Narrative Review

Targeting Copper Dyshomeostasis as a Pathophysiological Basis of Childhood Obesity: Latest Facts

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ABSTRACT

Context: Childhood pre-obesity and obesity rates have been rapidly growing worldwide over the past decades. Copper homeostasis is gaining increasing attention in the physiopathology of obesity. Strong evidence indicates that a disturbance of copper homeostasis plays an important role in the development of obesity and its related comorbidities. Under physiological conditions, copper plays a significant role in regulatory, immunologic, and antioxidant functions resulting in protection against inflammation and oxidative stress, and consequently against the known comorbidities of obesity. Nevertheless, despite the growing body of research, information about copper status in obesity, particularly in childhood obesity, is scarce.

Evidence Acquisition: This brief narrative review examines the latest data published in the last five years using various databases, such as PubMed, Scopus, Unpaywall (COBISS), and EBSCO to emphasize the major current findings in research related to this topic.

Results: The most recent studies have yielded strong evidence in support of altered copper status in childhood obesity; nevertheless.

Conclusions: Further studies are needed to clarify the role of copper in the physiopathology of childhood obesity.

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Context

According to the World Health Organization (WHO), overweight and obesity are defined as abnormal or excessive fat accumulation that may impair health and has become one of the most significant epidemics in the 21st century [1].

Alerting data show that overweight and obesity are increasing rapidly worldwide; overall, about 13% of the world's adult population and 340 million children and adolescents aged 5-19 years were overweight or obese in 2016 [1]. According to current trends, 1 in 5 adults worldwide is expected to be affected by obesity by 2025. These data clearly show that obesity is an alarmingly increasing global public health issue [2].

An anthropometric indicator that is commonly used as a screening tool for overweight and obesity in adults is body mass index (BMI, kg/m^2). BMI categories for children and teenagers are based on sex- and age-specific BMI percentiles (Table 1) [3].

Overweight and obesity are influenced by genetics, biology, psychosocial factors, and health behaviors. Furthermore, the primary risk factors for obesity, that is poor diet and physical inactivity, are among the top causes of preventable youth mortality, chronic disease, and economic health burden [4].

Obesity increases the risk of non-communicable chronic diseases and cardiometabolic risks [5] in children, such as metabolic syndrome, hypertension [6, 7], dyslipidemia [8], insulin resistance, and diabetes mellitus type 2 [9] nonalcoholic fatty liver disease [10], certain cancer [11], autoimmune diseases, as well as depression and cognitive disturbances that may contribute to poor school results [12]. Children who are overweight or obese are more prone to become obese adults and develop comorbidities at an earlier age than children who are regarded to be of healthy weight. There is also an increased risk of premature death and impairment in later life [13].

Although obesity is largely preventable, it is difficult to treat given its multifactorial nature. Weight management strategies include dietary modification, increased physical activity, and medical or surgical management for severe and morbid obesity [14]. The roles of oligoelements in obesity have recently attracted increased attention due to their oxidant or antioxidant actions, as well as their impacts on insulin/glucose and lipid metabolism, which may be linked to obesity [15]. Studies have shown that metabolic diseases, including obesity, are closely related to systemic inflammation, oxidative stress, and disorders of copper and iron metabolism [16]. Additionally, serum copper might increase as an acute-phase response in a variety of inflammatory conditions, including obesity-induced low-grade chronic inflammation [17]. The investigation of sophisticated molecular mechanisms that could potentially become suitable therapeutic targets remains one of the most important research aspirations worldwide, and this is where the suggested link between copper metabolism and obesity pathophysiology is in line.

Evidence Acquisition

English-language relevant literature from the past 5 years was considered, including studies from a broad range of methodologies: Original papers, meta-analyses, clinical trials, and reviews. Letters and case reports were not included. Research terms adopted, alone and/or combined, were obesity, overweight, adiposity, adolescents, children, trace elements, essential elements, copper, hypertension, and dyslipidemia. The following databases were used for the literature research: PubMed, Scopus, Unpaywall (COBISS), and EBSCO.

Results

Altered copper metabolism and childhood obesity: Is There a more comprehensible link?

Table 1. Child body mass index categories and their corresponding sex and age-specific body mass index percentiles

Body Mass Index Category	Body Mass Index Range
Underweight	<5th percentile
Healthy weight	5th percentile <85th percentile
Overweight	85th percentile <95th percentile
Obesity	95th percentile <

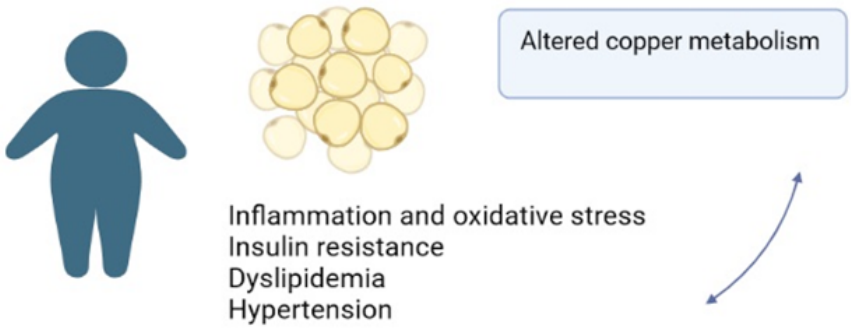

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Figure 1. Clinical and metabolic disorders possibly related to altered copper metabolism in childhood obesity

Copper is a redox-active substance that participates in many biological processes and may be involved in a multitude of pathogenic events, including insulin resistance, inflammation, oxidative stress, abnormal glucose metabolism, and dyslipidemia [18] (Figure 1).

