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Mercury accumulation and accelerated progression of carotid atherosclerosis: a population-based prospective 4-year follow-up study in men in eastern Finland

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Abstract

Basic research and our previous studies have suggested that mercury exposure enhances lipid peroxidation and the risk of myocardial infarction, but there are no studies concerning the association between mercury accumulation and atherosclerosis. We therefore investigated whether high hair mercury content is associated with accelerated progression of carotid atherosclerosis, determined by ultrasonographic assessment of common carotid intima-media thickness (IMT), in a prospective study among 1014 men aged 42–60 years. In a linear regression model adjusting for other atherosclerotic risk factors, high hair mercury content was one of the strongest predictors of the 4-year increase in the mean IMT ($P = 0.0007$). On the average, for each μg/g increase in hair mercury content, there was an increment of 8 μm (7.3% of the mean) in the 4-year IMT increase. Men with hair mercury content of < 0.49, 0.49–0.91, 0.92–1.49, 1.50–2.81 and > 2.81 μg/g (fifths) had an IMT increase of 0.105, 0.102, 0.113, 0.107 and 0.140 mm/4 years, respectively ($P = 0.041$ for heterogeneity between groups). The IMT increase was 0.034 mm/4 years (31.9%) greater in the highest fifth than in the other fifths ($P < 0.05$ for the difference). These findings suggest that mercury accumulation in the human body is associated with accelerated progression of carotid atherosclerosis.

Keywords: Arteriosclerosis; Atherosclerosis; B-mode ultrasound; Environmental cardiology; Heavy metals; Lipid peroxidation; Mercury; Trace elements

1. Introduction

The role of lipid peroxidation in atherogenesis has been confirmed in both basic research [1–4] and in epidemiologic studies [5–7]. Lipid peroxidation in the human body is regulated by free radical stress, availability of pro-oxidative catalytic metals and antioxidative defense systems [1–4,7]. Mercury, especially methylmercury, can promote lipid peroxidation. It is an environmental pollutant that has no physiological role in the human metabolism [8]. The principal sources of mercury intake are diet and, possibly, dental amalgam fillings. Predatory fish is the main dietary source of mercury in most industrialised countries. In fish, mercury is in organic form, mainly as methylmercury, which is well absorbed in the gut and is accumulated in epithelial tissues including hair. The mercury content of hair is an indicator of mercury intake over several months [8].

We observed in an epidemiologic cohort study over 2-fold risk of acute myocardial infarction (AMI) and mortality from coronary heart disease (CHD) and cardiovascular disease (CVD) in men in eastern Finland with an elevated hair content of mercury [9]. There also was a direct association between titres of immune complexes containing oxidised LDL and hair mercury content [9]. Our original findings was recently confirmed in the multi-centre EUREMIC case-control study, in which the mercury content of toenails had a consistent

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independent association with AMI [10]. There are, however, no published reports concerning the role of mercury accumulation in the human body in atherosclerosis.

Ultrasonographic examination of the arteries has made it possible to investigate noninvasively the prevalence, development and progression of atherosclerosis in unselected human populations [11,12]. The intima-media thickness (IMT) of the carotid arteries, assessed by B-mode ultrasonography, is a reliable and valid indicator of generalized atherosclerosis, correlates well with the extent of coronary atherosclerosis, and has predictive validity with regard to the risk of coronary and cerebrovascular events, and because of its non-invasiveness, can be used in population studies [11–16].

To investigate the role of mercury accumulation in the human body in atherosclerosis, we examined the association of baseline hair mercury content with the subsequent progression of carotid atherosclerosis, determined by ultrasonographic assessment of the common carotid IMT, in a prospective 4-year follow-up study in an unselected population-based sample of men from eastern Finland.

2. Methods

2.1. Study population

The subjects were participants in the Kuopio Ischaemic Heart Disease Risk Factor Study (KIHD), which is an ongoing population-based study designed to investigate unestablished risk factors for CVD, carotid atherosclerosis and related outcomes in men from eastern Finland [17]. One of the main purposes of the study was to investigate the role of lipid peroxidation, pro-oxidative minerals and antioxidants in atherosclerosis and CVD. Each subject gave written informed consent. The KIHD was approved by the Research Ethics Committee of the University of Kuopio.

