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Zeitschrift für
Gerontologie

Z Gerontol 27:324–327 (1994)

Weitere Originalia

Levels of trace elements in blood in healthy aging subjects

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Serumspiegel von Spurenelementen bei gesunden älteren Erwachsenen

Summary: The effects of age and sex on the serum levels of trace elements were determined after an overnight fast in 80 ambulatory, disease-free adults who had undergone rigorous health screening. Significant age and sex differences were found for Mn. Blood levels of Cu and Zn showed both age and sex differences. No age or sex differences were found for Pb, Cd, Cr, Ni, Se, and Al.

Zusammenfassung: Die Einflüsse von Alter und Geschlecht auf die Serumspiegel von Spurenelementen wurden nach einer Nacht Fasten bei 80 ambulant untersuchten, gesunden Erwachsenen bestimmt. Signifikante Alters- und geschlechtsspezifische Unterschiede wurden für Mn gefunden. Weitere Alters- und geschlechtsspezifische Unterschiede im Blutspiegel ließen sich für Cu und Zn nachweisen. Keine signifikanten Unterschiede wurden für Pb, Cd, Cr, Ni, Se und Al gefunden.

Key words: Aging – blood – trace elements – healthy human – gender effects

Schlüsselwörter: Blut – Alter – Spurenelemente – gesunde Personen – Geschlecht

Introduction

There are few studies on the effect of normal aging on tissues levels of trace elements in humans. The compilation of normal values for the elderly is complicated by a number of factors, including the presence of multisystem disease, the effects of diet and nutrition, the use of medication, and the psychological and anatomical changes associated with aging. It is necessary to exclude individuals in whom these values might have been altered by disease in order to estimate the extent to which values differ according to age and sex.

There are very few studies on trace elements in healthy subjects, that is, including young and old people. Recently, Minoia et al. (15) reported reference values for a great number of trace elements in urine, blood, and serum. Unfortunately, this comprehensive study did not investigate the influence of age. Favier and Ruffieux (6) found no gross changes with age for serum levels of Cu, Zn, and Mn in a population younger than 60 years.

Because most studies have not been concerned with a direct comparison between aged and young subjects in a well-defined population, the purpose of the present study was to measure blood levels of trace elements in healthy, ambulatory subjects recruited outside the hospital population and covering both young and old age ranges. The subjects were selected on the basis of rigorous health-related eligibility criteria.

Subjects and Methods

Subjects

Subjects were recruited by newspaper and circular advertisements and were paid for their participation in the study. Each subject was screened for general health in a semi-structured interview (8) and by physical examination. Subjects were invited to participate in the protocol if they had no chronic serious illness and if they had not been treated for an acute medical condition in the past 3 months. Specific details of the study design, population description, disease ascertainment, and methodology were reported previously (2), but certain relevant points are summarized here. Subjects were divided into four age groups: 17–23, 37–43, 57–63 and 76–85 years (10 men and 10 women per age group). There were no dietary restrictions. Subjects were of acceptable weight for height; the weight-to-height ratio did not provide evidence of energy imbalance. All the subjects lived in the same regional area and shared a common drinking water supply. The study was approved by the Medical Ethical Council of the University Hospital and all subjects gave their informed consent.

Procedure

Venous blood samples were collected after an overnight fast between 8:00 and 9:00 am, with the subject in a half-sitting position. Appropriate vacuum tubes were used (Beckton

Table 1. Methods of analysis. Abbreviations: S = Serum, ZGFAAS = Graphite Fumace Atomic Absorption Photometry with Zeemann correction, CV intra = intra-assay coefficient of variation, CV inter = inter-assay coefficient of variation

Analyte		Method	Analyzer	CV intra	CV inter
Al	S	ZGFAAS	Perkin Elmer 3030	12	8
Cd	S	ZGFAAS	Perkin Elmer 3030	11	18
Cr	S	ZGFAAS	Perkin Elmer 3030	3	2
Cu	S	ZGFAAS	Perkin Elmer 3030	2	4
Mn	S	ZGFAAS	Perkin Elmer 3030	5	5
Ni	S	ZGFAAS	Perkin Elmer 3030	8	7
Pb	S	ZGFAAS	Perkin Elmer 3030	15	8
Se	S	ZGFAAS	Perkin Elmer 3030	4	3
Zn	S	ZGFAAS	Perkin Elmer 3030	3	6

Table 2. Median values (md) and minimum (min) and maximum (max) blood levels of trace elements per age group and sex.

