

**Arteriosclerosis, Thrombosis,
and Vascular Biology**

ATVB/2006/129643
Supplemental Files? N
Downloaded on: August 21, 2006

Author Disclosures

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BALANCE OF ESSENCIAL TRACE ELEMENTS BESIDE PATIENT WITH HEREDITARY CONNECTIV TISSUES DISEASES

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Introduction

Hereditary connective tissue disorders (HCTD) or collagenopathies are characterized by relatively frequent incidence of the pathology both in pediatric and therapeutic practice, course progression, multiple organ damage, marked clinical polymorphism, early invalidisation of the patients and even lethality in young age¹.

Clinical syndrome complex of HCTD and its clinical syndrome of systemic mesenchymal dysplasia (SMD) are often accompanied by manifestations of hemorrhagic or rarer, but more dramatically manifested, thromboses complications².

The change in balance of essential micro/macroelements, biometals called “bioelementosis”, affects significantly many physiological and pathological processes³. In hemostasis in particular, normal balance of cations influences not only the rate of blood coagulation but also stability of platelet membrane, endothelium and reaction of intracellular platelets activation^{4,5}.

Research work of last 15 years revealed that cations of some biometals, Mg^{2+} , Zn^{2+} , Mn^{2+} , Li^+ , Ni^{3+} in particular, take part mainly in the processes of primary and secondary platelets activation, i.e. in adhesion and aggregation. To confirm this conclusion we have performed studies using composites of heavy metals (Mg^{2+} , Zn^{2+} , Mn^{2+} , Li^+ , Ni^{3+}) in order to specify the correction degree of revealed disturbances of platelet aggregation function and to estimate the efficacy of this technique⁶. Action mechanism of these preparations consists of stimulating anion phospholipids on platelet membrane. We also proved correcting influence of Mn^{2+} and Li^{2+} salts in combination with Mg^{2+} ions on ADP- and adrenalin aggregation in blood platelets disorders associated with membrane defect (Glanzmann's thrombasthenia)⁷.

Also we found out that Mg^{2+} ions take part in fibrin formation as natural anticoagulant⁸ preventing clot formation by blocking tromboxan- A_2 release from platelets granules⁹. The investigations in India proved that diet rich in such biometals as Mg^{2+} , K^+ , Ca^+ , Zn^{2+} and Se^{2+} can decrease sudden death rate in cardiac pathologies in patients incline to damage of heart coronary vessels^{6,10}.

Besides, recent studies determined that thrombocytes contain high molecular (macromolecular) kininogen (Fitzgerald factor) that is active on the surface of activated thrombocytes only in the presence of Zn^{2+} ions. Thus, we obtained the data that thrombocytes are acceptor link of contact-activation system^{11,12}.

At the same time there are no reliable data that biometals take part in final stage reactions of coagulation, as well as in pathogenesis of HCTD that have mainly coagulological defects in the form of various variants of blood platelet dysfunction and dysfibrinogenemias.

Patients, materials, and methods

Simple unmasked randomized trial was carried out at pediatric clinic of Novosibirsk Regional Clinical Hospital (Russian Federation).

We studied 194 patients at the age of 5-16 years old (the mean age was 10.5 ± 2.3) that were subdivided into 4 groups (Table. 1). Group I consisted of 13 patients (age 5-13) with severe hereditary collagenopathies [HCTD] verified within differentiated genetic syndromocomplexis. Group II included 76 adolescents with undifferentiated variants of hereditary collagenopathies. In the majority of these patient's clinical manifestation coincided with syndromocomplexis of systemic mesenchymal dysplasia. Group III consisted of 55 patients with severe forms of hereditary blood platelet dysfunction and von Willebrand syndrome that were not associated with systemic mesenchymal dysplasia. Control group included 50 healthy adolescents without evidence of bruising in past history and at the moment of the study.