The baseline examinations were conducted between March 1984 and December 1989. A total of 2682 men who were 42, 48, 54 or 60 years old at baseline (82.9% of those eligible) were recruited in two cohorts. The first cohort consisted of 1166 men who were 54 years old (83.3% of those eligible, enrolled between March 1984 and August 1986, and the second cohort included 1516 men who were 42, 48, 54 or 60 years old (82.6% of those eligible), enrolled between August 1986 and December 1989.

A total of 1229 men from the second cohort underwent ultrasound examination of the right and left common carotid arteries at baseline. This group was invited to participate in a 4-year follow-up study, which was conducted between March 1991 and December 1993. Of the 1229 men who were eligible for the follow-up examinations, 1038 (88.2%) participated, 107 refused, 52 could not participate because of death, severe illness or relocation and 32 could not be contacted. Twenty-four participants either refused to give or were unable to provide a hair specimen in the baseline examination. No marked sociodemographic differences have been found between participants and non-participant [18]. Average time to follow-up was 4.2 years (range 3.8–5.2 years).

The present study is based on data from the 1014 men who had complete information on hair mercury content and carotid atherosclerosis. Of the present study population, 73 men were in the pravastatin treatment group in the Kuopio Atherosclerosis Prevention Study (KAPS) [15].

2.2. Assessment of carotid atherosclerosis

The extent and severity of carotid atherosclerosis was assessed by high-resolution B-mode ultrasonographic examination of the right and left common carotid arteries (CCA) in a 1.0–1.5-cm section at the distal end of the CCA, proximal to the carotid bulb. Images were focused on the posterior (far) wall of the right and left CCA and recorded on videotape for later analysis. Near wall images were not assessed because of their greater measurement variability [19]. The IMT was measured as the distance from the leading edge of the first echogenic line to the leading edge of the second echogenic line, as explained earlier in detail [12]. Ultrasonographic examinations were conducted by one physician (R.S.) at baseline, and by four trained sonographers at 4-year follow-up. All examinations were performed with the subject in a supine position.

At baseline, ultrasonographic scanning was conducted with the ATL UM4 duplex ultrasound system with a 10-MHz sector transducer. At 4-year follow-up, the images were obtained with a Biosound Phase 2 equipped with a 10-MHz annular array probe [12]. Wedge phantom studies of this system, calibrated against an RMI 414B tissue phantom, have demonstrated measurement precision of ± 0.03 mm [14].

The baseline and follow-up intima-media thickness (IMT) measurements were made by computerized analysis of the videotaped ultrasound images using Prosound software (University of Southern California, Los Angeles, CA, USA). This software uses an edge-detection algorithm, specifically designed for use with ultrasound imaging [20], that allows automatic detection, tracking and recording of the intima–lumen and media–adventitia interfaces. IMT, calculated as the mean distance between these interfaces, was estimated

at approximately 100 points in both the right and left CCAs.

For the present study, two measures of IMT were used: (1) the mean IMT, calculated as the mean of all IMT estimates from the right and left CCAs and considered an overall measure of the atherosclerotic process, and (2) the maximal IMT, the average of the points of maximal thickness from the right and left CCAs and indicative of the depth of intrusion of IMT into the lumen in this part of the CCA. The progression of carotid atherosclerosis was calculated as the difference between the 4-year follow-up and baseline values for both of these IMT measures.

2.3. Blood, hair and urine sampling

The examination protocol and measurements have been described in detail earlier [11]. The subjects came to give blood and hair specimens between 08:00 and 10:00 on Tuesday, Wednesday or Thursday. They were instructed to abstain from ingesting alcohol for 3 days, from smoking for 12 h and from eating for 12 h. After the subject had rested in the supine position for 30 min, blood was drawn with Terumo Venoject vacuum tubes (Terumo, Tokyo). No tourniquet was used. In connection with the blood sampling, a hair sample averaging 40 mg was cut from the scalp hair of the subjects for mercury measurements.

2.4. Determination of hair mercury

Mercury in hair samples was determined between May 1992 and August 1993 by flow injection analysis-cold vapor atomic absorption spectrometry and amalgamation as described earlier [9]. Hair samples were processed in a random order at the Department of Chemistry of the University of Kuopio.

