Bloodlettings in Hemochromatosis Result in Increased Blood Lead (Pb) Concentrations

Mazyar Yazdani [1], Sonia Distante [1], Lars Mørkrid [1 2], Rune J Ulvik [3 4], Bjørn J Bolann [5 6]

•[1]Department of Medical Biochemistry, Oslo University Hospital, Oslo, Norway.
•[2]Department of Clinical Medicine, University of Oslo, Oslo, Norway.
•[3]Department of Clinical Science, University of Bergen, Bergen, Norway.
•[4]Department of Medicine, Section of Hematology, Haukeland University Hospital, Bergen, Norway.
•[5]Department of Clinical Science, University of Bergen, Bergen, Norway. bjorn.bolann@uib.no.
•[6]Department of Medical Biochemistry and Pharmacology, Haukeland University Hospital, Bergen, Norway.

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Introduction

Disturbances in iron metabolism affect the metabolism of metals other than iron. Multiple interrelationships between serum levels of iron and various trace elements have been demonstrated. Iron-binding proteins like transferrin and ferritin can bind other metals in addition to iron [1].

Barton et al. [2] found that hemochromatosis patients, especially homozygotes, absorb increased quantities of lead. In contrast, Åkesson [3] demonstrated that blood concentrations of cadmium, but not lead, were significantly higher in bloodletted hemochromatosis patients than in paired controls. The reason for this discrepancy is not clear. Beyond these and our previous study [4], we have found no other report on the effects of bloodlettings on trace element status in hemochromatosis patients.

The **aim** of this study was to see if bloodlettings in hemochromatosis patients affect whole blood concentrations of the environmental pollutants lead (Pb), mercury (Hg), and cadmium (Cd).

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Materials & Methods

Subjects: 28 newly diagnosed Hemochromatosis patients were recruited, a group of healthy persons (n=21) without hemochromatosis and not subject to bloodlettings were included as controls.

Exclusion criteria: less than 18 years age, major blood loss or transfusion within the last 3 months, concurrent disease, pregnancy, installed osteosynthesis materials (e.g., after fractures), or other metal items.

Methods: fasting blood samples were collected for trace elements (Pb, Hg and Cd) and hematological analyses and serum sample for iron status and clinical chemistry measurements. Urine samples were also collected for most of the patients.

Trace elements were measured by inductively-coupled plasma mass spectrometry (ICP-MS) on Perkin Elmer ELAN DRC-e (PerkinElmer, Toronto, Canada) using a standard mode. [4]

Intervention: all the patients were treated with venesection (450 mL), either weekly or biweekly until normalization of iron parameters, which could take up to 24 bloodlettings.

Statistics: Pre-phlebotomy *blood* and *urine* concentrations were compared with post-phlebotomy values in the same individuals using a prospective, pairwise design. All paired analyses were done in the same analytical run. Wilconox and Spearman's rho were calculated.

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Results

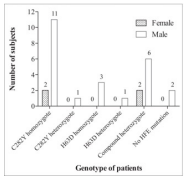

Fig. 1
Age and sex distribution of subjects

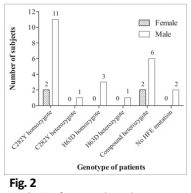

Fig. 2
Distribution of genotypes by gender

	Bloodletted	n	Hb	Creatinine	GGT	ALT	ALP
Ferritin	No	28	**0.439***	0.477	**0.610****	**0.791****	0.351
	Yes	28	0.294	**−0.407***	0.356	−0.262	−0.192
	Control	21	**0.515***	0.168	**0.468***	0.410	**0.593****

Table 1
Correlations among variables. Correlation (Spearman's rho coefficients) of serum ferritin with Hb and liver function test parameters in patients before and after bloodletting and in the control group . $^{*}p < 0.05$, $^{**}p < 0.01$.

