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Copper in depressive disorder: A systematic review and meta-analysis of observational studies

Ni Mengmei, You Yiping, Chen Jinyao*, Zhang Lishi*

Department of Nutrition, Food Safety and Toxicology, West China School of Public Health and Healthy Food Evaluation Research Center, Sichuan University, Chengdu 610041, Sichuan, China

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ABSTRACT

Copper (Cu) has been associated with mental disorders such as autism and epilepsy. So far, publications evaluating copper levels in patients with depressive disorder showed conflicted results. To derive a comprehensive estimation of the relationship between body burden of copper and depressive disorder and explore the possible role of copper in mental health, we performed a systematic review and meta-analysis. Relevant published data were obtained by searching PubMed, Web of Science, Chinese National Knowledge Infrastructure (CNKI) and Chinese Biomedical Database (CBM) before October 10, 2017. Weighted mean difference (WMD) with a 95% confidence interval (95%CI) was calculated using STATA 12.0. A total of 21 studies with 1487 patients and 943 controls were collected in this meta-analysis. Pooled analysis found that patients with depression had higher blood levels of copper than the controls without depression, while there was no difference of copper content in hair between the two groups. Subgroup analysis suggested that age had influence on the relationship between copper and depression. No evidence of publication bias was observed. This meta-analysis suggests that increased levels of blood copper might be associated with depressive disorder and therefore the possible role of copper as a biomarker of depression.

1. Introduction

Copper (Cu) is an essential element in mammalian nutrition. As an essential component, it acts as an electron donor or acceptor of multiple metalloenzymes (Stern et al., 2007). The main biological function of copper is to take part in maintaining hematopoietic function, affect energy metabolism and neurobehavioral and immune function (Uriuadams and Keen, 2005). Copper homeostasis is important to human health, and either copper deficiency or excess could cause health issues. Wilson disease (WD) is characterized by massive deposition of copper ions in the body, causing damage to multiple organs. Patients with WD often suffer from mental illness, depression and anxiety disorders (Chan et al., 2005).

Depression, as a mental health disorder, has become a global issue. In 2014, epidemiological data published in "*Nature*" showed that the prevalence rates of depression range from less than 3% in Japan to 22.5% in Afghanistan (Smith, 2014). According to a recent report from World Health Organization (2017), the total number of people with depression in the world was estimated to be 322 million in 2015 and depression is ranked by World Health Organization as the single largest contributor to global disability (7.5% of all years lived with disability in 2015) and also the major contributor to suicide deaths, close to 800 000 per year. The cause of depression is complex. It is the result of common effect of the biological, psychological and social factors. Genetic factors, neurobiochemical changes (5-hydroxytryptamine, 5-HT; norepinephrine, NE; dopamine, DA), neuroendocrine (hypothalamic-pituitary-adrenal (HPA) axis), cytokines (tumor necrosis factor, TNF-α;interleukin, IL-1β), neurotrophic factor (brain-derived neurotrophic factor, BDNF) and oxidative stress are all thought to be involved in the onset and progress of depression (Young et al., 2016). As an active ingredient of various enzymes, copper participates in the regulation of neurotransmitter and receptor function. It may affect the activation and concentration of noradrenaline and 5-HT. High copper levels could also block the function of dopamine β-hydroxylase, which is highly concentrated in locus coeruleus, resulting in impaired noradrenaline synthesis (Kornhuber, 1994). Thus, it has been suggested that cooper may play an important role in mental function. Meta-analysis showed that blood copper levels in patients with autistic or Alzheimer's disease were significantly higher than the controls (Saghazadeh et al., 2017; Li et al., 2017a), and blood copper concentrations were altered in patients receiving antiepileptic drugs (Saghazadeh et al., 2015).

Research has been carried out to investigate into the relationship

* Corresponding author.
E-mail addresses: umbrellayy@163.com (J. Chen), lishizhang_56@163.com (L. Zhang).

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between copper and depression, however, ended up with mixed conclusions. For instance, some studies (e.g. Fernández-González et al., 1998; Crayton and Walsh, 2007) showed that the concentration of copper in patients with depression was lower than that in the control group without depression. Maes et al. (1997), Salustri et al. (2010) and Styczen et al. (2016)suggested that there was no significant difference in serum concentration of copper between the patients and control group. While some other studies (Manser et al., 1989; Narang et al., 1991; Yu et al., 1997a; Schlegel-Zawadzka et al., 1999a; Chang et al., 2001; Ma et al., 2006; Wan et al., 2008; Liu, 2008; Li, 2014; Alghadir et al., 2015; Szkup et al., 2016) suggested that the depressed patients had higher levels of copper than in the control group without depression. Giving these conflicted reports, we conducted this systematic review and meta-analysis to pool the results of relevant studies on the role of copper in depression, in order to explore the possible association between copper and depression and increase the power of the conclusions.

2. Methods

2.1. Search strategy

PubMed, Web of Science, Chinese National Knowledge Infrastructure (CNKI), and Chinese Biomedical Database (CBM) were searched with the searching terms: “depressive disorder” or “depression” and “copper”. Language was limited to English or Chinese, and last search was updated on October 10, 2017. We also evaluated their reference lists in the selected studies and review articles to search for additional studies via Google Scholar to avoid missing studies. Only published studies with full-text articles were included.

