BRITISH JOURNAL OF BIOMEDICAL SCIENCE, 2016
VOL. 73, NO. 3, 147–149
http://dx.doi.org/10.1080/09674845.2016.1209895

BIOMEDICAL SCIENCE IN BRIEF

Seasonal variation of whole blood copper levels in children aged 0–14 years

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ARTICLE HISTORY Received 30 March 2016 Accepted 5 May 2016
KEYWORDS Seasonal variation; copper; children; blood; multivariable linear regression

It is well known that copper (Cu) is an essential trace element in human body and is required for nearly all biochemical and physiological processes, and it is one of the most abundant essential trace elements after iron and zinc.[1] Cu exists in all living organisms and acts as a critical cofactor for many vital metabolic enzymes that regulate physiological processes such as cellular respiration, pigment formation, neurotransmitter biosynthesis, peptide amidation, connective tissue formation, antioxidant defence and iron metabolism in eukaryocytes.[2–4]

Previous studies have shown that elevated serum Cu was highly associated with risk factors for coronary heart disease.[5–7] Higher serum Cu also contributed to an increased mortality risk in middle-aged men with the fourth quartile of Cu level was associated with a 50% increase in RRs (relative risks) for all-cause deaths (RR = 1.5, 95% CI: 1.1–2.1) compared with the first quartile of Cu level.[8] Moreover, there was study that children with the lower plasma Cu levels suffered with more severe and longer duration of diarrhoea.[9] All these studies indicated that either high or low levels of blood Cu could have detrimental effects on human health and that maintaining a stable level of blood Cu might be beneficial for health. In this study, the Cu levels in whole blood of 3210 children aged 0–14 years were determined and seasonal variation in Cu levels were analysed.

A total of 3210 children (2150 boys and 1060 girls), aged 0–14 years, who came for a routine health examination between January 2012 and December 2014 were recruited in the present study. Informed consents for the use of these children's detection results were obtained from their parents or guardians. This study was approved by the Ethics committee of Lu'an People's Hospital. Children were grouped by seasons when blood samples were collected. Seasons were defined as follows: spring (March–May), summer (June–August), autumn (September–November) and winter (December–February).

For all the children, about 2 mL of peripheral venous blood was collected into a vacuum tube (CHGD®, Gaode, Wenzhou, China) containing heparin sodium. Prior to Cu detection, all these blood samples were stored at 0–4 °C. Cu was analysed by flame atomic absorption spectrometry (BH5100, Bohui, Beijing, China) with hollow cathode lamp under 324.7 nm. Quality controls were conducted using certified reference materials GBW(E) 080915–080917 from the General Administration of Quality Supervision, Inspection and Quarantine of the People's Republic of China. Control samples were analysed every 10 routine sample detection and the previous 10 routine samples must be analysed again if the values of control exceeded the uncertainty provide by the certificate of reference materials.

Concentrations of Cu were expressed as mean ± SD (standard deviation). Statistical analysis was conducted with SPSS 19. The differences of mean values of Cu between seasons were analysed by one-way ANOVA with Bonferroni method for multiple pairwise comparisons. The association of season with Cu levels was analysed using multivariable linear regression.

The mean values of Cu levels in whole blood of children at different seasons are presented in Table 1. In total, the mean value of Cu in autumn was 19.5 ± 4.6 μmol/L, and this was the least compared to those in other seasons and was significant lower than those in spring and summer that with the values of 21.1 ± 4.2 and 20.4 ± 4.6 μmol/L, respectively. In both boys and girls, and different age groups except for infants there were significant seasonality of Cu levels ($p < 0.001$ for both sexes and $p < 0.01$ for different age groups) and the values in autumn were all significantly lower than those in spring ($p < 0.05$). Moreover, there were no differences of Cu levels between sexes at all four seasons. But there were significant differences of Cu levels between age groups at summer, autumn and winter, but not at spring, and the mean values of Cu were gradually decreased with age (Table 1).

