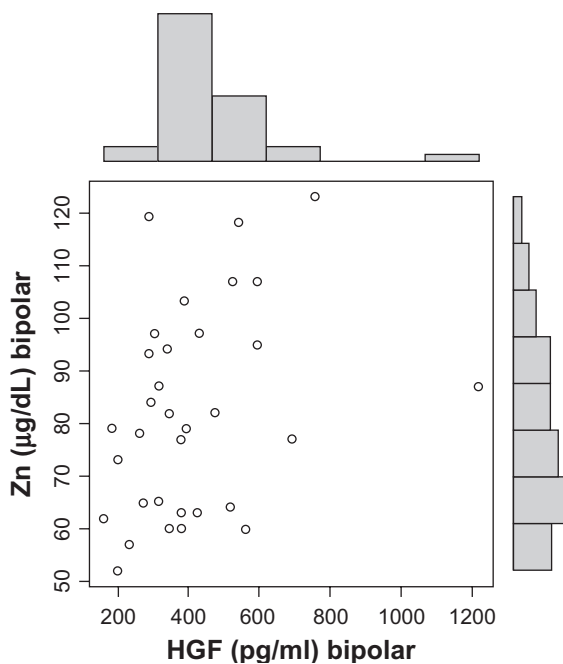
HGF has been found to be associated with a variety of diseases of the CNS. For instance, immunohistochemistry using anti-HGF antibody has revealed more intense immunolabeling in Alzheimer's disease (AD) than in control brains, and there appears to be a significant correlation between CSF HGF levels and white matter high-signal foci determined on brain magnetic resonance imaging (MRI) in AD patients.<sup>48</sup> In Amyotrophic lateral sclerosis (ALS), overexpression of hepatocyte growth factor (HGF) in the nervous system attenuates motoneuron death and axonal degeneration and prolongs the life span of transgenic mice overexpressing mutated  $\text{Cu}^{2+}/\text{Zn}^{2+}$  superoxide dismutase.<sup>49</sup> Overexpression of HGF after gene transfer prevented neuronal death in a Parkinson's Disease rat model,<sup>50</sup> and decreased levels of HGF has been found in autistic children with GI disease.<sup>51</sup>

Previous studies have shown a positive correlation between oxidative stress markers and bipolar disorder and have suggested a role of mitochondrial dysfunction in the etiology of the disease.<sup>52</sup>

**Table 2.** HGF levels pre and post therapy in bipolar disorder patients.

	HGF pre-therapy	HGF post-therapy
Mean	314.1	534.8
SD	108.4	244.6
SEM	23.7	65.4
N	21	14

**Notes:** The two-tailed  $P$  value equals 0.0009;  $t = 3.6511$ ;  $df = 33$ ; Standard error of difference = 60.449.



**Figure 1.** Significant dose dependent correlation between zinc and HGF levels ( $P = 0.04$ ).

Mitochondria-related genes may be abnormally expressed in bipolar disorder. Increasing evidence has shown the presence of mitochondrial dysfunctions such as deletion, mutation and abnormal expression of mitochondria-related genes, increased anaerobic glycolysis, and impaired phospholipid metabolism. Because mitochondrial oxidative phosphorylation is the major resource for the generation of reactive oxygen species, mitochondrial dysfunction indicates that oxidative stress may occur in bipolar disorder and that oxidative stress induced damage may be prevented by mood-stabilizing treatment.<sup>53</sup>

Zinc supplementation has also been found to prevent liver cell injury through attenuation of

**Table 3.** Zn levels pre and post therapy in bipolar disorder patients.

	Zn pre therapy	Zn post therapy
Mean	74.0	92.4
SD	13.9	21.5
SEM	3.1	5.7
N	20	14

**Notes:** The two-tailed  $P$  value equals 0.0046;  $t = 3.0490$ ;  $df = 32$ ; Standard error of difference = 6.044.

**Table 4.** Overall severity of bipolar symptoms pre and post therapy.

	Overall severity pre-therapy	Overall severity post-therapy
Mean	3.64	2.54
SD	0.74	0.61
SEM	0.17	0.18
N	19	11

**Notes:** The two-tailed  $P$  value equals 0.0003;  $t = 4.1391$ ;  $df = 28$ ; Standard error of difference = 0.265.

oxidative stress,<sup>54</sup> and there is evidence suggesting that alcohol-induced liver damage initiates hepatocyte proliferation, and zinc supplementation accelerates liver regeneration, through up-regulating cell proliferation-related proteins such as HGF.<sup>55</sup>

Our results demonstrate that HGF is significantly lower in Bipolar patients compared to controls and we suggest a potential role for HGF deficiency in the etiology of Bipolar Disease by modulating NMDA and GABAergic activity.

The present data, which demonstrates a dose dependent relationship between zinc and HGF, raise the intriguing possibility that HGF levels are raised by zinc therapy and that these higher levels may be associated with improved symptoms, also suggesting that HGF may be playing a role in the etiology of the disease.

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## Disclosure

This manuscript has been read and approved by the author. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The author and peer reviewers of this paper report no conflicts of interest. The author confirms that they have permission to reproduce any copyrighted material.



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