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Circulating levels of metals are related to carotid atherosclerosis in elderly

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ABSTRACT

The aim of this study was to investigate if blood levels of trace and/or heavy metals are related to atherosclerosis in a cross-sectional study in elderly.
In the population-based Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) study (1016 subjects, all aged 70), the prevalence of carotid artery plaques was recorded by ultrasound. The numbers of carotid arteries with plaques (0, 1 or 2) were recorded. Also the thickness (IMT) and gray scale (IM-GSM) of the intima-media complex were measured together with plaque echogenicity. Eleven heavy metals and trace elements were analyzed in whole blood, using inductively coupled plasma-sector field mass spectrometry. Nickel levels were related to the number of carotid arteries with plaques in an inverted U-shaped manner after multiple adjustment for gender, waist circumference, body mass index, fasting blood glucose, systolic and diastolic blood pressure, HDL and LDL cholesterol, serum triglycerides, smoking, antihypertensive treatment and statin use ($p = 0.026$). IM-GSM and plaque echogenicity were both inversely related to chromium in a linear fashion, and to aluminum in an inverted U-shaped manner (both $p<0.0001$ for IM-GSM). The relationships between metals and IMT were modest.
Circulating levels of some metals, like nickel, aluminum and chromium, were related to atherosclerotic plaques or the echogenicity of the IM-GSM and overt plaques independently of cardiovascular risk factors, including lipids.

1. Introduction

Metals, both trace elements and so called heavy metals, can be measured in a variety of body compartments, such as whole blood, serum, plasma, urine, hair and toenails in the epidemiological setting. Using metal determinations, it has been shown in different studies that Pb, Cd, Ni, Co and Hg levels are increased in patients with coronary artery disease, or in subjects developing myocardial infarction during a certain follow-up in cohort studies. In contrast, Cu, Zn and Cr were reported to be reduced in such studies (Afridi et al., 2010; Afridi et al., 2008: Alissa et al., 2009; Everett and Frithsen, 2008; Giannoglou et al., 2010: Guallar et al., 2002; Kazemi-Bajestani et al., 2007; Kazi et al., 2008; Krachler et al., 1997; Leach et al., 1985; Menke et al., 2009; Oster et al., 1989; Salonen et al., 2000; Virtanen et al., 2005; Vlad et al., 1994). Some essential metals can give adverse effects if the levels are decreased, but can also accumulate in the body, yielding higher levels, especially in the elderly (Afridi et al., 2010; Ashraf et al., 1994; Dar et al., 2008; Kazi et al., 2008; Khalique et al., 2005; Lopes et al., 2004). The hallmark of myocardial infarction is atherosclerosis. In the case of myocardial infarction, an atherosclerotic plaque in the coronary arteries ruptures and gives rise to an occluding thrombus. A number of studies have reported associations between metals and atherosclerosis, evaluated by carotid artery intima-media thickness (IMT).

In those studies, increased levels of Cd and Hg, and reduced levels of Zn, were related to a thickened IMT (Messner et al., 2009: Salonen et al., 2000: Skoczyńska et al., 2009) or severity of coronary lesions at angiography (Giannoglou et al., 2010). Furthermore, exposure to Cd increased, while administration of Zn and Cr reduced atherosclerosis development in the hypercholesterolemic rabbit and ApoE knock-out mice (Messner et al., 2009: Price Evans et al., 2009; Subramanyam et al., 1992), giving further support to the theory that metals might be involved in the pathogenesis of atherosclerosis.

Since coronary and carotid artery atherosclerosis often go hand in hand (Hulthe, et al., 1997), we hypothesized that subjects with high circulating levels of heavy metals and low levels of trace elements more often show carotid atherosclerotic plaques. Furthermore, since we recently found that the echogenicity of the intima-media complex (IM-GSM) in the carotid artery – a possible marker of lipid infiltration

Abbreviations: Al, aluminum; BMI, body mass index; Cd, cadmium; Co, cobalt; Cu, copper; Cr, chromium; CV, cardiovascular; DBP, diastolic blood pressure; HDL, high-density lipoprotein; Hg, mercury; ICP-SFMS, inductively coupled plasma-sector field mass spectrometry; IM-GSM, intima-media complex; IMT, intima-media thickness; LDL, low-density lipoprotein; Mn, manganese; Mo, molybdenum; Ni, nickel; Pb, lead; PIVUS, Prospective Investigation of the Vasculature in Uppsala Seniors; SBP, systolic blood pressure; Zn, zinc.

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in the vascular wall – is a powerful predictor of future cardiovascular (CV) death (Wohlin et al., 2009), we also investigated if metal levels were associated with IM-GSM. For these aims, we used the population-based Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) study (Lind et al., 2005) in which we have data on atherosclerosis and circulating metal levels in almost 1000 subjects.

2. Material and methods

2.1. Subjects

Eligible to the study were all subjects aged 70 living in the community of Uppsala, Sweden. The subjects were randomly chosen from the register of community residents. A total of 1016 subjects participated, giving a participation rate of 50.1%. The primary aim of the collection of data in the PIVUS study was to evaluate if measures of endothelium-dependent vasodilatation were independent predictors of future myocardial infarction and stroke. Since many cases of myocardial and stroke occur between 70 and 80 years of age, we did chose to investigate subjects at a baseline of 70 years, which would give us a good power to detect about 100 stroke cases and 100 myocardial infarction cases during 10 years follow-up with the present sample size. The study was approved by the Ethics Committee of the University of Uppsala.