Subsequently, the association of season with Cu levels was analysed using multivariable linear regression and the results are shown in Table 2. In total analysis, after

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adjusting for age, sex and year of samples collection, the association of season with Cu levels was significant with Cu levels in spring, summer and winter increased by 9.64% (β = 0.092; 95% CI: 0.071–0.113; $p < 0.001$), 5.34% (β = 0.052; 95% CI: 0.032–0.071; $p < 0.001$) and 4.19% (β = 0.041; 95% CI: 0.016–0.065; $p < 0.01$), respectively, compared to the value in autumn. When sex- and age-stratified associations between seasons and Cu levels were analysed we found that they were still significant except for at 0~ age group. Moreover, when compared to those in autumn, the change of Cu levels in spring was increased with age with the highest change more than 12.0% occurred in children older than 7 years (Table 2).

In this study, the data of Cu levels in whole blood of 3210 children aged 0–14 years were collected through 2012–2014 from the outpatient department of the Lu'an Affiliated Hospital of Anhui Medical University. Our results showed that there was significant seasonal variation in Cu levels in whole blood of children and this seasonality existed in total, both sexes, and nearly all age groups except for in infants (Tables 1 and 2). Moreover, this seasonal variation in children increased with age. The reasons for this seasonality are not clear. People here have different dietary habits and different kinds of foods are eaten in different seasons. Children also have different dietary habits with age. In addition, different kinds of foods contain different contents of Cu.[10,11] For example; the soybean and animal liver have the highest contents of Cu among plant-based foods and meat foods, respectively. Therefore, dietary habits of children here might be one major reason for seasonal variation in blood Cu levels and this might be the reason why infants who take breast milk as the only foods have no seasonality in Cu levels. More works are needed to explore the relationships between dietary habits and seasonality of Cu levels in whole blood of children.

Both Cu deficiency and excess are detrimental to human health. The deficiency of Cu could lead to neutropenia, thrombocytopenia, anaemia and bone malformation, increase the risk of developing osteoporosis in later life and cause alterations in cholesterol and glucose metabolism.[1,12] However, Cu excess could lead to the generation of free radicals, oxidative damage to membrane or macromolecules and increased lipid peroxidation in cell membranes and DNA damage.[1,4,13] Furthermore, both high and low Cu levels even within

Table 1. Seasonal variation in Cu levels in whole blood of children aged 0–14 years old[#].

Characteristics	Number	Cu (mean ± SD, μmol/L)				p-Value
		Spring	Summer	Autumn	Winter	
Total	3210	21.1 ± 4.2^{a}	20.4 ± 4.6^{b}	19.5 ± 4.6^{c}	20.2 ± 4.6^{bc}	<0.001
Sex						
Boys	2150	21.1 ± 4.1^{a}	20.5 ± 4.7^{ab}	19.5 ± 4.6^{bc}	20.3 ± 4.6^{c}	<0.001
Girls	1060	21.1 ± 4.5^{a}	20.1 ± 4.2***	19.4 ± 4.6^{b} **	19.9 ± 4.5**	<0.001
Age (years)						
0~	397	21.3 ± 4.4	21.0 ± 4.8	20.3 ± 5.0	20.2 ± 4.7	0.36
1~	555	21.6 ± 4.6^{a}	21.4 ± 4.5^{a}	20.0 ± 4.6^{b}	22.3 ± 5.7^{a}	<0.01
2~3	606	21.3 ± 4.3^{a}	20.5 ± 4.5	19.5 ± 4.6^{b}	20.4 ± 5.0	<0.01
4~6	743	21.0 ± 4.0^{a}	20.6 ± 4.5	19.6 ± 4.7^{b}	19.5 ± 3.9^{b}	<0.01
7~9	519	21.0 ± 4.0^{a}	19.6 ± 4.3^{b}	18.8 ± 4.4^{b}	20.1 ± 4.1	<0.01
10~14	390	20.3 ± 4.2^{a}	18.9 ± 4.5	18.0 ± 3.9^{b}	18.6 ± 3.5	<0.01

[#]Analysed by one-way ANOVA with multiple comparisons between seasons within each sub-groups conducted by Bonferroni method. Continuous variables within each season between different sexes and age groups were analysed by Student's t-test and Sidak method, respectively.
$^{***}p < 0.001$; $^{**}p < 0.01$; $^{*}p < 0.05$.
[a,b,c]Values marked with different letters at the same line within each sub-group were significantly different.