Table 1

Division of the patients into groups

Groups of the surveyed patients	Abs.	%
I group - hereditary connective tissue diseases (n=13):		
• Ehlers-Danlos syndrome (type IV, V, X)	3	1,35
• Marfan syndrome	3	1,35
• Ashard syndrome	2	0,90
• Vhrolic-Lobshtein syndrome (<i>osteogenesis imperfecta</i>)	4	1,81
• Franchesketti-Rollans syndrome	1	0,45
II group – undifferentiated forms of SMD (n=76):		
• Ehlers-Danlos similar phenotype	24	10,8
• Marfan similar phenotype	45	20,3
• MASS – phenotype	17	7,69
III group – without signs of SMD (n=55):		
• Hereditary platelet disorders	35	15,8
• Von Willebrand disease (syndrome)	20	9,05
IV group - control (healthy teenagers)	50	25,8

Venous blood for hemostasis studying was obtained from ulnar vein by broad needle into plastic tube. Then it was immediately mixed with 3.8 % solution of Na citrate at ratio 9:1 and centrifuged at rev/min (140-160 g) for 7 minutes. We got blood plasma enriched with blood platelets that was further used for studying blood platelets function. To perform coagulation tests obtained blood plasma enriched with blood platelets was centrifuged at 3000-4000 rev/min (1200-1400 g) for 15 minutes at room temperature (+18...+25°C). Obtained plasma with low platelets content was used for studying during the first 2 hours since the moment of blood exfusion.

Content of studied biometals in blood plasma was determined by atom adsorption spectrophotometer “Unicam-939” (England). Their content was expressed in mg/l.

Statistical analysis was made by personal computer with the help of Microsoft Excel 2000 and Statistica 6.0 for Windows XP.

Results

While determining the range of biometals balance disturbance all the patients were divided according to the group principal of systematization of the patients with hemostasis pathology.

Data of table 2 show that there are common laws of changing plasma content in the patients with systemic mesenchymal dysplasia that correlate with mean values of biometals concentration in plasma. Nevertheless, we revealed dissimilarity of concentration parameters in different laboratory variants of hemostasis pathology.

Table 2

Level of essential biometals in plasma on all group surveyed [n=161]

Groups Surveyed	Concentration of trace elements in plasma, mg/l (M±m)				
	Zn ²⁺	Cu ²⁺	Mg ²⁺	Ca ²⁺	Mn ²⁺
Group I (n=13)	3,15±0,04*	69,31±1,2*	29,77±2,61*	245,91±9,79*	0,76±0,01*
Group II (n=76)	2,76±0,08#	62,74±2,4*	34,59±2,82*	229,72±13,61*	2,16±0,12#
Group III (n=55)	7,04±0,09*◆	48,09±2,93◆	54,8±0,88*◆	405,43±15,89*◆	3,34±0,16◆
Control group (n=20)	2,81±0,024	42,06±0,01	47,27±0,03	327,23±5,17	2,26±0,053

Note: * - significant ($p < 0.05$) difference with the control group,

- difference with the control group ($p < 0.1$)

◆ - significant ($p < 0, 05$) difference with groups I and II.