As the quality control materials for hair we used a hair pool (UPPS85) with a certified mercury content of 1.11 ± 0.11 μg/g, BCR pig kidney reference material No 186 with a Hg content of 1.97 ± 0.04 1 μg/g (Commission of the European Communities, Community Bureau of Reference, Brussels, Belgium) and hair from a subject. The mean values of Hg content in the UPPS85 hair pool and in the BCR material were 1.10 and 1.97 μg/g and the coefficients of variation between sample batches were 7.3 and 6.1%, respectively. The variation coefficients for a subject's hair were 8.6 ($n = 48$), 7.8 ($n = 52$) and 7.7% ($n = 92$) in three periods, during each of which one batch was used. To study the tracking of hair mercury values over time, repeat hair samples were collected and the mercury contents were measured for 21 subjects 4–9 years (mean 6 years) after the baseline examination. The Pearson's correlation coefficient between the original and the repeat measurements was 0.91.

2.5. Other chemical measurements

For serum LDL cholesterol analysis, fresh serum was centrifuged for 16 h at 115 000 × g and 10°C (TGA-65 ultracentrifuge, Kontron Instruments, Milano, Italy) as described previously [21]. VLDL was removed from the top of the tube. LDL was precipitated from the bottom fraction with dextran sulphate and magnesium chloride and HDL cholesterol was measured from supernatant [21]. Cholesterol concentration was determined by an enzymatic colorimetric method (CHOD-PAP, Boehringer Mannheim, Germany) before and after the precipitation, and LDL cholesterol was calculated as the difference between these two measurements.

Serum triglycerides and fructosamine (glycated protein) were measured from frozen serum samples by an autoanalyzer (Kone Specific, Kone, Espoo, Finland) using reagents from Boehringer Mannheim. Blood glucose was measured using a glucose dehydrogenase method (Merck, Darmstadt, Germany) after precipitation of proteins by trichloroacetic acid. Serum fatty acids were measured with gas-chromatographic equipment (Hewlett-Packard 5890 series II with a flame ionization detector, Avondale, PA). An NB-35 1 capillary column was used (HNU-Nordion, Helsinki, Finland). Plasma fibrinogen was determined in fresh samples with a coagulometer based on clotting of extra thrombin (Amelung KC4, Heinrich Amelung, Lemgo, Germany).

2.6. Assessment of dietary intakes

The consumption of foods was assessed at the time of blood sampling with an instructed and interview-checked 4-day food recording by household measures [22]. The instructions were given and the completed food records were checked by a nutritionist. The intake of nutrients, including mercury, was estimated using Nutrica software. The databank of Nutrica is compiled using mainly Finnish values for the nutrient composition of foods.

2.7. Other measurements

The number of cigarettes, cigars and pipefuls of tobacco currently smoked daily and the duration of regular smoking in years were recorded using a self-administered questionnaire, which was checked by an interviewer. Re-interviews to obtain medical history were conducted by a physician. The family history of diabetes was defined positive, if either the biological father, mother, sister or brother of the subject had a history of diabetes.

A subject was defined as a smoker if he had ever smoked on a regular basis and had smoked cigarettes, cigars, or a pipe within the past 30 days. The consump-

tion of alcohol in the previous 12 months was assessed with the quantity–frequency method by using the Nordic Alcohol Consumption Inventory which contains 15 items [23]. The socioeconomic status was measured with a summary index that combined measures of income, education, occupation, occupational prestige, material standard of living, and housing conditions [24]. The maximal oxygen uptake ($VO_{2_{max}}$) was measured with the direct method in a maximal exercise test [25]. Blood pressure was measured with a random-zero mercury sphygmomanometer (Hawksley, UK) between 08:00 and 10:00. The measuring protocol included, after a supine rest of 5 min, three measurements in supine, one in the standing, and two in the sitting position at 5 min intervals. Data on the mean of six blood pressure values are presented in this paper. Body-mass index (weight per the square of height) and the waist-to-hip circumference ratio were assessed as described previously [25].

2.8. Statistical methods

The association of baseline hair mercury content and other risk factors with the 4-year change in the common carotid IMT was estimated and tested for statistical significance by correlation and regression analysis of the SPSS statistical software for IBM RS/6000 [26]. The heterogeneity of means of 4-year change in the common carotid IMT across the fifths of the hair mercury content was analyzed using linear covariance analysis of SPSS. The Duncan test was used to test the statistical significance of differences between individual quintile-specific means. This test takes into account the number of tests conducted.