2.2. Selection criteria

Studies eligible for this meta-analysis had to meet all the following inclusion criteria: (1) human study, (2) case-control study or prospective study, (3) determination of copper in blood or in hair, (4) depressive patients were clinical diagnosed according to the universally accepted diagnostic criteria, (5) data of copper levels for both patients and control subjects (sample size, mean, standard deviation at least).

The exclusion criteria were as follows: (1) conference abstracts, reviews, case reports and commentaries that fails to provide original data for analysis, (2) animal experiments, (3) studies reported duplicated data, (4) studies with participants on depression during pregnancy or postpartum depression, (5) studies with the patients who had other cognitive impairment or depression was a concomitant symptom of other diseases (e.g. WD and bipolar affective disorder).

2.3. Data extraction and quality assessment

The following variables from each publication were collected, i.e., first author's last name, year of publication, country where the study was performed, language, sample size, subjects gender, the mean age and corresponding standard deviation (or the age range) of the two groups, diagnostic criteria for depression, samples and methods of copper determination. The mean copper levels and the corresponding standard deviations were also extracted for main data analysis. Two independent reviewers extracted the above variables.

The quality of the included studies was evaluated by the Newcastle–Ottawa Scale (NOS) (Wells et al., 2014). Two independent reviewers scaled the studied separately. For the purpose of this analysis, studies with ≥ 5 stars were considered high quality and were included; those with ≤ 4 stars were considered low quality and excluded. Any disagreement as to study quality or data extraction was resolved by discussion with a third reviewer until consensus.

2.4. Data analysis

All statistical analyses were performed using STATA 12.0 (Stata Corp, College Station, TX, USA). We converted the unit of blood copper to micromolar per liter (μmol/L) (The molecular weight of copper used is 63.5). Besides, in some articles, the data was only available for male and female or varying severity, separately. The following formulas were calculated to combine data:

$$\overline{x}_c = \frac{\sum^{\overline{x}_i} n_i}{N} s_C^2 = \frac{\sum^{(n_i-1)} s_i^2 + \sum^{n_i} \overline{x}_i^2 - N\overline{x}_c^2}{N-1}$$

$\overline{x}_c$: the pooled mean; s_C: the pooled standard deviation; n_i: the sample size of each group; $\overline{x}_i$: the mean of each group; s_i: the standard deviation of each group; N: total sample size.

Heterogeneity amongst studies was evaluated using the chi-squared test and inconsistency index (I^2).To pool studies with significant heterogeneity ($I^2 \geq 50\%$, $P \leq 0.1$), a random effects model was applied, but when no significant heterogeneity was detected ($I^2 < 50\%$, $P > 0.1$), a fixed effects model was adopted to calculate the weighted mean difference (*WMD*).

To find the possible sources of heterogeneity, subgroup analysis was used to identify the possible associations between the levels of copper and other relevant characteristics of studies (the age of cases and controls, language of the article, and the country where the study was performed) and sensitivity analysis were performed by sequential omission of individual study or a few studies whose research characteristics differ from the others.

Publication bias was tested by Beggar's and Egger's regression tests.

All results were reported with 95% confidence intervals (*CI*) and all *P*-values were two-tailed. $P < 0.05$ was defined to be statistically significant.

3. Results

A total of 2199 studies were identified using the search strategy. The flow chart of study selection is summarized in Fig. 1 (reports excluded based on detailed-review are listed in Appendix A), and the detailed characteristics of the included studies are summarized in Table 1. After a series of screening, 21 eligible studies were included in this meta-analysis: 12 literatures in English and 10 literatures in Chinese published from 1989 to 2017. The age range of the subjects was 7–67 years old. One study (Alghadir et al., 2015) was aimed at teenagers, whose age range was 7–18 years old. Another study (Szkup et al., 2016) was for menopausal women, with an average age of 56.26 ± 5.55 years old. The average levels of blood copper ranged from 12.76 to 25.65 μmol/L and from 11.80 to 21.09 μmol/L in case groups and control groups, respectively. The average levels of copper in hair ranged from 7.29 to 16.52 μg/g and from 10.00 to 17.72 μg/g in case groups and control groups, respectively.

We performed separate meta-analysis of the copper in blood (16 studies) and hair (3 studies) and conducted a qualitative analysis of the three prospective studies. The NOS scoring for the case-control studies is shown in Table 2.

3.1. Copper in blood

Among the 19 studies included, 16 studies reported data of the blood copper levels of 1167 depressed and 765 control subjects. As significant heterogeneity was found ($I^2 = 96.4\%$, $P < 0.001$), therefore a random effect model was used. The 95% confidence range of the average effect scale of the 16 studies was 0.642–3.329, with an average of 1.985. Combining *WMD* test, $z = 2.90$, $P = 0.004 < 0.05$, it can be concluded that the blood copper levels of depressed patients are higher than that of controls without depression (Fig. 2).