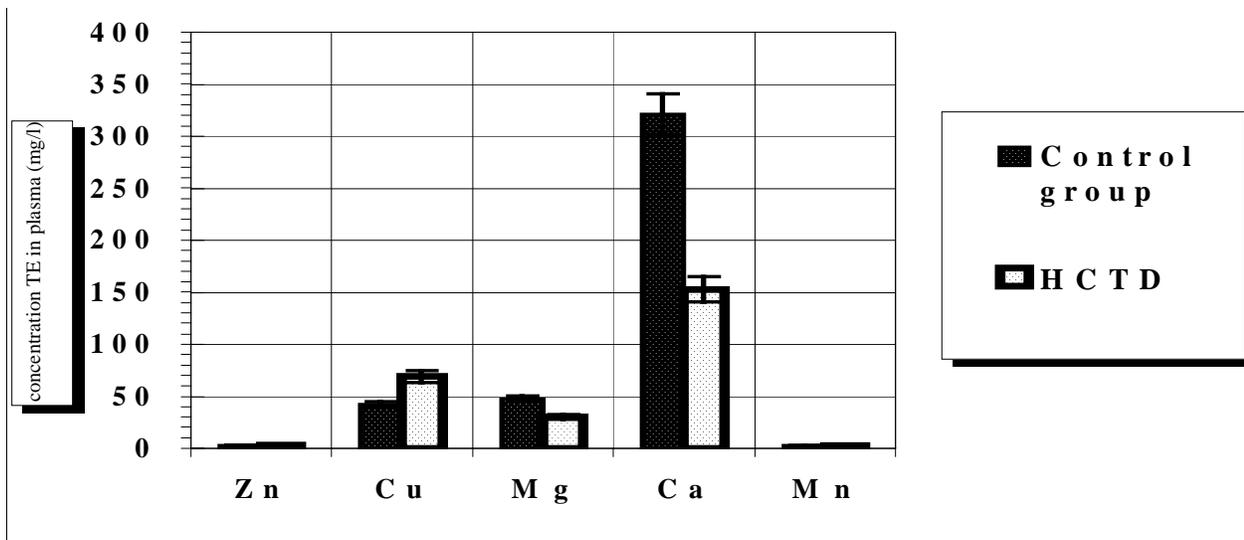


Fig. 1. Comparison of biometals content in groups I, II and control group (n=139)

Figure 1 shows total concentrations of the studied biometals in the patients with systemic mesenchymal dysplasia. From tab. 2 and picture 1 one can see that concentration of the majority of the studied biometals truly differ from that of the control group. E.g. Zn^{2+} level in group I was as much as 1.12 times higher than in the control group, and this value was 2.5 times higher in patients without signs of systemic mesenchymal dysplasia in comparison with the control patients. Moreover, we noted that patients with HCTD had Mg^{2+} deficit- 1.59 times, Ca^{2+} deficit- 2.14 times and Mn^{2+} deficit- 2.97 times higher than control group. Cu^{2+} content in plasma of group I patients was 1.65 times higher than that of the control group.

Plasma of the patients with HCTD had excess amount of copper (1.65 times higher) and on the contrary there was deficit of Mg and Ca ions (1.59 and 2.14 times correspondingly). We revealed marked lack of Mn as much as 2.97 times higher. As for Zn its level did not differ significantly from that of the control group.

As systemic mesenchymal dysplasia syndrome can cause variable changes in coagulation parameters, there is logical dissimilarity of changes in essential biometals spectrum depending on the type and character of predominant disturbances in hemostasis system.

Thus, thorough clinic-laboratory study revealed the following concentration characteristics of biometals with different laboratory variants of systemic mesenchymal dysplasia (their verification was done taking into account modern recommendations of Russian and foreign hemostasiologists) (tab.3). Data from table 3 show common objective laws in changing of plasma ion content in the patient's ill with systemic mesenchymal dysplasia, it being correlated with the mean values of biometals concentration in plasma (tab.2). Nevertheless, we revealed dissimilarity of concentration characteristics in different laboratory variants of this pathology. Plasma of the patients with isolated hereditary disaggregation platelets disorders (HDPD) had excess amount of Zn^{2+} and Mg^{2+} (2.13 and 1.13 times correspondingly) that testifies that these microelements are involved in the process of physiological platelets hemostasis.

Biometals level in the patients with the signs of subtotal HDPD had an excess amount of Zn^{2+} (1.2 times) and Cu^{2+} (1.72 times) in comparison with the control group on the one hand and at the same time they had deficit of the rest of studied biometals (Ca^{2+} , Mg^{2+} , Mn^{2+}) on an average as much as 1.43 times on the other hand.

The patients with laboratory signs of HDPD caused by disturbance of pool of storage and reaction of ADP release (characterized by changing in stability of intracellular storage granules and intrathrombocyte introgranular transport) had excess of Zn^{2+} (1.46 times) and moderate deficit of Mn^{2+} (1.31 times) and Mg^{2+} (1.41 times). In our opinion it was associated with involvement of Zn^{2+} into the processes of intrathrombocyte activation at the level of arachidonic acid exchange because Zn^{2+} -containing enzyme alkaline phosphatase catalyzes converting of diacylglycerol into phosphatidyl-inositol-3-phosphate and the latter is a predecessor of a powerful inductor of blood platelets aggregation – TxA_2 ^{13,14}.

