Soluble transferrin receptors, glycosylated ferritin and other markers of iron metabolism in patients with multiple blood transfusions. Russian multicenter prospective observational study

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Vsevolod G. Potapenko [1,11], Yulia V. Zabutova [1], Natalia A. Kotova [1], Valeria V. Kozyro [1], Alina Y. Zavyalova [1], Olga V. Nebelitskaya [1], Irina A. Samorodova [1], Irina V. Kholopova [7], Natalia V. Skorobogatova [1], Nina N. Petrova [1], Olga P. Mironova [1], Natalia Y. Chernoockaya [1], Sergey Y. Simeniv [9], Alexander V. Serkov [1], Ksenia A. Skoryukova [1], Ekaterina A. Ukrainchenko [2], Oksana E. Ochirova [3], Yana S. Onikiychuk [4], Alina S. Chuprakova [4], Angelika F. Rakhmani [5], Alexander N. Levanov [6], Sergey V. Lapin [7], Margarita Y. Pervakova [7], Elena A. Surkova [7], Tatiana V. Blinova [7], Irina A. Dubina [7], Tatiana V. Shelekhova [6], Tatiana V. Fedorenko [1], Vasily A. Shuvaev [8,10], Nadezhda V. Medvedeva [1].

[1] City Clinical Hospital No. 31, St. Petersburg, Russia; [2] City Clinical Hospital No. 17, St. Petersburg, Russia; [3] N.A. Semashko Republican Clinical Hospital, Ulan-Ude, Russia; [4] Central City Clinical Hospital, Kalinigrad, Russia; [5] Botkin City Clinical Hospital, Moscow, Russia; [6] Saratov State Medical University named after V.I. Razumovsky, Saratov, Russia; [7] Pavlov First St. Petersburg State Medical University, St. Petersburg, Russia; [8] A.F. Tsyba Medical Radiological Research Center - branch of the NMRC of Radiology, Obninsk, Russia. [9] I.M. Sechenov First Moscow State Medical University (Sechenov University), Moscow, Russia. [10] Russian Medical Academy of Continuing Professional Education, Moscow, Russia. [11] S.M. Kirov Military Medical Academy, St. Petersburg, Russia

Introduction. Iron overload syndrome is a complex of symptoms associated with excessive iron accumulation. Ferritin is the main marker of iron overload, but also an important marker of an inflammatory process in the body and even mild inflammation can change its concentration. Therefore, more specific markers, such as soluble transferrin receptor (sTRT) and glycosylated ferritin (GF) should be considered. Elevated total ferritin concentration in inflammation is explained by the release of non-glycosylated tissue-type fraction of ferritin into the blood while glycosylated form ferritin retains its stability. It is believed that inflammation does not affect sTRT levels.

Purpose. The purpose of this study was to characterize and analyze the levels of soluble transferrin receptor, glycosylated ferritin, and other iron metabolism markers in patients with blood malignancies and iron overload.

Materials and Methods. A prospective observational multicenter study was performed. Inclusion criteria: age ≥18 years, total blood ferritin >2000 ng/mL and >1 year of monthly blood transfusions. Exclusion criteria: any reasons and conditions the patient's physician considers valid to remove the patient from the study. The study participants were divided in two groups: those who receive chelation therapy (deferasirox) and those who do not. In each group inflammation and iron overload markers – transferrin, serum iron, sTRT, total and glycosylated ferritin, C-reactive protein (C-RP) and albumin – were analyzed. For some patients repeated blood tests were taken. In order to distinguish deviations in the laboratory findings for patients with and without chelation therapy, pair approach was used.

Results. The study enrolled 44 patients – 15 males and 29 females with a median age of 63.5 (20–92) years. A total of 93 measurements were taken: 57 in chelation (median 2 per patient, range 1-15) and 36 in non-chelation (median 1, range 1-5) group. All patients had blood malignancies, each group included 22 patients. Patients are characterized in table 1.