3. Results

3.1. Study population

The distributions of relevant demographic, clinical and biochemical characteristics of the subjects at baseline are shown in Table 1. The 4-year change in the mean common carotid IMT had a mean of 0.11 mm, a minimum of −0.69 mm and a maximum of 1.29 mm. The respective values for the change in the maximal common carotid IMT were 0.26, −0.82 and 1.58 mm.

3.2. Hair mercury content and risk factors for carotid atherosclerotic progression

The baseline hair mercury content had significant direct crude correlations with age, plasma fibrinogen, waist-to-hip circumference ratio and serum HDL cholesterol and a significant negative correlation with the $VO_{2_{max}}$ (Table 2). The 4-year change in the mean common carotid IMT had significant direct associations with systolic blood pressure, hair mercury content ($r = 0.117$, $P = 0.0002$, slope 0.0087, SE of slope 0.0023), waist-to-hip circumference ratio, plasma fibrinogen and cigarette smoking and significant inverse association with the $VO_{2_{max}}$. Of variables not shown in Table 2, the

Table 1
Baseline characteristics of the study subjects ($n = 1014$)

Characteristic	Mean	S.D.	Minimum	Maximum
Mean common carotid IMT (mm)	0.77	0.17	0.42	2.12
Maximal common carotid IMT (mm)	0.95	0.24	0.54	2.71
Hair mercury content (μg/g)	1.8	1.98	0.0	23.3
Systolic blood pressure (mmHg)	131.9	16	88.7	211.7
Treatment for dyslipidemia (yes vs. no)	1.1%	N.a.[a]	0	1
Dietary iron intake (mg/day)	18.6	5.9	6.9	51.8
Cigarette smoking (pack-years)	8	15.3	0	117
Hangover frequency (times/year)	4.2	10.2	0	104
Age (years)	51.93	6.7	42	61.3
Maximal oxygen uptake (ml/kg × min)	31.2	7.5	6.4	58.2
Serum total cholesterol (mmol/l)	5.76	1.02	2.6	14.4
Serum LDL cholesterol (mmol/l)	3.85	0.93	0.68	8.46
Serum HDL cholesterol (mmol/l)	1.3	0.3	0.58	2.78
Serum triglycerides (mmo/l)	1.43	0.88	0.25	7.84
Dietary intake of vitamin C (mg/day)	86	53	6.6	550
Body-mass index (kg/m^2)	26.7	3.3	18.8	40.3
Waist-to-hip circumference ratio	0.94	0.06	0.75	1.51
Plasma fibrinogen (g/l)	3.00	0.56	1.74	6.71
Blood glucose (mmol/l)	4.68	0.98	3.2	16.1
Serum fructosamine (μmol/l)	250	35	132	576
Ratio of serum saturated fatty acids to the sum of monoenes and polyenes	0.52	0.06	0.15	0.76

[a] N.a., denotes not applicable.

Table 2
Intercorrelations between baseline characteristics of the study subjects[a]

	Hair Hg	SBP	Iron	Pack-years	Age	$VO_{2_{max}}$	WHR	Vitamin C	HDL	Fibrinogen	Fructosam	FA ratio[b]
Four-year change in mean common carotid IMT (mm)	0.12	0.12	0.06	0.07	0	0	0.10	0	0	0.08	0	0.02
Hair mercury content (μg/g)		0	0.03	0.03	**0.21**	**−0.20**	0.10	0	0.10	0.11	0	0.02
Systolic blood pressure (mmHg)			0	0	0.10	−0.10	**0.21**	0	0	0.07	0.11	0.12
Dietary iron intake (mg/day)				−0.10	0	**0.21**	−0.10	**0.27**	0	−0.10	0	−0.10
Cigarette pack-years					0	−0.10	0	**−0.19**	0	**0.25**	−0.10	0.05
Age (years)						**−0.50**	0.11	−0.10	0	0.12	0	0.08
Maximal oxygen uptake (ml/kg × min)							**−0.40**	0.13	**0.20**	**−0.25**	0	**−0.20**
Waist/hip circumference ratio								−0.10	**−0.20**	0.17	0	0.23
Dietary intake of vitamin C (mg/day)									0	−0.10	0	−0.10
Serum HDL cholesterol (mmol/l)										−0.11	0	−0.13
Plasma fibrinogen (g/l)											−0.10	0.02
Serum fructosamine (mmol/l)												**0.16**

[a] Correlation coefficients >0.06 are statistically significant at $P<0.05$ (two-sided, no correction for multiples). Coefficients with an absolute value <0.01 are marked as 0.
[b] Ratio of the sum of serum saturated fatty acids to the sum of monoenes and polyenes.