Table 3

Level of biometals in a blood plasma at various forms HCTD and Clinical variants SMD

Dominating laboratory attribute	Concentration of trace elements in plasma, mg/l (M±m)				
	Zn^{2+}	Cu^{2+}	Mg^{2+}	Ca^{2+}	Mn^{2+}
1. Marfan syndrome and phenotype	5,98±0,29*	49,84±3,43*	53,41±2,8*	315,04±16,8	1,17±0,05
2. Ehlers-Danlos syndrome and phenotype	3,35±0,07	72,4±4,9*	37,5±1,92*	236,93±18,7*	1,76±0,08*
3. Vhrolic-Lobshtein syndrome (<i>osteogenesis imperfecta</i>)	4,09±0,19*	48,31±2,69*	36,17±1,92*	170,23±10,9*	1,54±0,09*
4. MASS-phenotype	3,7±0,19*	68,9±4,6*	38,21±3,2*	123,23±9,1*	0,25±0,01*
5. Francheschetti and Ashard syndrome	1,5±0,02	49,34±1,8*	14,8±1,23*	154,98±11,12*	0,18±0,06
6. HSMD	0,28±0,014*	81,46±4,2*	16,7±0,61*	118,19±8,1*	0,35±0,001*
Totally on all group (n=109)	3,15±0,04*	61,7±2,3*	32,78±2,76*	184,43±10,2*	0,87±0,014*
Control	2,81±0,024	42,061±0,01	47,273±0,03	327,234±5,17	2,258±0,05

Note: * - authentic difference with the control ($p < 0.05$), HSMD - undifferentiated variant of SMD

Thus different disturbances of platelet aggregation adhesion ability were revealed in all the patients studied and there was an increased concentration of Mg^{2+} in plasma. This phenomenon is explained by the fact that Mg^{2+} ion functions as natural coagulant since systemic magnesium deficiency in plasma contributes to increase of blood platelets aggregation potential that in its turn increases thromboembolic complications^{9,10,15}. On the base of the data obtained one can suggest that systemic hypomagnesaemia leads to decrease of platelet aggregation. In the majority of the patients that had significant signs of systemic mesenchymal dysplasia accompanied with defects of clotting system (31.3 % of all the patients with HCTD) we revealed marked disbalance of the variety of studied biometals as deficit of Zn^{2+} , Mg^{2+} , Mn^{2+} and Ca^{2+} (10.1; 2.8:6.5 and 2.77 times correspondingly) in the presence of excessive amount of Cu^{2+} (1.94 times).

To sum all mentioned above one can draw a conclusion that systemic mesenchymal dysplasia affects many processes of systemic metabolism and causes disturbances in different kinds of exchanges, biometals exchange being among them. This study helps to prove that biometals exchange disturbances contribute to pathology of connective tissue in children with clinically bleeding syndrome. The study also confirms intensively of systemic metabolism in children with systemic mesenchymal dysplasia syndrome.

We revealed that the main group had valid correlation between the values studied:

- Activity 3PF - Mg ($r = +0,5788$, $p=0,003$) and Ca ($r = +0,62$, $p=0,001$) - direct dependence;
- Thrombin time - Zn ($r = -0,4638$, $p=0,022$) - return correlation;
- Degree thrombin-induced of platelets aggregation - Mn ($r = -0,4985$, $p=0,013$) - inverse relationship;
- Active Partial Thromboplastin Time - Mn ($r=0,1556$, $p = -0,468$) - return correlation;
- Agkistrodont time - Zn ($r=0,6773$, $p = 0,000$) - direct correlation

The analysis of plasma biometals content in the group of patients with undifferentiated variants of systemic mesenchymal dysplasia revealed that plasma concentrations of Zn^{2+} and Cu^{2+} were on average 1.87 times higher than in the control group. Moreover, these patients had deficit of Ca^{2+} , Mn^{2+} and Mg^{2+} on average as much as 1.87 times higher. We noted excess amount of the majority of studied biometals in plasma of the comparison group patients. Thus, Zn^{2+} level was as much as 2.5 times, Mg^{2+} - 1.15 times, Cu^{2+} - 1.14 times and Ca^{2+} - 1.24 times higher the corresponding index in the control group. Only Mn^{2+} concentration did not differ significantly from the control one.

