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Original Article

Association of Aging with Minerals in Male Japanese Adults

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KEY WORDS: Aging; Mercury; Calcium; Magnesium; Cupper; Zinc; Mineralome;Anti-aging

Abstract

In order to examine possible association of aging with minerals, we measured hair concentrations of 24 bio-elements including essential minerals and toxic metals in over 1500 male Japanese adults aged 20-60 years. Several minerals were found to be significantly and positively or inversely correlated to aging. The most age-correlated element was mercury (Hg) with the highest regression coefficient of $r = 0.417$, followed by boron (B) ($r = 0.189$), potassium (K) ($r = 0.186$), arsenic (As) ($r = 0.178$), selenium (Se) ($r = 0.153$) and sodium (Na) ($r = 0.131$) with the p-value of $p < 0.0000$ for every element. Using the regression equation of Age = 13.9 Log Hg – 12.5 obtained, a 10-fold increase in mercury level was estimated to associate with a 13.9-year increment in aging. The most inverse-correlated mineral to aging was calcium (Ca) ($r = -0.207$), followed by magnesium (Mg) ($r = -0.174$), cupper (Cu) ($r = -0.147$), and zinc ($r = -0.105$; $p < 0.0001$).

These findings suggest that some minerals contribute to aging and higher dietary mercury intake may be associated with acceleration of aging. Dietary intake of the competitive minerals against mercury, such as calcium, magnesium, cupper and zinc, may be useful for controlling aging in Japanese.

Introduction

For the last several years, we have been measuring scalp hair mineral concentrations in over 50 thousand people ranging from infant to elderly, in order to assess the relationship between minerals and physical or mental disorders. In previous study on hair toxic metal levels in a total of 5846 Japanese, we demonstrated that there are two types in accumulation profile of toxic metals, and that infants and children are under high exposure to lead, cadmium or aluminum [1,2].

Mercury, especially organic methylmercury is well known to accumulate in kidney, liver and fat-rich tissues like brain and adipose tissue, and to exhibit an age-dependent increase profile with gender-difference in Japanese [1-3]. This toxic metal is well known to not only inhibit various enzymatic reactions and metabolic processes but also enhance lipid peroxidation, progression of atherosclerosis and the risk of myocardial infarction [4-7].

Aging is a complex, progressive and irreversible processes occurring to molecules, to cells and to the whole organisms, finally ending with death. Better understanding of molecular mechanisms of aging could not only improve medical care of the elderly, but also hold out some hope in finding feasible solution to slow down the aging process. The purpose of this study was to examine possible role of toxic metals and essential minerals in aging. In this study, 24 minerals in hair were measured in over 1500 of male Japanese adults aged 20-60 years, the relationship between the each mineral and aging was examined, and the association of mineral status “mineralome” with aging/anti-aging was discussed.

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Materials and Methods

·Materials

Hair is a suitable medium for monitoring human exposure to mercury and other heavy metals. Scalp hair samples (about 0.2 g) were collected on the basis of informed consent from 1540 male subjects aged 20-60 years old in the Tokyo metropolitan district, and used for mineral analysis

·Hair mineral analysis

Hair sample of 75 mg was weighed into 50ml plastic tube, and washed twice with acetone and then with 0.01% Triton solution, in accordance with the procedures recommended by the Hair Analysis Standardization Board [8]. The washed hair sample was mixed with 10 ml of 6.25% tetramethylammonium hydroxide (TMAH, Tama Chemical) and 50 μl of 0.1% gold solution (SPEX Certi Prep.), and then dissolved at 75 ℃ by shaking for 2 hours. After cooling the solution to room temperature and adjusting its volume gravimetric, the obtained solution was used for mineral analysis. The mineral concentrations were measured with inductively coupled plasma mass spectrometry (ICP-MS; Agilent-7500i and 7500c) [9], and were expressed as ng/g hair (ppb) or μ g/g (ppm).

·Statistical analysis

The hair mineral concentrations were distributed nearly in lognormal manner, and the values of mineral contents were converted to the logarithm for statistical analysis. The geometric rather than arithmetic means were used as representative of hair mineral levels. The relation between aging and minerals was investigated by multiple linear regression analysis. Statistical significance was determined using the Welch's t-test.