Table 2. Association of season with Cu levels (ln-transformation) based on multiple linear regression stratified by sex and age.

Groups	Autumn	Spring			Summer			Winter		
		β	95% CI	Change[a]	β	95% CI	Change[a]	β	95% CI	Change[a]
Total	Reference	0.092***	0.071, 0.113	9.64	0.052***	0.032, 0.071	5.34	0.041**	0.016, 0.065	4.19
Sex[b]										
Boys	Reference	0.094***	0.069, 0.120	9.86	0.055***	0.031, 0.079	5.65	0.044**	0.014, 0.073	4.50
Girls		0.089***	0.052, 0.125	9.31	0.045**	0.012, 0.079	4.60	0.032	−0.011, 0.076	3.25
Age (years)[c]										
0~	Reference	0.062	−0.005, 0.128	6.40	0.037	−0.020, 0.093	3.77	0.006	−0.065, 0.077	0.60
1~		0.086**	0.036, 0.136	8.98	0.073**	0.026, 0.119	7.57	0.111**	0.045, 0.176	11.74
2~3		0.097***	0.049, 0.144	10.19	0.051*	0.006, 0.096	5.23	0.046	−0.012, 0.104	4.71
4~6		0.080***	0.039, 0.122	8.33	0.057**	0.016, 0.097	5.87	0.008	−0.039, 0.055	0.80
7~9		0.115***	0.061, 0.169	12.19	0.039	−0.009, 0.088	3.98	0.065*	0.005, 0.126	6.72
10~14		0.117***	0.056, 0.178	12.41	0.047	−0.009, 0.102	4.81	0.039	−0.037, 0.115	3.98

[a]The changes of concentration in multivariable linear regression were calculated as $(1 - e^{\beta}) \times 100\%$.
[b]Adjusted for age and year of samples collection.
[c]Adjusted for sex and year of samples collection.
$^{***}p < 0.001$; $^{**}p < 0.01$; $^{*}p < 0.05$.

normal range are associated with risk factors for some diseases. High-serum Cu was significantly associated with risk factors for coronary heart disease and an increased mortality risk in middle-aged men, and children with the lower plasma Cu suffered with more severe and longer duration of diarrhoea.[5–9] All these results imply that an apparent fluctuation of blood Cu levels in children may have detrimental effects on their health.

Our results suggested that blood Cu levels had significant seasonal fluctuations, especially in older children with the highest change of 12.41% occurred in children aged 10–14 years compared to those in autumn (Tables 1 and 2). Studies in adults reported previously indicated that, compared to people having no classical risk factors for coronary heart disease, the increase of serum Cu levels by 7.01~9.24% accompanied with significant increase of major risk factors for the disease and people who died from coronary heart disease had 5% higher of serum Cu levels than those who died from other causes. [5,6] Moreover, studies demonstrated that the serum Cu levels of children suffering from chronic rhinosinusitis [14] and acute diarrhoea [9] decreased significantly by 18.1 and 12.8%, respectively, compared to normal children, and the serum Cu levels of children suffering from autism spectrum disorders [15] and Helicobacter pylori infection [16] increased significantly by 7.2% and about 7.5%, respectively, compared to normal children. Although these studies suggested some relationships between changes of blood Cu levels and the development of some diseases, it is still not known if seasonal variation of blood Cu levels has any detrimental effects on children's health and this deserves more in-depth studies.

In summary, there was significant seasonal variation in Cu levels in whole blood of children aged 0–14 years, and this seasonality existed in both sexes and all age groups, except for in infants, with the highest Cu levels was in spring compared to those in other seasons. This work represents an advance in biomedical science because seasonal variation of blood Cu levels was detected for first time in children and suggested that further works are needed to evaluate the impacts of this seasonality on health.

Acknowledgements

We thank Chenyu Peng, Guangnan Li and Lili Xu for collecting blood samples.

Disclosure statement

The authors declare that there are no conflicts of interest.

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