Children with HDPD without signs of systemic mesenchymal dysplasia had high level of studied biometals on average as much as 1.5 times (except for Mn^{2+}). Apparently it was caused by destabilizing action of Ca^{2+} , Mg^{2+} , Zn^{2+} , Cu^{2+} ions on platelet membrane that in its turn leads to platelet dysfunction. In disease and von Willebrand syndrome we revealed that Zn^{2+} in plasma is 2.08 higher than in the control group, Cu^{2+} - 1.38 times, Mg^{2+} - 1.27 times. But at the same time Ca^{2+} and Mn^{2+} levels did not differ significantly from the corresponding control ones. We think that deficit of plasma cofactors of coagulation (Willebrand factor also belonging to them) results in insignificant compensatory increase of some biometals (Mg^{2+} , Zn^{2+} and Cu^{2+} in particular) that are responsible for physiological transmembrane exchange. Alteration in this physiological transmembrane exchange logically leads to disturbance of platelet activation process.

This study testifies that essential biometals act as secondary messengers that in a varying degree provide directed course of biochemical reactions on the level of pre- and

after aggregation activation of platelet pool, as well as their interaction with coagulation system components and vascular wall structures^{5,16,17}.

Obtained data let to broaden our ideas about quite complex and polycomponental pathogeneses of hereditary platelet dysfunctions. On the base of all these data we determined presumptive correspondence of essential biometals and maintenance of platelet activation reactions.

1. Mn^{2+} takes part in processes of membrane activation at the level of synthesis and biotransformation of membrane glycoproteids and their complexes.

2. Zn^{2+} is necessary for cascade of enzyme-mediated reactions of introgranular metabolism of arachidonic acid, processes of release of intracellular storage granules content, as well as neuron-mediated potentiations of platelet activation in the presence of various endogenic neurotransmitter (e.g. serotonin in particular)¹⁸.

3. Cu^{2+} provides platelet adhesion process mediated through interaction of von Willebrand factor with complementary to the latter GP Ib that is due to these ions optimal concentration in plasma⁸. Moreover, Cu^{2+} ions together with Mg^{2+} ions provide stability of intracellular α , δ -granules and release of endogenic aggregation agonists from them.

4. Ca^{2+} and Mg^{2+} ions are necessary as factors of primary platelet aggregation, for transmembrane exchange processes that develop both on the level of blood corpuscular elements and in connective tissue derivatives, as well as mesenchimal structures including vascular endothelial lining^{7,19}.

5. Interaction of platelets with coagulation factors of plasma is determined by sufficient concentration of extracellular calcium as well as adequate stability of structure and function of phospholipids matrix of cells containing thromboplastin (Tissue Factor-containing cells)²⁰.

6. Final stage processes of clotting (cascade polymerization of fibrin-monomers and consensual fibrinogen metabolism) take place under conditions of adequate balance between levels of extra- and intracellular Ca^{2+} that is the main and universal regulation and mediation agent in processes of systemic functioning of physiological blood clot formation^{5,19}.

Accenting, coming from problems persisting studies, on interest trace elements in final stage of blood coagulation reaction of the rolling up (the polymerization of fibrin monomer and consolidation of fibrin clot) is leaned scheme reaction consequent self assembly fibrin monomer at participation full-fledged of fibrinogen (fig.2).