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	Bloodletted	*n*	Iron	TIBC	Ferritin	Hb	Tfsat	Creat	GGT	ALT	ALP
Pb	No	28	− 0.269	0.120	0.195	0.329	− 0.308	0.095	**0.477***	0.194	**0.388***
	Yes	28	− 0.028	− 0.230	− 0.008	**0.450***	− 0.070	− 0.092	0.152	− 0.013	**0.465***
	Control	20	0.307	0.161	− 0.037	0.145	0.300	0.120	0.397	**0.451***	0.217
Hg[1]	No	22	− **0.510***	0.232	0.016	0.249	− **0.481***	**0.431***	0.401	0.111	0.032
	Yes	22	0.108	0.202	− **0.445***	0.056	− 0.014	**0.614****	**0.453***	− 0.006	0.231
	Control	16	− 0.031	− 0.187	0.394	0.436	0.124	**0.538***	0.438	**0.530***	0.436
Cd[1]	No	18	− 0.119	− **0.593****	0.138	0.287	0.007	0.043	0.081	0.050	**0.542***
	Yes	20	− 0.255	− **0.615****	− 0.078	− 0.015	− 0.070	− 0.001	− 0.109	0.011	0.376
	Control	8	0.310	0.108	− 0.357	0.190	0.286	− 0.071	0.263	0.095	0.095

Table 2
Correlations among variables. Correlation (Spearman's rho coefficients) of trace metal concentrations with Hb, liver function test parameters, and iron profiles in patients before and after bloodletting and in the control group

		Bloodletted?	Hg (*n*)[1]	Cd (*n*)[1]
Blood	Pb	No	**0.514*** (22)	0.407(18)
		Yes	0.182 (22)	0.448 (20)
		Control	**0.688**** (16)	**0.922**** (8)
	Hg	No		0.159 (15)
		Yes		− 0.388 (16)
		Control		0.760 (7)
Urine	Pb	No	NA	0.454 (15)
		Yes	NA	**0.674**** (16)
		Control	0.394 (10)	**0.693*** (19)
	Hg	No		NA (2)
		Yes		NA (1)
		Control		0.083 (9)

Table 3
Correlations among variables. Correlation (Spearman's rho coefficients) between trace metal concentrations in patients before and after bloodletting and in the control group

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	Control	Patient: Before bloodletting	Patient: After bloodletting	Relative change in median (%)	n
	Median (n) Range (SD)	Median Range (SD)			
Iron (µmol/L)	15.9 (21) 10.1 – 28.2 (7.16)	27.8 12.0 – 47.7 (9.1)	22.5 9.0 – 42.2 (9.3)	-19	28
TIBC (µmol/L)	67 (21) 55 – 89 (8.16)	53.0 40.0 – 68.0 (7.2)	61.5 43.0 – 93.0 (11.1)	16	28
Ferritin (µg/L)	65 (21) 9 – 514 (113)	527 249 – 2555 (445)	62 18 – 346 (87)	-88	28
Hemoglobin (g/dL)	14.1 (21) 11.8 – 17.0 (1.49)	15.22 12.8 – 17.2 (1.1)	14.85 12.7 – 17.3 (1.26)	- 2	28
Tfsat (%)	22.7 (21) 14 – 57 (11.4)	48.6 22.2 – 86.1 (18.6)	34.4 13.3 – 79.2 (18.0)	-29	28
Creatinine (µmol/L)	73 (20) 58 – 96 (9.8)	77 50 – 135 (17.5)	79 51 – 112 (15.6)	3	27
GGT (U/L)	16.0 (21) 7 – 32 (6.5)	33 12 – 139 (31.6)	33 13 – 199 (37.7)	0	27
ALP (U/L)	61 (21) 43 – 144 (22)	69 45 – 105 (17.6)	73 42 – 97 (15.5)	6	25
ALT (U/L)	21 (21) 10 – 34 (10.3)	35 9 – 180 (44.1)	28 9 – 223 (44.0)	-20	28