	Age group	Men			Women		
		md	min	max	md	min	max
Cu	17–23	13.1	10.6	18.5	18.8	14.1	29.0
	37–43	15.0	10.8	26.3	18.6	14.0	21.7
	57–63	17.2	14.3	18.9	17.9	14.2	22.3
	76–85	20.0	14.5	23.1	18.8	14.5	20.6
Zn	17–23	17.35	15.00	21.40	14.85	13.30	18.60
	37–43	16.70	14.10	18.90	16.05	14.60	18.00
	57–63	15.95	13.60	18.90	15.75	13.20	18.30
	76–85	14.80	6.10	15.70	15.80	13.20	17.70
Pb	17–23	0.26	0.11	0.77	0.23	0.10	0.36
	37–43	0.29	0.25	0.53	0.22	0.12	0.57
	57–63	0.26	0.13	0,52	0.35	0.20	0.49
	76–85	0.29	0.19	0.50	0.30	0.14	0.56
Cd	17–23	3.5	1	22	8.0	1	23
	37–43	5.5	1	10	5.5	1	24
	57–63	9.0	1	19	5.0	2	20
	76–85	7.0	3	16	6.5	3	12
Se	17–23	1.00	0.78	1.14	1.06	0.80	1.22
	37–43	1.17	1.06	1.58	1.08	0.94	1.33
	57–63	0.98	0.85	1.27	1.12	0.98	1.49
	76–85	0.96	0.89	1.02	1.11	0.96	1.60
Al	17–23	0.33	0.11	0.74	0.35	0.11	0.48
	37–43	0.22	0.11	0.59	0.15	0.11	0.33
	57–63	0.20	0.11	0.41	0.22	0.11	0.44
	76–85	0.22	0.10	0.48	0.26	0.10	0.44
Cr	17–23	6.0	2	11	5.5	2	9
	37–43	6.0	2	9	5.5	2	10
	57–63	8.0	3	15	8.5	2	13
	76–85	6.5	2	9	8.0	2	10
Mn	17–23	12.0	7	20	17.0	13	25
	37–43	14.5	11	20	17.0	12	23
	57–63	19.0	9	22	19.0	9	23
	76–85	10.5	4	17	12.5	8	23
Ni	17–23	9.0	3	22	10.5	6	20
	37–43	10.5	4	46	9.0	3	18
	57–63	8.5	4	13	9.0	3	21
	76–85	8.0	2	35	7.5	4.0	12

Dickinson, Trace Elements) and approximately 100 ml blood was obtained from each subject. The mean time between withdrawal and centrifugation was less than 30 min. The tubes were centrifuged for 15 min at 4000 rps. Serum levels of trace elements (Al, Cd, Cr, Cu, Mn, Ni, Pb, Se, and Zn) were measured using the methods listed in Table 1. A questionnaire was completed for information concerning the use of alcohol, tobacco, and caffeine, and for information about weight and height.

Statistical analysis

Because many of the laboratory values deviated markedly from a Gaussian distribution, ranks over all observations were calculated and used for a two-way ANOVA with the factors age (4 levels) and sex (2 levels) (17). Because of the risk of inflating the statistical error as a result of performing multiple F-tests, the Bonferroni correction (11) was applied to adjust the significance levels. A probability level for the overall two-way ANOVA F-tests of less than 0.005 (0.05/9) was considered significant. In addition, Duncan's multiple range test was used as a post hoc test to evaluate significant main and interactive effects (17).

There were no significant differences between age groups in the number of subjects who consumed alcohol ($F(1.75) < 1$, ns) or who used caffeine ($F(1.75) = 1.46$, ns), nor were there differences in smoking habits ($F(1.75) = 1.49$, ns) or height ($F(1.75) = 1.49$, ns). The groups had different weights ($F(1.75) = 3.49$), $p < 0.05$), the second and the third age groups being the heaviest.

Results

The results of laboratory analysis by age and sex are summarized in Table 2. Table 3 presents the results of the two-way ANOVA for the main and interactive effects of age and sex on the selected blood analytes.

Table 3. Differences in trace elements in blood by age, sex, and the interaction of age and sex (results of the two-way ANOVA on ranks (5)). F-values are presented with significance levels. The Bonferroni correction for error inflation was applied for the overall two-way ANOVA F-test (significance level < 0.006). If the overall F-tests were significant, additional tests for age, sex and interaction were performed.