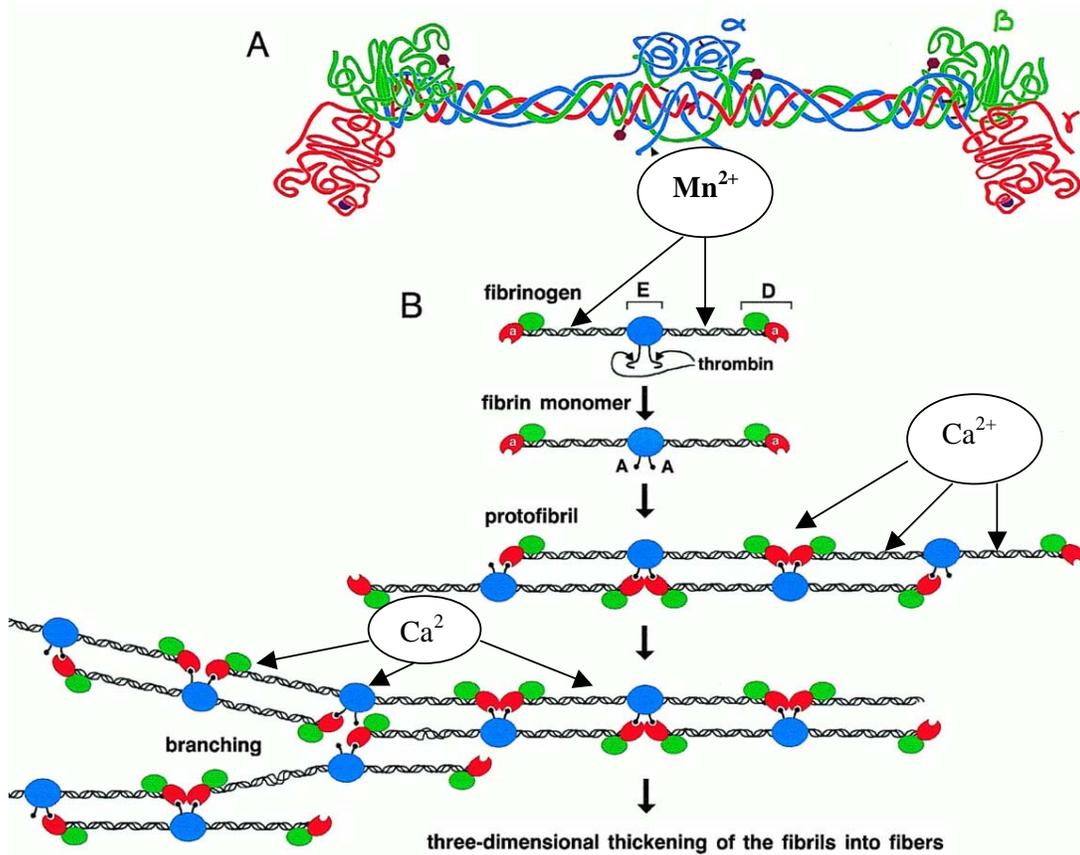


Fig. 2. A schematic representation of the normal fibrin monomers polymerization to consolidation of protofibrils way D-E-interdomains interaction with locus essential trace elements influences. Modified with permission from Blomback B., et al., 1996 [21].

Analyzing participation biometalls in final stage reaction of blood clotting, in particular thrombin-induced fibrin monomers polymerization possible expect following:

- Ions of Ca^{2+} participate in building calcium-linking site in γC and βC -domains, providing from interaction of polymerization centre in γ -chains fragment of fibrinogen "hole" and β -chains "hole". Moreover, NH_2 -ended fragment of α -chains (α -"knob") and β -chains (β -"knob") accordingly in reaction "knob-hole interaction", are once participated^{7,19}.
- Mn^{2+} -containing enzymes (galactosyl- and ksilosyltransferase) responsible for provision full-fledged disulfide-branching relationships between D, DD and E-fragments of fibrinogens molecules that provides the arrival full-fledged glycopeptides in тромбин-mediated enzymatic phase of the final stage of blood coagulation²¹.

Specified relationship between D and E- fragments the fibrinogen and is broken hemorrhagic variants of dysfibrinogenemias, quite often being pathognomic clinical syndrome of HCTD^{1,2}.

This paper does not cover thrombosis manifestations in mesenchymal dysplasia which are the most dramatic and prognostically unfavorable consequences of

mesenchymal deficiency. That is why it is necessary to carry out antithrombotic prevention in such category of patients.

