Nutrition and Metabolic Insights

ORIGINAL RESEARCH

Decreased Zinc and Increased Copper in Individuals with Anxiety

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Abstract

Aim: To assess plasma zinc and copper levels in individuals with anxiety and to test the hypothesis that there is a relationship between copper and zinc concentration and improved symptoms.

Subjects and methods: Serum from 38 individuals with anxiety and 16 neurotypical age, gender and size similar controls were tested for plasma zinc and copper concentration using inductively-coupled plasma-mass spectrometry. Zinc and copper levels, pre and post therapy, were compared and assessed for perceived anxiety symptoms.

Results: In this preliminary study, individuals with anxiety had significantly higher plasma levels of Cu ($P = 0.0348$), Cu/Zn ($P = 0.0493$) and lower Zn ($P = 0.0294$) compared to controls. Zn levels normalized (increased to the normal range) and Cu/Zn significantly decreased after zinc therapy ($P = 0.0004$, $P = 0.0033$, respectively), but Cu did not significantly decrease (0.3577). These same patients improved significantly with respect to perceived overall symptoms after zinc and anti-oxidant therapy ($P = 0.013$).

Discussion: These results suggest an association between Zn plasma levels and individuals with anxiety, demonstrate that zinc therapy is effective in increasing zinc plasma levels, and show that zinc supplementation may play a role in improved symptoms.

Keywords: anxiety, zinc, vitamin B-6, zinc therapy

Nutrition and Metabolic Insights 2011:4 1–5

doi: 10.4137/NMI.S6349

This article is available from http://www.la-press.com.

Introduction

Anxiety is a normal emotional response to a threat or potential threat. However, when this emotion is inappropriate, extreme and persistent, and is not proportionate to the nature of the peril, it is classified as pathological.[1,2] In response to threatening situations, the feeling of anxiety is usually accompanied by emotional stress, which involves behavioral, expressive and physiological features, such as an avoidance of the source of the danger, assuming defensive postures and increasing blood pressure, respectively.[1,3]

Anxiety disorders are the most common class of psychiatric disorders in the US[4] and many other countries.[5–8] Yet, population-based studies have shown that this disease frequently goes untreated.[9,10] Anxiety is implicated in a number of psychiatric disorders, such as depression, panic attacks and post-traumatic stress disorder[2] and affects approximately 30% of the US population,[4] and one-eighth of the total population worldwide.[11] This imposes a social burden that amounts to billions of dollars each year.[12]

Zinc has a unique and extensive role in biological processes. Since the discovery of this element as an essential nutrient for living organisms,[13–15] many diverse biochemical roles for it have been identified. These include roles in enzyme function,[16] nucleic acid metabolism,[17,18] cell signaling[19] and apoptosis.[20] Zinc is essential for physiological processes including growth and development,[21] lipid metabolism,[22] brain and immune function.[21,23]

Dietary factors that reduce the availability of zinc are the most common cause of zinc deficiency, however, inherited defects can also result in reduced zinc. Both nutritional and inherited zinc deficiency produce similar symptoms, such as dermatitis, diarrhoea, alopecia and loss of appetite.[24] With more prolonged deficiency causing growth impairment and neuropsychological changes such as emotional instability, irritability and depression.[25–28]

Low intracellular zinc has been found to be associated with DNA damage, oxidative stress, antioxidant defenses, and DNA repair,[29,30] and zinc may serve as an important anti-oxidant.[31]

Because of the potential association between zinc and the etiology of neurological diseases, we tested patients with anxiety for plasma zinc concentration, and compared those levels with perceived symptoms, pre and post zinc therapy.

Materials and Methods

Subjects

Experimental and controls

Serum from individuals with diagnosed anxiety (N = 38; 18 female; mean age 35.1 +/– 19.2 years; mean weight 141.2 +/– 48.8 lbs) and controls (N = 16; 8 female; mean age 41.3 +/– 27.4 years; mean weight 145.3 +/– 43.3 lbs) was obtained from patients presenting at the Health Research Institute/Pfeiffer Treatment Center. There was not a significant difference in age ($P = 0.23$) or weight ($P = 0.77$) between experimental and control individuals. Most of individuals with anxiety were diagnosed using The Hamilton Rating Scale for Anxiety before presenting for treatment at the Pfeiffer Treatment Center, Warrenville, Il*.

When comparing anxiety patients who were not taking drug therapy (N = 20) with those taking therapy (SSRIs (N = 6), anti-anxiety (N = 4), anti-convulsants (N = 2), stimulants (N = 2), blood pressure medication (N = 4), and sedatives (N = 2)), there was no significant difference in Cu ($P = 0.636$), Zn ($P = 0.14904$), Cu/Zn ($P = 0.555$), overall symptoms ($P = 0.467$) or specific anxiety symptoms ($P = 0.841$).

Patient consent was obtained from all patients involved in this study and this study was approved by the IRB of the Health Research Institute/Pfeiffer Treatment Center*.

Severity of disease

A modified Hamilton Scale was used to determine the severity of depression. Patients were asked to rate their depressive behavior such as; irritability and anger, lack of ability to focus/concentrate, racing thoughts, trouble sleeping, light sensitivity, migraines, OCD behavior, intrusive thoughts, overall anxiety, disorganization, panic, obsessive behavior, and overall anxiety. The patients were rated on a scale of 0–5 (5 being the most severe) for each of these behaviors. We evaluated the overall severity of anxiety behavior by establishing the mean of all of the scores for each patient.