Results

Twenty-four mineral concentrations in the hair of 1540 male Japanese adults were measured with ICP-MS, and their geometric mean values for the age brackets are shown in ***Table 1***. The scattered plots showing the association of aging and the representative minerals with the highest positive and inverse regression coefficient are shown in ***Fig. 1 and 2***, respectively. The most correlated mineral to aging was mercury (Hg) with the highest regression coefficient of r = 0.417, followed by boron (B; r = 0.189), potassium (K; r = 0.186), arsenic (As; r = 0.178), selenium (Se; r = 0.153), and sodium (Na; r = 0.131), with the low p-value of $p < 0.0000$ for every element (***Table 2***). Iodine (I) also tended to be positive-correlated with aging ($p < 0.0001$). In contrast, the most inverse-related mineral to aging was calcium (Ca; r = -0.207), and followed by magnesium (Mg; r = -0.174), cupper (Cu; r = -0.147), nickel (Ni; r = -0.118) and zinc (Zn; r = -0.105) with $p < 0.0001$ for every element.

The regression equation between aging and mercury or calcium was calculated Age = 13.9 Log Hg – 12.5 or Age = – 6.0 Log Ca + 71.2 (***Fig. 3***). Using these regression lines, we estimated a 13.9-year increment associated with an increase in concurrent hair mercury levels from 1.0 to 10 ppm, and a 3.0-year decrement associated with an increase in the calcium level from 100 to 320 ppm.

Table 1 ***Geometric Means of Hair Mineral Concentrations in Male Japanese***

	Mean Hair Mineral Concentration (ppb)				
	Age Bracket				
	Twenties (n = 403)	Thirties (n = 552)	Fourties (n = 331)	Fifties (n = 236)	Sixty (n = 29)
Age	25.7	34.3	44.0	54.4	60.0
Na	24,265	25,403	30,393	32,932	42,527
K	17,536	21,179	24,128	30,140	34,835
Mg	60,687	51,429	46,908	40,223	30,068
Ca	519,201	439,623	393,512	326,704	251,891
Cr	53.9	53.5	52.4	62.3	64.5
Mo	30.4	32.6	32.7	32.5	39.4
Mn	121	128	132	137	110
Fe	5,701	5,753	5,740	6,122	6,012
Cu	22,410	20,987	20,227	17,212	13,772
Zn	142,378	141,367	138,700	131,968	120,749
P	149,802	153,976	155,240	150,739	150,789
Se	531	572	607	615	644
V	20.2	22.8	21.6	17.7	19.2
Co	3.6	3.4	3.2	3.0	2.0
Ni	267	227	207	191	174
B	315	373	411	487	588
Ge	89.1	90.0	93.9	94.2	108.9
Br	3,638	3,399	3,566	3,588	5,337
I	377	428	412	534	644
Cd	13.9	13.2	12.9	11.5	10.7
Hg	2,828	3,821	5,424	6,296	6,831
Al	3,770	3,756	3,588	3,652	3,499
Pb	560	583	518	460	439
As	38.6	44.8	47.5	55.8	75.6

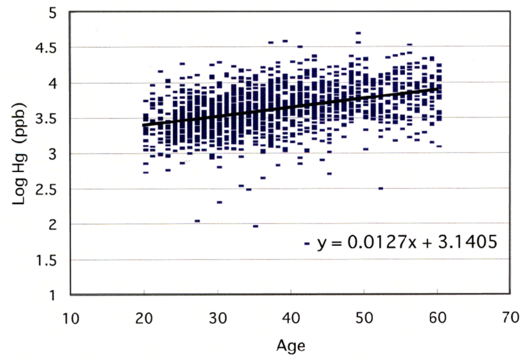

Fig. 1. Relationship between aging and hair mercury level in male Japanese adults.
The ordinate is expressed as the logarithmic value of hair mercury concentration (ppb). The regression equation was obtained from the data of 1552 male Japanese adults.

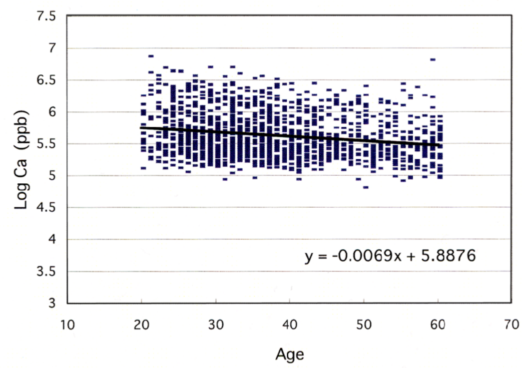

Fig. 2. Relationship between aging and hair calcium level in male Japanese adults.
The ordinate is expressed as the logarithmic value of hair calcium concentration (ppb). The regression equation was obtained from the data of 1552 male Japanese adults.