Table 3
The strongest baseline risk factors for the increase of the mean common carotid wall thickness multivariate regression model ($n = 1014$)[a]

Predictor	Regression coefficient	95% Confidence interval	Standardized regression coefficient	P-value
Systolic blood pressure (mmHg)	0.001	0.001, 0.002	0.12	0.0001
Hair mercury content (μg/g)	0.008	0.003, 0.012	0.102	0.0007
Antidyslipidemic medication (yes vs. no)	0.133	0.050, 0.216	0.093	0.0017
Dietary iron intake (g/day)	0.002	0.001, 0.004	0.085	0.0046
Cigarette pack-years	0.001	0.0002, 0.001	0.08	0.0068
Age (years)	0.002	0.0001, 0.003	0.069	0.0485

[a] The multiple correlation squared was 16.8% ($P<0.0001$) for the model including also the zoom left side, and the baseline mean IMT, an indicator variable for sonographer, follow-up days and maximal oxygen uptake (ml/kg × min). Other variables presented in Table 1 were tested for entry (pin = 0.200) but did not enter the model.

Table 4
The strongest baseline risk factors for the increase of the mean maximal common carotid in a step-up multivariate regression model ($n = 1014$)[a]

Predictor	Regression coefficient	95% Confidence interval	Standardized regression coefficient	P-value
Systolic blood pressure (mmHg)	0.002	0.0001, 0.002	0.121	0.0001
Maximal oxygen uptake (ml/kg × min)	−0.003	−0.005, −0.001	−0.103	0.0013
Cigarette pack-years	0.001	0.0003, 0.002	0.079	0.0083
Dietary iron intake (g/day)	0.003	0.001, 0.005	0.078	0.0105
Antidyslipidemic medication (yes vs. no)	0.148	0.031, 0.265	0.075	0.0131
Hair mercury content (μg/g)	0.008	0.001, 0.014	0.073	0.0174

[a] The multiple correlation squared was 14.3% ($P<0.0001$) for the model including also the zoom left side, and the baseline mean maximal IMT, an indicator variable for sonographer, follow-up days, and frequency of hangovers in the last 12 months. Other variables presented in Table 1 were tested for entry (pin = 0.200) but did not enter the model.

change in the mean common carotid IMT had significant unadjusted associations with treatment for dyslipidemia (yes versus no, Spearman $r = 0.10$) and serum triglycerides ($r = 0.07$).

3.3. Strongest risk factors for carotid atherosclerotic progression

In a multivariate linear step-up regression model, the strongest predictors of the increase in the mean common carotid IMT were elevated systolic blood pressure, high hair mercury content, treatment for dyslipidemia, high dietary intake of iron, cigarette smoking and old age (Table 3). The strongest predictors of the maximal common carotid IMT were elevated systolic blood pressure, high $VO_{2_{max}}$, cigarette smoking, high dietary intake of iron and treatment for dyslipidemia (Table 4).

3.4. Hair mercury content and carotid atherosclerotic progression

In a linear step-up regression model adjusting for other predictors for carotid atherosclerotic progression (Table 3), for each μg/g of hair mercury content, there was on the average an increment of 8 μm (7.3% of the mean) in the 4-year increase in the common carotid IMT.

There was a statistically significant difference in the increase in the mean common carotid IMT in the fifths of the hair mercury content, adjusting for relevant confounders ($P = 0.041$ for the differences between the fifths) (Fig. 1). This association remained statistically significant ($P < 0.05$) after the entry of extensive selection of measurements of psychological, social and economic factors, the intakes of other nutrients, such as cholesterol, different fatty acids, fibers, vitamins, selenium and other heavy metals, serum or plasma lipids, fatty acids, vitamins and selenium, medical history and measurements of cardiovascular health status.