All subjects were investigated in the morning after an overnight fast. No medication or smoking was allowed after midnight. An arterial cannula was inserted in the brachial artery for blood sampling and later regional infusions of vasodilators. The participants were asked to answer a questionnaire about their medical history, smoking habits and regular medication.

Blood pressure was measured by a calibrated mercury sphygmomanometer in the non-cannulated arm to nearest mm Hg after at least 30 min of rest, whereupon the average of three recordings was used. Lipid variables and fasting blood glucose were measured by standard laboratory techniques (Carlsson et al., 2010; Lind et al., 2005). Basic characteristics medical history, and regular medication are given in Tables 1 and 2.

2.2. Carotid artery ultrasound evaluation

The carotid artery was assessed by external B-mode ultrasound imaging (Acuson XP128 with a 10 MHz linear transducer, Acuson Mountain View, California, USA).

The common carotid artery, the bulb and the internal carotid artery at both sides were visually investigated for the presence of plaque. A plaque was judged to be present in a particular carotid artery if a local thickening of the IMT was seen that was more than 50% thicker than the surrounding IMT in any part of the carotid artery investigated. We recorded whether carotid plaques were present in none, one or both of the carotid arteries.

The images were digitized and imported into the AMS (Artery Measurement Software) automated software (Liang et al., 2000) for dedicated analysis of IMT and the gray scale median of the IM-GSM. A maximal 10 mm segment with good image quality was chosen for IMT analysis from the carotid artery. The program automatically identifies the borders of the IMT of the far wall and the inner diameter of the vessel, and calculates IMT and the diameter from around 100 discrete measurements through the 10 mm long segment. This automated analysis could be manually corrected if not found appropriate at visual inspection. The given value for carotid artery IMT is the mean value from both sides.

A region of interest (ROI) was placed manually around the intima-media segment that was evaluated for IMT, whereby the program calculates the echogenicity in the IM-GSM from an analysis of the individual pixels within the region of interest on a scale from 0 (black) to 256 (white). The blood was used as the reference for black and the adventitia was the reference for white. The given GSM value is the mean value from both sides.

An ROI was also placed manually around plaques for measurement of plaque GSM.

GSM of the plaques was evaluated with the same software as used for IM-GSM. This measurement was repeated in 25 random subjects, giving a coefficient of variation of 8.3% for GSM in the plaques. The mean length of the evaluated intima-media segments was 9.0 (SD 2.1) mm when subjects with a segment recording less than 5 mm were excluded, leaving 946 subjects with valid recordings. The measurements of the intima-media were repeated in 30 random subjects, giving a coefficient of variation of carotid artery IMT of 7.2% and 7.5% for echogenicity in the IM-GSM.

2.3. Analysis of metals in whole blood

All 11 elements (Al, Cd, Co, Cu, Cr, Hg Mn, Mo, Ni, Pb, and Zn) in this study were determined in whole blood. The analysis was performed using inductively coupled plasma-sector field mass spectrometry, ICP-SFMS, after microwave assisted digestion with nitric acid (Rodushkin et al., 2000) according to a method accredited for 10 of

Table 1
Basic characteristics in the investigated sample, with means and standard deviation (SD) in parenthesis. SBP = systolic blood pressure; DBP = diastolic blood pressure; BMI = body mass index; LDL = low density lipoprotein; HDL = high density lipoprotein.

n	1016
Females (%)	50.2
Height (cm)	169 (9.1)
Weight (kg)	77 (14)
Waist circumference (cm)	91 (12)
BMI (kg/m2)	27.0 (4.3)
Waist/hip ratio	0.90 (0.075)
SBP (mm Hg)	150 (23)
DBP (mm Hg)	79 (10)
Serum cholesterol (mmol/L)	5.4 (1.0)
LDL cholesterol (mmol/L)	3.3 (0.88)
HDL cholesterol (mmol/L)	1.5 (0.42)
Serum triglycerides (mmol/L)	1.3 (0.60)
Fasting blood glucose (mmol/L)	5.3 (1.6)
Current smoking (%)	11

Table 2
Self-reported history of cardiovascular (CV) disorders and regular drug intake given in percentage (%) in the investigated sample. CABG/PTCA indicates coronary revascularization; GTN, any nitroglycerine preparation.

n	1016
Myocardial infarction	7.1
Stroke	3.7
Angina pectoris	8.1
CABG/PTCA	5.3
Congestive heart failure	3.8
Diabetes	8.7
Any regular drug	70
Any CV drug	45
Any antihypertensive medication	32
Beta-blockers	22
Calcium antagonists	11
Diuretics	13
ACE-inhibitors	8.5
Angiotensin II-blockers	8.3
GTN	3.0
Digoxin	2.1
Statins	15
Other antihyperlipidemic drugs	1.2
Insulin	1.8
Oral antidiabetic drugs	6.1
Warfarin	3.2
Aspirin/Clopidogrel	18
Other antiarrythmic drugs	0.2