Table 4
Paired comparisons of serum iron profiles, Hb, serum creatinine, and liver function test parameters in patients and controls/independent samples Mann–Whitney *U* test for inter-group comparisons

	Control	Patients: Before bloodletting	Patients: After bloodletting	Relative change in median (%)	n
	Median (n) Range (SD)	*Median Range (SD)*			
Hg (nmol/L)	15.10 (16) 4.99 – 30.60 (7.50)	12.25 5.08 – 56.60 (13.22)	12.05 5.21 – 39.76 (11.07)	-2	21
Cd (nmol/L)	2.12 (13) X[c] – 4.71 (1.01[a])	2.13 X[c] – 22.92 (5.50[a])	2.65 X[c] – 27.95 (6.30[a])	+24	28
Urine Cd/creatinine (nmol/µmol)[f]	0.371 (19) 0.136 – 0.845 (0.164)	0.522 0.117 – 1.760 (0.512)	0.685 0.131 – 2.900 (0.831)	+31	9
Pb (µmol/L)	0.070 (20) 0.024 – 0.166 (0.038)	0.078 0.022 – 0.172 (0.041)	0.098 0.024 – 0.262 (0.064)	+26	28
Urine Pb/creatinine (nmol/µmol)	0.433 (21) 0.069 – 1.201 (0.366)	0.566 0.116 – 1.746 (0.424)	0.640 0.120 – 4.261 (1.017)	+13	14

Table 5
Paired comparisons of trace metal concentrations in patients and controls
[a]Independent samples Mann–Whitney *U* test for inter-group comparisons
[b]Related samples Wilcoxon signed-rank test for paired comparisons
[c]Values < LQ in u-Cd excluded
[d]X = Result below LQ
[e]Values below LQ excluded
Letters ([c] or [a]) above groups denotes significant difference.

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Table 6 Increase in Pb concentrations: relationships with pre-treatment variables. Increase in blood lead concentrations in subjects with different hemochromatosis genotypes (µmol/L)

	Median	Range	*n*
C282Y homozygote	0.034	− 0.004 to 0.114	13
C282Y heterozygote	0.008		1
H63D homozygote	0.002	− 0.012 to 0.011	3
H63D heterozygote	0.000		1
Compound heterozygote	0.024	− 0.007 to 0.063	8
No HFE mutation	0.026	− 0.010 to 0.062	2
Total	0.029	− 0.012 to 0.114	28

Table 7 Increase in Pb concentrations: relationships with pre-treatment variables. Correlation (Spearman's rho coefficients) between increase in Pb and serum iron profiles, Hb, serum creatinine, liver function test parameters, and C282Y homozygote genotype

		Ferritin	Iron	TIBC	Tfsat	Hb	GGT	ALT	ALP	Creat	Genotype[a]
Increase in b-Pb	Spearman's rho	0.103	0.260	− 0.322	0.321	0.143	− 0.019	− 0.062	0.662	− 0.145	0.337
	p	0.603	0.182	0.095	0.096	0.468	0.922	0.754	**<0.001**	0.462	**0.048**
	n	28	28	28	28	28	28	28	28	28	28

[a]C282Y homozygote vs. all others
The significant *p* values have been highlighted in bold fonts

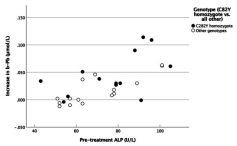

Fig. 3
Relationship of Pb levels with pre-treatment ALP levels in blood

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Conclusions

The present and previous works demonstrate that repeated bloodlettings in hemochromatosis affect the blood levels of several metals, not only iron.

While serum iron declines, the effect on other metals, if any, is generally an increase. In the treatment of hemochromatosis, one should be aware that repeated bloodlettings may induce increased absorption or mobilization of toxic metals in the body.

Whether this effect is due to increased absorption or redistribution in the body is not clear, and further studies are needed.

References:

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