Trace element	Overall F-test	Main effects		Sex · Age interaction
		Age	Sex	
	F(1.72)	F(1.75)	F(1.78)	F(1.73)
Cu	6.46***	3.12*	11.36**	4.96**
Zn	3.67**	4.01*	1.78 ns	3.98*
Pb	1.61 ns			
Al	1.08 ns			
Se	2.63 ns			
Cd	1.33 ns			
Cr	< 1 ns			
Mn	4.47***	6.85***	9.55**	
Ni	< 1 ns			

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

As seen in Tables 2 and 3, significant and independent age and sex differences were found for the levels of Mn. Mn levels increased with aging, followed by a decline in the oldest age group. Women had higher levels than men. Interactive effects between age and sex were found for the levels of Cu and Zn. Cu levels were highest in young women, whereafter the values were relatively stable with increasing age. In contrast, the levels of Cu rose in men over all age groups. The levels of Zn decreased with increasing age, especially in men. There were no significant overall differences between the two sexes in the mean Zn concentrations, although elderly women had higher levels than elderly men. No significant sex or age differences were found for Se, Cr, Pb, Ni, Al, and Pb.

The effects of smoking on the blood concentrations of trace elements were evaluated. ANOVA revealed a significant main effect only for the levels of Cd ($F = 11.73$, $p < 0.001$). Subjects who smoked more than 10 cigarettes per day had significantly higher levels of Cd in their blood.

Discussion

Studies on normal disease-free biological aging must exclude as many subjects as possible with signs indicative of disease. Even in healthy, disease-free elderly subjects, the physiological changes associated with aging gradually impair the regulatory mechanisms of multiple organ systems, such as renal function and cardiac output (16). Studies of apparently healthy elderly persons therefore require a strict definition of the health status of "normal" subjects.

There is little literature on the effect of aging on trace elements. Zn appears to have been studied the most, although the data are conflicting. In studies confined to human adults, some authors suggest that there is no age-dependent effect (6). Woodward et al. (23) found a consistent decline in serum Zn levels in aging mice. Our findings of declining Zn levels with age, especially in men, are in accordance with the data of Licastro et al. (13), Struck and Hillesheim (19), and West and Ash (22). No sex effects were demonstrated by West and Ash (22), whereas there are other reports of lower Zn levels in women (6).

It is now well established that Cu is an essential trace element for the optimal activity of enzymes in a number of tissues and that Cu may play a role in the pathogenesis of osteoporosis (4). Favier and Ruffieux (6) found serum Cu levels to be lower in men than in women which is consistent with the findings of Cartwright and Wintrobe (3), West and Ash (22), and the present results. The present findings of an age-related increase in levels of Cu are in accordance with the data reported by Struck and Hillesheim (19). In contrast, Favier and Ruffieux (6) found no significant variation with age.

We did not find levels of Se to vary significantly with age or sex. Similarly, Miller et al. (14) and Lane et al. (12) found no significant decreases in serum Se concentrations with age. In contrast, Verlinden (20) found a decrease in elderly people over 60 years. Although Schroeder et al. (18) suggested that a Cr deficiency developed with aging, there are later studies which confirm our present findings that there is not a significant decrease in Cr blood levels with age (1, 21). Mn is another element for which there are few reports in the literature. Favier and Ruffieux (6) found that mean serum Mn levels were identical for both men and women, and that there was a moderate decrease with age in men (results in women presented a greater variance). We found that there was an increase in Mn levels over the first three age groups, but that levels declined in the oldest age group. In addition, women had higher levels than men.

We could demonstrate neither sex nor age-related variations in blood levels of Pb, Cd, Ni, and Al in our study population. Iyengar (9) found that women had lower blood levels of Pb than men. The effects of smoking on Cd levels are well established (10). The fact that we found no differences in Cd levels with age may indicate that the habit of smoking is a much stronger determinant of Cd levels than aging. Ni is poorly documented in the literature (10), and has mostly be investigated in the context of occupational exposure (7) without special reference to aging. There are – to our knowledge – no studies on the effect of aging in healthy subjects. It is clear that the determination of Al is very sensitive to external contamination, and it is possible that many erroneous results have been published in the literature (10).

Although the sample size was relatively small when broken down into age or sex groups, our results suggest that there are age and/or sex differences for several of the elements studied. It needs to be stressed that the sample size in the present study was too small for the definition of reference values. The design of the study, however, was chosen for its sensitivity in studying the effects of aging because subjects were allocated to four distinctly limited age groups. It can be concluded that serum concentrations of three of the nine trace elements studied are influenced significantly by age and/or sex and that this influence should be reflected in the reference information provided by clinical laboratories.

Acknowledgements

The authors wish to express their gratitude to the personnel of the Laboratory of Clinical Chemistry of the University Hospital Maastricht and to Mrs. German Wijnen for their excellent technical assistance.

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Received November 12, 1993

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