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Review Article

High serum copper level is associated with an increased risk of preeclampsia in Asians: A meta-analysis

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ABSTRACT

Epidemiological studies evaluating the associations between serum copper and ratios of Cu/Zn and the preeclampsia (PE) risk in Asian population have produced inconsistent results. Therefore, we conducted a meta-analysis to summarize the relationships. We hypothesize that higher serum copper and ratios of Cu/Zn may increase the PE risk. A systematic literature search was performed in PubMed, Web of Science, Embase, Chinese National Knowledge Infrastructure (CNKI), VIP (Database of Chinese Scientific and Technical Periodicals) and Wangfang databases for relevant studies up to November 2016. Pooled standardized mean difference (SMD) was calculated with random effects model. The results showed that PE patients had a higher serum copper level [SMD (95% CI): 1.05 (0.34, 1.77), Z = 2.88, *P* for Z = 0.004; I^2 = 96.9%, *P* for I^2< 0.0001] compared with healthy pregnancy controls. In subgroup analyses, a higher serum copper level in PE patients was observed in case–control studies [SMD (95% CI): 1.39 (0.44, 2.34)]. No significant difference was found between PE patients and healthy pregnancy controls for ratios of Cu/Zn [(SMD (95% CI): 0.26 (–0.77, 1.29), Z = 0.49, *P* for Z = 0.625; I^2 = 95.8%, *P* for I^2< 0.0001)]. In conclusion, our meta-analysis indicates that a higher serum copper level is associated with an increased risk of PE. Further studies are needed to confirm these results in future research.

Article Outline

Abbreviations: PE, preeclampsia; CC, case–control study; CS, cross-sectional study; SD, standard deviation; SMD, standardized mean difference; CI, confidence interval; AAS, atomic absorption spectroscopy.

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1. Introduction

Preeclampsia (PE) is a systemic disease defined by hypertension (blood pressure of 140 mmHg systolic or higher or 90 mmHg diastolic or higher) and proteinuria [1]. This disorder occurs in 2–8% of all pregnancies and it is one of the leading causes of maternal mortality and preterm delivery throughout the world [2]. PE accounts for 20–80% of the strikingly high maternal mortality in developing countries [3], and nearly one tenth of all maternal deaths in Asia are associated with hypertensive diseases in pregnancy, including PE [4]. PE is caused by genetic, nutritional and environmental factors, and some studies have indicated that PE is associated with an imbalance of increased lipid peroxides and decreased antioxidants as well as endothelial cell dysfunction [5-7]. Copper is an essential trace element which is a cofactor of antioxidant enzymes, thus appropriate copper is necessary for health and reducing the risk of PE. Nonetheless, excessive copper may be harmful and can generate oxidative stress, which means imbalances of antioxidant systems [8,9]. Ratios of Cu/Zn are more reliable indicators of vascular complications and vascular endothelial damage than Zn or Cu status alone [10]. The recent meta-analysis indicated that serum zinc level in PE patients was significantly lower than that in healthy pregnancy controls [11-13]. Many studies attempted to explore the relationships between serum copper level and ratios of Cu/Zn in pregnant women and PE, but the results are conflicting. Some studies reported significantly higher levels of serum copper and ratios of Cu/Zn in PE patients than the control group [9,14-22]. However, other studies found significantly lower levels of serum copper and ratios of Cu/Zn in PE patients [23-25]. Meanwhile, some studies didn't find associations [22,26-29].

In the present study, we hypothesize that a higher serum copper level and ratios of Cu/Zn are associated with increased risk of PE. Given that individual studies may have insufficient power to obtain a more definitive conclusion, we systematically performed a meta-analysis to: (1) assess the association between copper and ratios of Cu/Zn and the PE risk; (2) explore the potential between-study heterogeneity; and (3) investigate the potential publication bias.

2. Approach

Preferred Reporting items for Systematic review and Meta-analyses (PRISMA) guidelines were consulted in this analysis [30].

2.1. Search strategy

We searched for the relevant studies from PubMed, Web of Science, Embase, CNKI, VIP and the Wangfang databases up to November 2016 in either English or Chinese. Search terms included 'Cu', 'copper', 'Zn', 'zinc', 'Cu/Zn ratios', 'preeclampsia', 'pregnancy toxemias', 'edema proteinuria hypertension gestosis', 'EPH toxemias', 'EPH gestosis'. Reference lists of the relevant articles were also reviewed to identify studies not captured by our search terms. A flow chart of our literature search is shown in Fig. 1.

2.2. Inclusion criteria

For inclusion, studies had to fulfill the following criteria: (1) The exposure of interests were serum copper level or ratios of Cu/Zn; (2) The outcome of interest was PE, and diagnosis of PE patients was in accordance with the criteria of the American College of Obstetricians and Gynecologists (ACOG) [1]; (3) Mean and SD were available, or data were provided from which mean and SD could be calculated; (4) The controls were healthy pregnant women; (5) The participants included in the study are from the Asian population; (6) The detection method was atomic absorption spectrometry. The following exclusion criteria were also used: (1) Reviews and (2) Studies whose units of measurement were not given.

If data were published more than once, the one that was most recently published or had the largest number of cases was included in our meta-analysis. Two investigators searched for the articles and reviewed all possible studies independently. If the eligibility of an article was controversial, it was resolved by consensus.

2.3. Data extraction

The following data were extracted from each study independently by two investigators: the first author's name, publish year, country where the study was performed, study type, the number of cases and controls, mean ± SD levels of serum copper(μg/L) and ratios of Cu/Zn, sample type, fasting status, maternal age, gestational age, match of potential confounders. The data from different groups according to the severity of disease were also extracted. If the standard error (SEM) was provided in this study, the standard deviation was calculated by the following formula: $SEM = SD/\sqrt{n}$.

2.4. Statistical analyses

We used the standard mean difference (SMD) with 95% CI to evaluate the associations between serum copper level and