In conclusion one should note that because of difficulty of directed action on genetically defective collagen matrix, therapeutic correction of hereditary collagenopathies (connective tissue disorders) must consist of combination of blood clotting preparations, chosen taking into account particular character of bleeding disturbances, and must include collagen derivatives metabolism correctors (including essential biomaterials) for normalization of metabolic processes both at the level of mesenchymal tissues and endothelial wall^{22,23}. It also becomes real to use recombinant preparations of human fibrinogen compensating directionally disturbances in the structure of functional sites of abnormal fibrinogen molecule that provides new perspectives for pathogenetic therapy in scientific and clinic hemostasiology and is of particular interest for further investigation.

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BALANCE OF ESSENCIAL TRACE ELEMENTS BESIDE PATIENT WITH HEREDITARY CONNECTIV TISSUES DISEASES

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Summary:

Trace elements (TE) in system of a blood coagulation influence current of the coagulation cascade, stability of a membrane of platelets, an endothelium and reaction platelets activation. Mg^{2+} ions participate in reactions of fibrin formation as natural anticoagulant, promoting the prevention of thrombosis by blocking output $Tx-A_2$ from platelets granules. Zn^{2+} , Mn^{2+} , Li^+ , Ni^{3+} is capable to stimulate phospholipids anionic on a membrane of platelets. Hereditary connective tissue disorders (HCTD) are a frequent pathology in pediatrics and in the literature there is no reliable data about importance TE in reactions of a final stage of coagulation, pathogenesis HCTD, having primary coagulation defects in the form of various variants platelets disorders and dysfibrinogenemias. Contents Mg^{2+} , Zn^{2+} , Mn^{2+} , Cu^{2+} and Ca^{2+} in plasma of children with genetic defects of a collagen and indifferenciations variants of systemic mesenchimal dysplasia (SMD) is researched. Authors discovered decreasing level of Zn^{2+} , Mg^{2+} , Ca^{2+} , and Mn^{2+} at children, was suffered. This was estimated disturbance correlation between platelet cells and compounds of connective tissue (in particular, collagen). The concentration of plasmatic biometalls at children with different clinical-pathogenic forms HCTD by very variability is characterized. Increasing of level Mg^{2+} , Ca^{2+} and Zn^{2+} in plasma at SMD is proved. This data connect, evidently, with the role of essential biometalls in mechanisms of intravascular platelet activation. Carried out research proves a role of essential biometals as secondary messengers, the biochemical reactions providing referred current referred on ante- and postaggregation activation of platelet hemostasis, and also interaction of

the last with components of blood coagulation system and structures of a vascular wall. Obtained data allow dilating comprehension of a complex and polycomponental pathogenesis HCTD and platelets dysfunctions. Sees the justified incorporation in a therapeutic course of proof-readers of a metabolism of collagen derivatives, including complexes of TE for normalization metabolic processes both at a level of mesenchymal tissues, and at a level of an endothelial wall.