These results suggest that the individuals with accelerated aging have some mineral imbalance in the body, namely a high mercury accumulation and low di-valence electrolyte levels with high mono-valence electrolyte levels, and also low cupper and/or zinc levels.

Table 2 Relationship between Aging and Hair Minerals

Mineral	Reg. Coef.	P value	Significance	Mineral	Reg. Coef.	P value	Significance
Hg	0.417	0.0000	****	Ca	-0.207	0.0000	****
B	0.189	0.0000	****	Mg	-0.174	0.0000	****
K	0.186	0.0000	****	Cu	-0.147	0.0000	****
As	0.178	0.0000	****	Ni	-0.118	0.0000	****
Se	0.153	0.0000	****	Zn	-0.105	0.0001	****
Na	0.131	0.0000	****	Pb	-0.089	0.0009	***
I	0.095	0.0001	***	Cd	-0.067	0.0189	*
Fe	0.061	0.0193	*	Co	-0.053	0.0172	*
Mo	0.056	0.0125	*	Al	-0.025		
Mn	0.054	0.0356	*	V	-0.024		
Ge	0.054	0.0046	**				
Cr	0.052	0.0419	*				
Br	0.015						
P	0.007						

Reg. Coef.: Regression coefficient
****: P < 0.0001 ***: P < 0.001 **: P < 0.01 *: P < 0.05

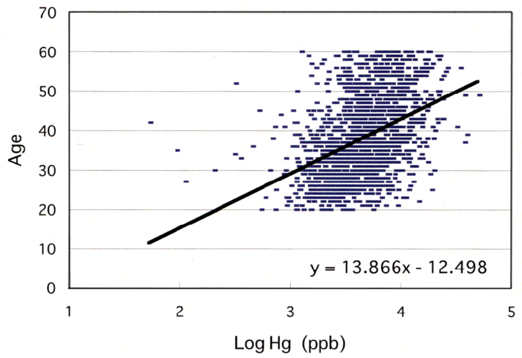

Fig. 3. Relationship between hair mercury level and aging in male Japanese adults
The abscissa is expressed as the logarithmic value of hair mercury concentration (ppb). The regression equation was obtained from the data of 1552 male Japanese adults.

Discussion

Hair mineral analysis has been used in forensic medicine, in screening populations for toxic metal poisoning and in monitoring environmental pollutants [10-12]. Furthermore, its diagnostic use for individual disease and symptom has been tried, but remains to be confirmed scientifically [13]. Our previous studies clarified that hair levels of some toxic metals such as lead, cadmium and aluminum are extraordinarily high in infants and children [1], that autistic children are suffered from a global mineral deficiency in various essential trace elements [9], and also that there is a significant relationship between mercury accumulation and body mass index [14].

Aging is generally accepted to be natural and physiological response, and its controlling or anti-aging was thought a non-scientific tale and not a subject for scientific research. Since the last century's end, scientific research reports on aging and anti-aging are increasing, and also even anti-aging medicine are expected.

This paper demonstrated that mercury exhibits the highest-significant correlation to aging, with the regression coefficient of $r = 0.417$ ($p < 0.0000$). This finding suggests that mercury accumulation plays a considerable role in physiological senescence, particularly in Japanese.

This paper also showed that there are high-significant, positive or negative relationships between aging and the four principal electrolyte levels in hair (***Fig. 2*** and ***Table 2***). Mono-cation electrolytes, potassium and sodium, were significantly correlated positively to aging. In contrast, di-cation electrolytes, calcium and magnesium, correlated inversely to aging; the higher di-cation levels, the lower aging. These findings suggest the possibility that these four electrolytes play an important role in controlling aging, and low dietary intake of calcium and magnesium may lead to accelerate aging.

It is well accepted that magnesium ion, Mg^{2+}, is essential for myriad biochemical processes and regulates various Ca^{2+} -induced physiological responses. Furthermore, the disorder of mineral homeostasis relates to the pathogenesis of hypertension and arteriosclerosis, relating to the incidence of heart attack events [15-17]. In addition, hypo-magnesemia is reported to be common in hospitalized patients, especially in elderly patients with coronary artery disease (CAD) and/or those with chronic heart failure, and is associated with increased mortality from CAD [18-20].