While the increase in the mean common carotid IMT did not differ between the four lowest fifths of hair mercury content, the increase in the mean IMT was 0.037 mm/4 years (35.0%) greater in the highest fifth of hair mercury compared to the other fifths without adjustment ($P < 0.05$ in the Duncan test) and 0.034 mm/4 years (31.9%) greater after adjustment for relevant confounders (Fig. 1).

4. Discussion

This 4-year follow-up study in middle-aged men provides the first prospective evidence that the accumulation of mercury in the human body, as indicated by

high hair mercury content, is independently associated with accelerated progression of carotid atherosclerosis. In fact, high hair mercury content was one of the strongest risk factors for the increase in the common carotid IMT. Men in the highest fifth of hair mercury content had a 32% faster increase in the mean common carotid IMT than men in the other fifths. Together with our previous findings of the association of high hair mercury content with increased lipid peroxidation in vivo and with excess risk of myocardial infarction [9], the present finding provides evidence for the role mercury in the etiology of atherosclerosis and CVD.

High hair mercury content was associated with accelerated progression of carotid atherosclerosis, after controlling for a number of other risk factors for carotid atherosclerotic progression, including age, systolic blood pressure, serum lipids, treatment for dyslipidemia, cigarette smoking, the $VO_{2_{max}}$, plasma fibrinogen, the dietary intake of iron and vitamin C, serum fatty acids and the frequency of hangovers. The statistical control for age and $VO_{2_{max}}$ may be overly conservative, as the accumulation of mercury may be one reason for the increased occurrence of atherosclerosis in older ages and secondly, the $VO_{2_{max}}$ may have been lowered due to reduced left ventricular function as a result of atherosclerotic disease possibly caused by mercury. Adjusting for any other variable had only a minor effect on the strength of the association between hair mercury content and carotid atherosclerotic progression. For instance, neither the statistical adjustments for psychosocial factors, for the place of residence nor that for any nutrient, affected the association noticeably. On the basis of these extensive statistical analyses, high hair mercury content appeared to be an independent risk factor for carotid atherosclerotic progression.

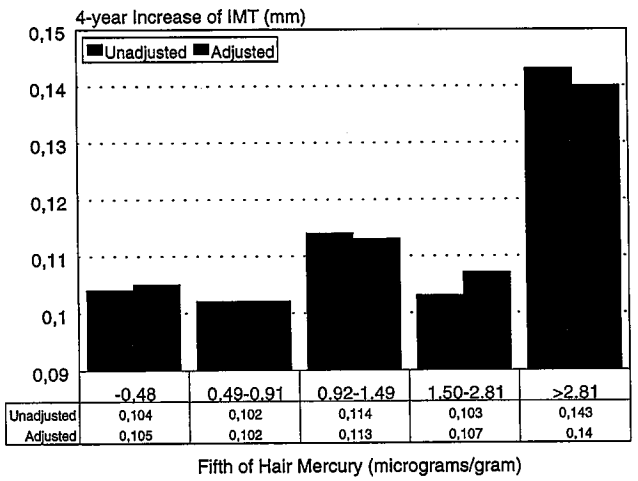

Fig. 1. Bar graph showing the unadjusted and adjusted mean 4-year change of the common carotid wall thickness (mean IMT) in men in the fifths of baseline hair mercury content. The means are adjusted for baseline mean systolic blood pressure, antidyslipidemic medication use, dietary iron intake, age, cigarette pack-years, vitamin C intake, plasma fibrinogen, serum HDL cholesterol, maximal oxygen uptake, serum fructosamine, serum fatty acid ratio, waist-to-hip circumference ratio, hangover frequency, serum triglycerides, mean wall thickness (IMT) at baseline and indicator variables for focusing depth, sonographer, length of follow-up, examination years and the use of pravastatin during follow-up.

Mercury may be a major environmental risk factor for atherosclerosis in humans even at subtoxic levels, which have not been recognised as harmful previously. The human body has no mechanisms to excrete mercury actively [9]. For this reason, mercury keeps accumulating in the body throughout life. An illustration of the irreversible nature of mercury deposition in the body is given by a case study in which increased levels of mercury were demonstrated in various organs in an autopsy 17 years after a single exposure to metallic mercury vapor [27].