Table 1. Age, diagnosis, chelation and transfusions duration

	Chelation	
	Yes	No
Age (median, range)§	62.6 (67-89)	66 (23-92)
Duration of transfusions, months.	63±60	25±16
Duration of chelation, months.	19±15	-
Diagnosis		
Myelodysplastic syndrome	13	9
Chronic myeloproliferative neoplasms	1	2
Beta-thalassemia	1	-
Aplastic anemia	3	-
Multiple myeloma	-	1
Unspecified anemia	-	1
Acute myeloid leukemia	1	6
Non-Hodgkin's lymphoma	1	2
Partial red cell aplasia	2	1
Chronic myelomonocytic leukemia	-	1
Total	22	22

§The difference is not statistically significant

Table 2. Biochemical profiles of patients after multiple blood transfusions

Marker	Normal	Chelation therapy	
		Absent	Conducted
Soluble transferrin receptors, mg/l§	0.62-1.5	0.79 ± 0.95	0.72 ± 1.18
Ferritin, total, ng/ml	До 310	3412± 3642.2	3509.6± 1724.5
glycosylated, ng/ml	-	2081.33 ± 1886.4	2706.5± 1480.2
glycosylated, %	78.3-87.1	64.7±17.3	75.26 ± 18.2
C-reactive protein, mg/l	0-5	31.9± 48.4	15.1± 32.3
Albumin, g/l	35-50	34.7± 5.5	37±6.4
Transferrin, g/l	2-3.6	1.7±4.6	1.9±7
Iron, mcmol/l	12.5-32.5	29.18 ± 11.55	45.87 ± 21.76

§The difference is not statistically significant

Patients in the non-chelation group showed higher concentrations of inflammation markers in absence of acute infection. C-reactive protein was higher and albumin was lower compared to the deferasirox group. The exceptions were transferrin and ferritin (total and glycosylated) with higher levels in the chelation group. Profiles are summarized in table 2.

Table 3. Correlation analysis

Marker		Duration of transfusions	Ferritin	C-RP	Albumin	Transferrin	Iron	sTRT	GF, ng/ml	GF, %
Dur. of transfusions	No chelation						0,35*			0,36*
C-RP					-0,46**	-0,32*				
Albumin				-0,46**		0,65**	0,54**			
Transferrin				-0,32*	0,65**		0,42**			
Iron		0,35*			0,54**	0,42**				
sTRT				-0,24						0,41**
GF, ng/ml			0,91**							0,45**
Ferritin									0,91**	
GF %		0,36*						0,41**	0,45**	
Dur. of transfusions	Chelation		0,35*	-0,31*	0,59**				0,53**	
Ferritin		0,35*		-0,4**				-0,45**	0,91**	
C-RP		-0,31*	-0,4**		-0,55**	-0,5**	-0,54**	0,49**	-0,39*	-0,33*
sTRT			-0,45**	0,49**		-0,3*	-0,42**		-0,44**	
GF, %				-0,33*					0,41**	
Transferrin				-0,5**	0,56**		0,72**	-0,3*		
Albumin		0,59**		-0,55**		0,56**	0,56**			
Iron				-0,54**	0,56**	0,72**		-0,42**		
GF, ng/ml		0,53**	0,91**	-0,39*				-0,44**		0,41**
Dur.of chelation				0.4*		-0.38*		0.72**		

Significance: *p<0,05, ** p<0,01
C-RP—C-reactive protein, sTRT - soluble transferrin receptor, GF - glycosylated ferritin

The correlation analysis (table 3) in non-chelation group found connection between two inflammatory markers: the higher was the C-RP, the lower became the albumin concentration. The blood transfusions duration did not effect ferritin (total) and sTRT concentrations. The iron and ferritin glycosylation levels directly correlated with the transfusions duration. This may indicate a less aggressive underlying disease course, longer survival and longer transfusions period.

In the chelation group the ferritin concentration (total and glycosylated) was associated with longer transfusions period. This may reflect a more favorable course of blood malignancy resulting in longer transfusions period and subsequent iron overload. In contrast, the sTRT concentration was inversely related to the chelation duration, transferrin, iron and ferritin (total and glycosylated) concentrations. So the longer the chelation continued, the more the sTRT concentration increased, which may indirectly indicate less severe overload but they were within the normal values.

Conclusions. In patients with blood malignancies even a minimal inflammation makes it difficult to assess iron metabolism using traditional markers. Concentration of soluble transferrin receptors is less affected by inflammation and could be considered as a potential marker of iron overload and chelation efficacy.

Contact: Dr. Vsevolod G. Potapenko. Phone: +7 (905) 284 5138. E-mail: potapenko.vsevolod@mail.ru