Shechter et al. [18,19] demonstrated the therapeutic effect of oral magnesium supplementation in double blind clinical study. Witte et al. [21,22] reported that long-term multiple micronutrient supplementation can improve left ventricular (LV) volumes, left ventricular ejection fraction (LVEF) and quality-of-life (QOL) scores in elderly patients with heart failure due to LV systolic dysfunction. Dairy higher-calcium diet is also reported to attenuate weight gain and accelerate fat loss to a greater degree than do supplemental sources of calcium [23]. Higher dietary calcium intake is also known to inhibit lipogenesis and promote lipolysis, lipid oxidation and thermogenesis. Thus, evidence is accumulating that a strategy of long-term micronutrient supplementation might improve symptoms and cardiac function in elderly patients with chronic heart failure, leading to a good quality of aging life [21-23].

In toxic metals, mercury exhibited the highest-significant correlation to aging with the regression coefficient of $r = 0.417$ (Age = 13.9 Log Hg – 12.5; $p < 0.0000$) (***Fig. 1 and 3***). Using this regression equation, a 10-fold increase in hair mercury level was estimated to associate with a 13.9-year increment in aging. Mercury is considered to be toxic at any level in the body, and at high concentrations causes liver and kidney damage and also neurological symptoms/disorders [24]. In addition, this toxic metal is well known to not only inhibit various enzymatic reactions and metabolic processes including lipid metabolism but also enhance lipid peroxidation, progression of atherosclerosis and the risk of myocardial infarction and/or stroke, leading to death [5-7]. Much of mercury accumulated in body is derived from dental amalgam fillings [29,30] and dietary intake of methylmercury-contaminated food, for example, fishes (especially large fishes like tuna, swordfish or shark) and shellfishes [2,3]. Recently, Yasuda et al [14] reported that male Japanese hair mercury concentration is related to their body-mass index, which is well known to be associated with overall mortality. Higher BMI is reported to be a high risk factor for various cancers [25-27], and also to be one of the most predictive of death from cardiovascular disease in men (relative risk, 2.90) [28].

It is noted that calcium, magnesium, cupper and zinc, representative competitor elements against mercury, are inversely correlated to aging in contrast to mercury (***Table 2***). The estimated aging increment associated with an increase in hair mercury level from 1 to 10 ppm was a 13.9-year. While, associated with an increase in the calcium from 100 to 320 ppm, a 3.0-year decrement was estimated. These findings suggest the possibility that the intake of mercury induces an acceleration of aging, while the intake of appropriate amount of calcium leads to improve the accelerated aging.

In elderly people, the importance of zinc, particularly for behavioral and mental function, immune and antioxidant system, and bone metabolism has been reviewed [31]. Restoring functional mineral homeostasis in aging people is an attractive field for anti-aging research [32] and anti-aging medicine [33-35].

Some minerals are reported to relate to the pathogenesis of cancer. Akbaraly et al. reported in the EVA study with an elderly population that mortality rates during the 9-year follow-up were significantly higher in individuals with low selenium and the underlying causes of death were cancer-related [36]. At present, a large-scale Phase III clinical study, the Selenium and Vitamin E Cancer Prevention Trial (SELECT), sponsored by the National Cancer Institute, is going with final results anticipated in 2013 [37].

Hair mineral analysis provides global information about the deficiency/excess profile of multiple minerals (mineralome) that contribute to various physiological and/or adverse events in the human body, and therefore is useful for health and risk assessment. And, it is possible that well-adjusted body mineral levels and their balance are effective not only for maintaining health, but also for better aging. Further understanding of molecular and cellular mechanisms of aging could not only improve medical care of the elderly but also hold out some hope in finding feasible solutions to slow down the aging process.

Conclusions

In this study, a high-significant and positive or inverse relationship between aging and some essential minerals was demonstrated in male Japanese adults. In particular, mercury was found to high-positively correlate to aging, and a 10-fold increase in mercury level was estimated to associate with a 13.9-year increment in aging. These findings suggest that the aging of Japanese is partly regulated by electrolytes, trace bio-elements and their balance in body, and also fairly affected by dietary mercury intake. The present findings in this cross-sectional study remain to be confirmed by diachronic studies.

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Legend to figures

Fig. 1. Relationship between aging and hair mercury level in male Japanese adults.

The ordinate is expressed as the logarithmic value of hair mercury concentration (ppb). The regression equation was obtained from the data of 1552 male Japanese adults.

Fig. 2. Relationship between aging and hair calcium level in male Japanese adults.

The ordinate is expressed as the logarithmic value of hair calcium concentration (ppb). The regression equation was obtained from the data of 1552 male Japanese adults.

Fig. 3. Relationship between hair mercury level and aging in male Japanese adults.

The abscissa is expressed as the logarithmic value of hair mercury concentration (ppb). The regression equation was obtained from the data of 1552 male Japanese adults.