Zinc and anti-oxidant therapy

Individuals in this study who presented to the Pfeiffer Treatment Center with anxiety were tested for zinc, copper and anti-oxidant levels. Based on deficiencies,

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

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 (Vitamin C, E, B-6 as well as Magnesium, and Manganese if warranted), and zinc supplementation (as zinc picolinate), daily, for a minimum of 8 weeks.

Plasma

All experimental and control plasmas were treated in an identical fashion. Blood was drawn into tubes containing EDTA as an anti-coagulant, refrigerated and sent to LabCorp, Naperville Il for separation and analysis.

Copper and zinc serum concentration

Copper and zinc plasma concentration was performed by LabCorp, Inc. (Naperville, IL 60563) using inductively-coupled plasma-mass spectrometry, as previously described.[32]

Statistics

Inferential statistics were derived from t-test with 95% confidence intervals.

Results

Individuals with anxiety had significantly higher plasma levels of Cu ($P = 0.0348$), Cu/Zn ($P = 0.0493$) and lower Zn ($P = 0.0294$) compared to controls (Table 1).

Twenty of the 38 anxiety patients (chosen randomly) were given zinc and vitamin B-6 therapy. Zn levels normalized (increased to the normal range) and Cu/Zn significantly decreased after zinc and B-6 therapy ($P = 0.0004$, $P = 0.0033$, respectively), but Cu did not significantly decrease (0.3577) (Table 2).

Symptoms (a scale of 1 to 5; 5 being the most symptomatic) of these same patients improved significantly post therapy ($P = 0.013$) (Table 3).

Table 1. Cu, Cu/Zn and Zn serum concentration (mg/dL) in anxiety patients compared to controls.

	Cu anxiety	**Cu controls**
Mean	101.58	84.56
SD	26.21	26.68
N	38	16
The two-tailed *P* value equals 0.0348		
	Cu/Zn anxiety	**Cu/Zn controls**
Mean	1.42	1.14
SD	0.46	0.48
N	38	16
The two-tailed *P* value equals 0.0493		
	Zn anxiety	**Zn controls**
Mean	74.47	87.69
SD	16.99	25.43
N	38	16
The two-tailed *P* value equals 0.0294		

Note: Significant differences in zinc and copper concentrations (mg/dL) and Cu/Zn between individuals with anxiety and neurotypical controls.

Discussion

The results reported here support previous findings of our lab and others who have found zinc deficiency in patients with depression,[33–35] and anxiety,[36] and have suggested zinc homeostasis for possible therapy.[37–39]

In addition, elevated copper has been associated with women having a history of post-partum depression[40] and clinical depression has been associated with high copper in patients with Wilson's disease.[41]

There is much support for the role of GABA and glutamate in mood disorders, particularly anxiety and depression.[42] Zinc has also been found to be associated with GABA and glutamate regulation, particularly through anxiolytic activity, modulating GABAergic inhibition and seizure susceptibility.[43–45] Zinc deficiency has also been found to be associated with GABAergic impairment.[46]

Zinc is well known as one of the most important trace elements in the body. Dietary zinc deficiency

Table 2. Cu, Cu/Zn and Zn serum concentration (mg/dL) in anxiety patients pre and post therapy.

	Cu anxiety pre therapy	**Cu anxiety post therapy**
Mean	101.58	93.8
SD	26.21	37.15
N	38	20
The two-tailed *P* value equals 0.3577		
	Zn anxiety pre therapy	**Zn anxiety post therapy**
Mean	74.47	92.85
SD	16.99	18.75
N	38	20
The two-tailed *P* value equals 0.0004		
Group	**Cu/Zn anxiety pre therapy**	**Cu/Zn anxiety post therapy**
Mean	1.42	1.03
SD	0.46	0.45
N	38	20
The two-tailed *P* value equals 0.0033		

Note: Significant differences in zinc and Cu/Zn between individuals with anxiety pre and post therapy.

Table 3. Anxiety symptoms pre and post therapy.

Anxiety symptoms pre therapy	Anxiety symptoms post therapy
Mean = 3.05643 Standard deviation = 0.72578 N = 16 ***P* = 0.0133**	Mean = 2.11176 Standard deviation = 1.16514 N = 22

Note: Severity of anxiety symptoms decrease significantly after zinc therapy.

is associated with a variety of physiological defects including anorexia, skin lesion, and growth retardation.[47] 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.[48–50]

Studies have shown a potential association between oxidative stress and the etiology of anxiety. As an example, oxidative stress-related anxiety can be reversed in mice upon inhibition of NADPH oxidase or phosphodiesterase-2, enzymes that are indirectly implicated in oxidative stress mechanisms.[51] Surprisingly, diazepam, a well-known anxiolytic, does not fully reverse oxidative stress-related anxiety.[51] These results point to a possible utility for antioxidants in the prevention or reduction of anxiety. Further research will be necessary to show whether anxious subjects need more antioxidants than non-anxious subjects. Recent work[51,52] has shown that some dietary polyphenols have both anxiolytic and antioxidant effects, which may be beneficial to anxious subjects. The potential relationship between oxidative stress and anxiety may generate interest in antioxidant therapy.

Zinc supplementation has also been found to prevent liver cell injury through attenuation of oxidative stress,[53] 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.[54]

Based on the results presented in this study, we suggest that the low levels of zinc, possibly associated with concurrent oxidative stress, may cause lower GABA and glutamate, having an anxiogenic effect, and that zinc supplementation, raising GABA levels, may help improve anxiety symptoms. To evaluate this possible association, future studies will assess more patients with anxiety and evaluate GABA and glutamate levels along with zinc concentration, pre and post zinc therapy.

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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