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The association between blood copper concentration and biomarkers related to cardiovascular disease risk – analysis of 206 individuals in the Northern Finland Birth Cohort 1966

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ABSTRACT

Background: Copper is an abundant trace element in humans where alterations in the circulating concentration could inform on chronic disease aetiology. To date, data are lacking to study how copper may associate with cardiovascular disease (CVD) risk factors in young and healthy population. Molecular evidence suggests an important role of copper in liver metabolism, an essential organ in maintaining cardiovascular health and inflammation, therefore supporting copper as an associated biomarker of the risk.

Objective: We performed a cross-sectional analysis to examine the possible associations between blood copper levels and risk factors for CVD and pre-inflammatory process.

Design: The data has been collected from a sub-sample set of the Northern Finland Birth Cohort 1966 (NFBC1966) at 31 years.

Participants: The study included 206 individuals, 116 men and 90 women. To reduce environmental individual variations affecting both copper and the metabolic profile in the study sample, the participants were selected as: i) being born in Finnish Lapland and ii) living in their birth place for the last five years preceding blood sampling.

Main outcome measures: Fasting blood copper concentration was measured by inductively coupled plasma mass spectrometer. The CVD risk factors included 6 metabolic clusters (30 cardiovascular and pro-inflammatory factors) assessed by nuclear magnetic resonance. Multivariate linear regression analysis was performed to test the linear association between blood copper and 6 metabolic clusters for CVD risk. Associations were assessed under correction for multiple testing.

Results: Copper (Cu) levels were comparable in men and women, with no difference between sexes (*p-value* < 0.60). In multiple regression models, sex adjusted, copper was associated with 9 metabolites from 4 metabolic clusters. After adjustment with BMI, copper was associated with 4 metabolites from 3 metabolic clusters: glutamine, beta-hydroxybutyrate, alpha-1-acid glycoprotein (AGP) and high-sensitive C-reactive protein (hs-CRP). After correction for multiple testing, Cu was found positively associated with only 2 biomarkers of inflammation including AGP [$p = 0.04$] and hs-CRP [$p = 0.0001$].

Conclusions: Considering the strength and limitation of the study design, the present study does not support evidence for an independent role of copper on biomarkers for CVD risk. Nevertheless, we are reporting a robust association of copper with the inflammatory load that is important to consider in light with the inflammatory

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component of chronic health. In addition, the association of copper with metabolites may be attributable to BMI or environmental factors associated to it, and warrants further research in large population samples.

1. Introduction

Cardiovascular disorders and diseases are a major cause of death where scientific efforts are needed to identify early risk factors and potential preventive biomarkers in non-affected populations. After Iron and Zinc, Copper (Cu) is the third most important trace element circulating in the body [1,2] originating principally from dietary sources *i.e.* food and water [2]. Cu^{++} can be extremely toxic due to its oxidoreductase function [3,4] and is transported in the circulation by the carrier-protein ceruloplasmin [5]. There is contrasting evidence for the influence of Cu on pro- or anti-oxidative pathways and subsequent risk of atherosclerosis in humans [6]. To-date Cu plays a role in nineteen enzymatic reactions involved in oxidative stress and metabolic homeostasis [4] including the Cu/Zn dependent superoxide dismutase (SOD), the cytochrome *c* oxidase and the ceruloplasmin [4]. In addition, there is no clinical threshold defining a healthy range of fasting blood copper. While modulation of dietary intake of copper could be implemented as a strategy to influence cardiometabolic health [7,8], fundamental questions remains to be solved before clear recommendation can be announced. A wider knowledge of the metabolic pathways linking copper to altered cardiovascular health can be needed. Following the advent of wider metabolomic profiling [9] we are gaining a dimension in the molecular pathways involved aside from the classical markers of cardiovascular disease especially LDL-C, triglycerides and HDL-C [10]. This includes variations in lipoprotein structure and composition, some amino-acids, ketone bodies and pro-inflammatory factors [11]. To date 30 metabolites are suggested to influence cardiovascular health and might be influenced by copper concentration of copper metabolism related pathways [10].

In line with the biological functions of copper and the current bodies of evidence, the present study aimed at testing the hypothesis, in a non-affected sample of young and healthy adults at 31 years, that fasting blood copper is associated with CVD risk biomarkers as defined from previous large scale metabolomic study [10]. Identifying potential new biomarkers such as copper might help detecting very early disease state with the aim to also inform on the molecular pathway involved. The objectives of the present study were therefore to characterise blood concentration in a young and healthy non-affected sample with cardiovascular disease and test the linear association of copper with known risk factors established from the study of the metabolome and inflammatory load related to the aetiology of chronic cardio-metabolic diseases.

2. Materials and methods

2.1. Study design and material

The study was based on the 31-year follow-up of the Northern Finland Birth Cohort (NFBC1966) [12]. Briefly the NFBC1966 is a prospective birth cohort of 12,058 (96% of total population) live-born

Table 1
Descriptive statistics and fasting blood copper concentration by anthropometric, lifestyle and socio-demographic factors.

	Total (N = 206 – 195)**	[Cu] ng/mL Mean (SD)	*P*-value*
Age (years)	31		
Men (n %)	116 (56.31)	835.66 (154.49)	
Women (n %)	90 (43.69)	883.52 (146.49)	0.60
BMI (kg/m^2) [Mean (SD)]	25.23 (4.34)		
Normal weight (n %)	110 (53.4)	835.63 (137.78)	
Overweight and Obese (n %)	96 (46.6)	880.57 (165.38)	0.07
Socioeconomic status (n %)[a]			
I + II (Professional)	24 (12.18)	894.50 (178.19)	
III (Skilled worker)	56 (28.43)	876.91 (123.76)	
IV (Unskilled worker)	66 (33.50)	822.35 (169.22)	0.16
V (Farmer)	9 (4.57)	886.22 (127.96)	
VI (Other)	42 (21.32)	876.86 (150.09)	
Diet score[b] **(n %)**			
0-1	55 (27.50)	879.42 (145.59)	
2-3	116 (58.00)	862.82 (156.39)	0.10
4-5	29 (14.50)	805.34 (151.61)	
Smoking status[c] **(n %)**			
No smoker	109 (55.61	835.59 (144.38)	
Smokers	87 (44.39)	888.56 (159.82)	0.32
Alcohol consumption (g/day)[d] **(n %)**			
Abstainer	14 (7.18)	900.29 (198.01)	
Low risk drinker	172 (88.21)	854.66 (149.28)	0.46
At-risk drinker	9 (4.62)	891.78 (148.97)	

Values are presented as mean (standard deviation) or number (%).

* *P*-value was calculated using Student's *t*-test for continuous variables and ANOVA for categorical variables.

** N varies due to missing data for some of the variables.

[a] Data available on N = 197 individuals; N = 9 observations missing with socioeconomic position.

[b] Data available on N = 200 individuals; N = 6 observations missing with diet score.

[c] Data available on N = 196 individuals; N = 10 observations missing with smoking status.

[d] Data available on N = 195 individuals; N = 11 observations missing with alcohol consumption; Alcohol classification according to WHO sex-specific classification as abstainer, low risk drinker (≤ 20 g/day and ≤ 40 g/day for women and men, respectively) or at-risk drinker (> 20 g/day and > 40 g/day for women and men, respectively).