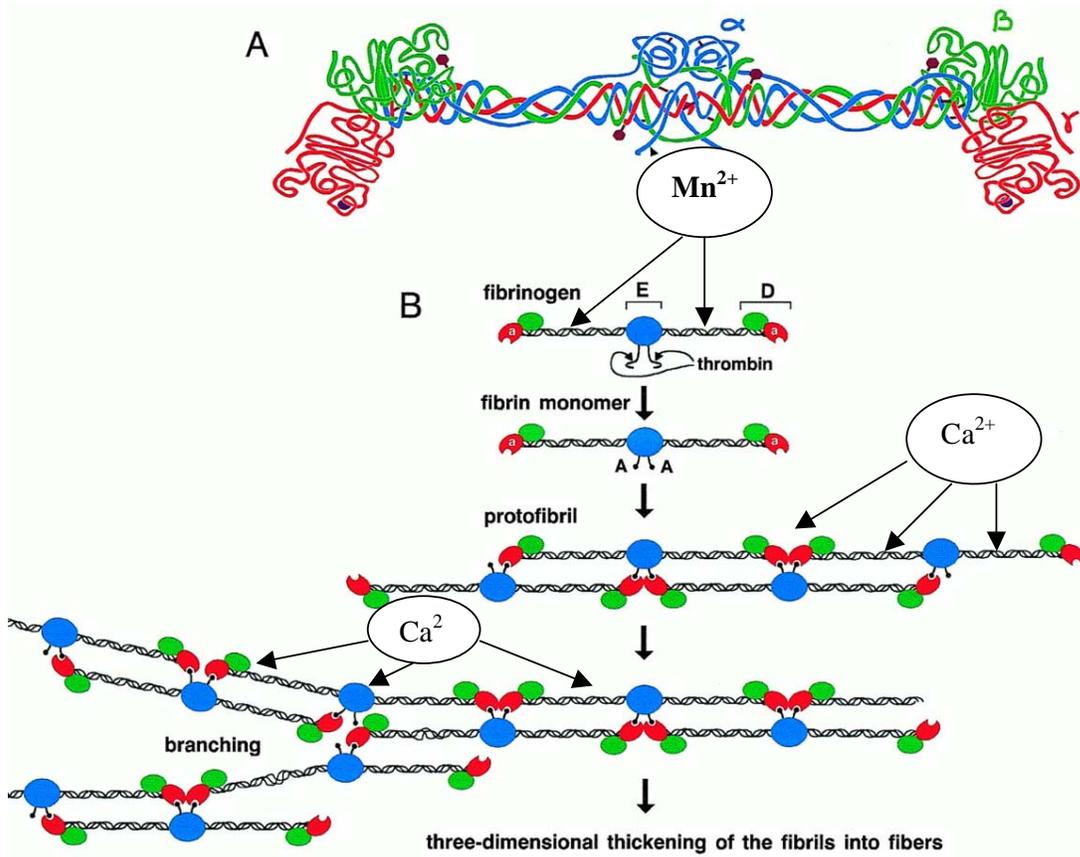


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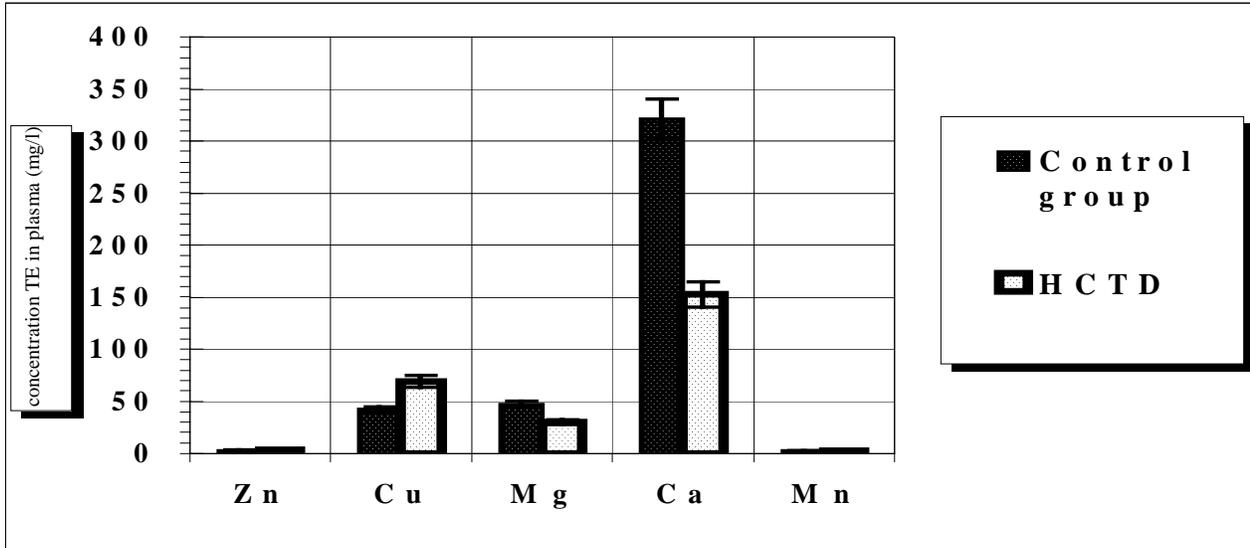


Fig. 1. Comparison of biometals content in groups I, II and control group (n=139)