Under physiological conditions, as cofactors for enzymes, copper ions are required for various processes, such as cellular energy production, modulation of synaptic transmission, iron metabolism, angiogenesis, inflammatory response, and antioxidant defense [19, 20]. Paradoxically, an excessive level of serum copper can cause an increase in reactive oxygen species in the organism, which is in agreement with the increased oxidative stress found in childhood obesity [19]. The copper status of obese individuals is usually evaluated by measuring levels of copper and ceruloplasmin in serum, adipose, and hepatic tissues [21].

Although reported in some studies, information about copper homeostasis in human obesity is limited [20]. Accordingly, information about copper homeostasis in childhood obesity is even more scarce. Nevertheless, the serum copper alterations have been proposed to have mostly positive associations among children with obesity [18, 22, 23].

Discussion

Chandrashekhar et al. (2023) established a correlation between serum copper and obesity in 51 adolescents aged 13-16 years with BMI <95th percentile, demonstrating an excess of serum copper in obese individuals [24]. In a study conducted by Castillo-Valenzuela et al. (2023) which included 1235 normal-weight and obese participants, it was found that children between the ages of 4 and 14 years had deficiencies in vitamin D, as well as copper, calcium, and zinc to a lesser extent [25]. Many studies have documented elevated circulating copper levels in obese children [18, 23, 25-30]. In addition, Meggyesy et al. (2020) demonstrated in a diet-induced obesity mouse model that copper ionophores administered daily per os, augmented hepatic copper and decreased mouse body weight, which established copper ionophores as a potential class of anti-obesity agents [31]. Wang et al. (2023) hypothesized that the altered lipid profiles associated with copper overload may contribute to obesity-related systemic inflammation and oxidative stress [15]. However, some studies demonstrated that the serum copper levels were significantly lower in children with obesity as compared to controls [22]. Meanwhile, some authors have reported no significant difference in serum copper levels between obese and normal-weight children [32] or any relation between metabolic syndrome and plasma copper in investigated children [33] González-Domínguez et al. (2023) studied an observational cohort comprising 46 prepubertal and 48 pubertal children with obesity, and have demonstrated that non-obese children going through puberty had better control over inflammation and oxidative stress. Additionally, they had higher levels of essential elements that are involved in the antioxidant system and metabolic control (such as zinc, molybdenum, selenium, and manganese). Inversely, total copper and free iron were found to be reduced in their blood [34]. These results show that copper is a significant modulator of adipocyte metabolism; nevertheless, the fundamental mechanism of copper's contribution to fat cell pathophysiology is still mostly unclear [35].

Together with some other trace elements, data show that copper plays an indispensable role in cardiovascular protection [36] and cholesterol modulation [37], two conditions that are significantly affected by pre-obesity and obesity even in childhood. Some studies show that copper deficiency has been suggested to contribute to cardiovascular disease, which is one of the best-known consequences of obesity. Accordingly, Tong et al. (2022)

found that childhood hypertension was negatively correlated with the dietary intake of copper, and was found positively correlated with triglyceride level ≥1.69 mmol/L, low-density lipoprotein cholesterol level ≥2.84 mmol/L, BMI Z-score, and central obesity [38]. As opposed to these findings, high serum copper contents have been reported to be independent risk factors and biomarkers of cardiovascular diseases as well [27, 36]. Additionally, a National Health and Nutrition Examination Survey (2011-2016) in the United States of America suggested that high serum copper concentrations were significantly associated with elevated blood pressure in US children and adolescents [39].

The results of the cross-sectional study which included 3982 children and adolescents who participated in the US National Health and Nutrition Examination survey 1999-2006 showed that higher dietary copper intake increases the prevalence of hypertriglyceridemia, especially among US adolescents with a BMI ≥23 kg/m^2 [40]. A partial underlying mechanism was suggested by Zhong et al. (2022), who found that copper excess activated oxidative stress and autophagy, up-regulated lipogenesis and lipid metabolism [41]. Similar findings were reported by González-Domínguez et al. (2022), who showed that abnormalities related to trace elements including high serum copper were generally more prevalent in obese children and associated with dyslipidemia, inflammation, oxidative stress, and improper glucose metabolism [18]. Nevertheless, Blades et al. (2021) proposed a different copper and lipid metabolism interrelationship, claiming that the increased cellular copper downregulates lipids and lipogenic genes, and vice versa. In this study, obesity and increased dietary cholesterol corresponded with decreased tissue copper [37], which is an interesting and distinct outcome from the majority of the other research given in this review.

Conclusion

After conducting a thorough examination of the latest scientific literature on copper metabolism and childhood obesity, our findings suggest that there is a significant association between childhood obesity and elevated serum copper concentrations, as evidenced by the majority (but not all) of studies conducted in this area. However, while this correlation is evident, further research is needed to determine the exact causal relationship between the two, as well as to uncover the underlying cellular and subcellular mechanisms that drive this relationship. The existing literature presents scarce explanations for the observed association. Some researchers have proposed that copper may contribute to the development of obesity by promoting lipid synthesis and storage, while others have suggested that copper may exacerbate inflammation in adipose tissue, leading to insulin resistance and other metabolic dysfunctions associated with obesity. Despite these potential explanations, there remains a significant gap in our understanding of the role of copper in childhood obesity. As such, future research must focus on elucidating the causal relationship between copper and obesity, as well as the underlying biological mechanisms involved.

Ethical Considerations

Compliance with ethical guidelines

This article is a narrative review with no human or animal sample.

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Authors contributions

Conceptualization and methodology: Marina Jakšić; Writing the original draft: All authors; Review and editing: Marina Jakšić and Milica Martinović.

Conflicts of interest

The authors declared no conflict of interest.

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