We have earlier discussed in detail the possible mechanisms by which mercury exposure can increase the risk of CHD [9]. We have hypothesised that the atherogenic effect of methylmercury is a consequence of its lipid peroxidation enhancing effects.

Cell culture studies have established that mercury exposure promotes the generation of reactive oxygen-species (ROS). Cleavage of methylmercury gives rise to the generation of oxygen radicals, ultimately leading to lipid peroxidation [28]. Mercury(II) ions have in micromolar concentrations increased the production of superoxide anions in human neutrophils [29] and caused an up to 5-fold concentration-dependent increase in mitochondrial H_2O_2 production [30]. In another study, there were concentration-related depolarization of the inner mitochondrial membrane, increased H_2O_2 formation, glutathione depletion and formation of thiobarbituric acid reactive substances following the addition of mercury(II) to mitochondria isolated from kidneys of untreated rats [31]. Micromolar MeHgCl exposure of monocytes caused the generation of ROS, thiol depletion, altered mitochondrial function and apoptosis [32]. A number of studies have confirmed the mitochondrial dysfunction and apoptosis causing effect of both inorganic mercury(II) ions and methylmercury [33,34].

In an experiment in intact animals, the exposure of mice to mercury enhanced lipid peroxidation caused by carbon tetrachloride, as measured by organ content of MDA [35]. In another animal study, parenteral administration of mercuric chloride to rats enhanced lipid peroxidation in liver, kidneys, lung, testis and serum, as measured by MDA [36,37].

Secondly, mercury has a very high affinity to sulfhydryl groups [1–9], which in plasma proteins have been estimated to account for as much as 10–50% of the antioxidative capacity of plasma [38]. By binding to sulfhydryl groups mercury inactivates antioxidative thiolic compounds such as glutathione [39]. Glutathione has a central role in the regeneration of the tocopheroxyl radical to tocopherol. Mercury poisoning,

which is associated with increased lipid peroxidation in the liver and in the kidneys, also results in inactivation of superoxide dismutase and catalase [39], two important enzymes that scavenge H_2O_2. Mercury also inactivates paraoxonase [40], an extracellular antioxidative enzyme, in which a genetic defect is associated with an increased risk of AMI [41]. It is conceivable that the role of mercury accumulation might be greater in individuals and in populations with lowered antioxidative defences, such as lowered paraoxonase activity.

Thirdly, mercury forms an insoluble compound with selenium, the mercuric selenide [42], thus binding selenium in an inactive form that cannot serve as a component for glutathione peroxidase [43], an important scavenger of H_2O_2 and lipid peroxides. Selenium has been observed to protect against the peroxidative liver injury caused by mercury [44]. We demonstrated in a randomized placebo-controlled trial that supplementation of men and women who had low serum selenium with 100 μg organic selenium daily for 4 months decreased the total mercury concentration of pubic hair by 34% [45].

We have reported earlier that both high hair mercury content and high urinary mercury excretion were associated with elevated titres of immune complexes containing oxidised LDL in a population-based sample of middle-aged men from eastern Finland [9]. Also, as we have reported earlier, low serum selenium concentration was associated with increased titre of autoantibodies against oxidised LDL [5]. These data are consistent with the role of mercury in lipid peroxidation in vivo.

Hair mercury content is considered a good indicator of long-term intake of mercury [8]. It mostly reflects the dietary intake of organic mercury, principally methylmercury, which is almost totally absorbed in the gastrointestinal tract [8]. The biological half-life of methylmercury is almost 3 months in the human [46]. Thus, mercury has a very slow turnover in the human body. This is reflected as very good long-term tracking of the hair mercury content in the present study population ($r = 0.91$ for long term reproducibility).

The present study is the first documentation of the association between the accumulation of mercury in the human body and accelerated progression of atherosclerosis. This novel finding needs to be retested in additional population studies, mercury feeding studies in animals and eventually, in mercury depletion trials in humans. Also, hair or toenail samples should be collected in all prospective population studies to enable mercury measurements. As mercury pollution is widely spread over the entire world, its health effects are of considerable scientific and public health importance. If our observations are confirmed, the limitation of mercury intake may be considered an important measure in the primary prevention of atherosclerotic CVD.

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