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The Etiological Relation between Serum Iron Level and Infection Incidence in Hemodialysis Uremic Patients

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A B S T R A C T

Through the treatment of anaemia in dialysis patients part of the iron ions remain free in the serum which is at the bacterias disposal for growth and the strengthening of their virulence. The linear relation of the increased serum iron level and tissue iron stores in the body and the infection incidence in dialysed patients has become more emphasised. The need of a clearly defined upper threshold of the serum iron concentration limit has been mentioned in scientific journals intensely, and consequently the demand for more precise professional instructions for anaemia treatment. For the purpose of participating in these professional and scientific discussions, we have observed the relation between the iron overload of the organism and complication incidence in 120 of our haemodialysis uremic patients, with special emphasis on infections. It has been established that the sepses incidence is much higher in patients with a serum ferritin concentration above 500 μg/L, than in those patients with a ferritin level lower than the mentioned value (χ^2=7.857, p=0.005). The incidence of vascular access infection is significantly higher in those patients with a serum ferritin level above 500 μg/L than in those patients with a ferritin level lower than the mentioned value (χ^2=23.186, p=0.001). Furthermore, it has been determined that the incidence of total infection in patients is 3.8 episodes per 100 patients months, which is in accordance to the referral values of other authors. Conclusion – In the analysis of the achieved results, it has been determined that the infection incidence is significantly higher in dialysed patients with a serum iron level higher than 500 g/L, than in those patients with lower values.

Key words: *chronic renal failure, hemodialysis, iron overload, infection*

Introduction

Anaemia is an accompanying phenomenon in patients with end-stage renal disease. The loss of blood in dialysed patients occurs in different ways: by extracorporeal dialysis with accompanying haemolyse, the loss by the rest of the blood in the dialysis liner and filter, by complications associated to the vascular access, occult interstitial haemorrhaging as well as by the vascular access punction[1–3], and especially by deficient renal production of erythropoietins[4,5]. After implementing haemodialysis in treating uremic patients, anaemia was corrected by a fresh blood transfusion[6,7] for a long period of time. The annual loss of blood in some patients, expressed in iron loss, would even be up to 1500 mg of iron[4]. Therefore, some of those patients would receive consecutive transfusions of up to 4 L of blood[1,2,3,8].

Alongside the transfusion application, the correction of the iron deficit as well as the oral, and in time parenteral application of iron preparations, which is sometimes observed and controlled insufficiently, as well as erythropoietin[9–11], started to be implemented. A low serum ferritin level always indicates iron deficiency. However, normal and increased levels of serum ferritin, accompanied by a low transferrin saturation (<20%) do not simultaneously indicate that the organism is well supplied by iron, yet it indicates the development a state of

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»functional iron deficiency«[12]. The erythropoietins application demands the introduction of iron into the organism in order to prevent it from creating unresponsiveness to erythropoietin therapy. Providing that the aforementioned therapeutic procedures are insufficiently controlled, a side effect is the increase of the iron concentration in the serum and tissue iron storage of the organism, with negative side effects for the organism treated with chronic haemodialysis.

High therapeutic dosages of iron preparations can lead to a state in which the intake amount of oral or parenteral iron surpasses the capacity of transferrin for binding the iron ions[5]. In normal circumstances, all iron ions brought into the organism are bound to transferrin, and thus become inactive for other systems[5,13]. Bound in such a way they also even become unavailable for bacteria[14,15]. However, Lindsay et al.[15] established that staphylococcus aureus could be used for the growth and development of virility even by iron bound to transferrin. Iron ions not bound to transferrin are free in the serum and they become the catalysts for the creation of hydroxyl (oxidative) radicals, which disturb the phagocyte function in addition to the chemotaxis of neutrophile leukocytes[13,16,17], and being exposed to bacteria they support their growth and virility[18]. From all the things aforementioned, we can conclude that it is easy to cross the threshold of binding capacity of transferrins for iron ions.

Various discussions throughout medical journals have taken place concerned with the issue of what the ratio of iron overload[5,8,9,19–21] is in the morbidity and mortality incidence of dialysed patients. In the era of transfusion implementation in treating anaemia of this population of patients, Hakim et al.[22] found a high iron level in 41% of patients, estimated by the serum ferritn level (>650 μg/L). However, by reducing transfusions and implementing recombinant human erythropoietin into the anaemia treatment, as well as the intake of a prescribed amount of iron preparations, the iron overload incidence has recently declined, and thus the increased iron level, as stated by Hoen et al.[19], normally ranges between 10% to 15% of dialysed patients.

Different data concerning the infection frequency in haemodialysis uremic patients has been published in scientific journals. After we insert the iron overload of the organism into the equation, determined according to the serum ferritin level and the frequency of bacterial infection, we gain an insight into the significance of the iron overload in dialysed patients[8,17,23,24]. This refers to the increased bacterial infection[25] risk in dialysed patients with an iron overload. Tielemans et al.[7] claim that only the iron overload in the serum, regardless of the genesis, increases the growth and virility of the bacteria *in vitro* and *in vivo*. Boleaert et al.[8,23] established that the infection risk is three times greater in patients with a serum ferritin level above 1000 μg/L than in those patients with lower values. It was also mentioned that there are multifactor influences onto the risk of bacterial infection development in dialysed patients with an iron overload in the serum[5,19,26].

The intake of iron preparations into the organism of dialysed patients, especially the sodium ferric gluconat complex, together with the erythropoietin, decreases the risk of bacterial infection[3,10,11,27]. Due to accompanying effects of the bacterial infection incidence, Michael et al.[3,27] are of the opinion that the routine practice of liberal consumption of iron preparations of this population should be terminated. On the other hand, the peroral intake of iron preparations cannot, in these organisms, retain a safe and stable equilibrium of neither the serum nor the stored iron[27,28]. Therefore, in order to maintain the balance of the serum iron concentration as steady as possible, the parenteral intake of iron with pronounced caution on dosages[11,26,29,30] is being implemented more and more. High dosages of therapeutic iron, as considered by Hörl et al.[31], develop the conditions for bacterial infections, cardiovascular complications as well as carcinomas.

Treating end-stage renal disease patients with chronic haemodialysis was implemented in the Mostar University Clinical Hospital more than four decades ago. We have studied the relation between the iron overload of these organisms and the infection incidence in patients on a chronic haemodialysis program.

Patients and Methods

The haemodialysis uremic patients with end-stage renal disease have been treated at the Dialysis Ward at the Mostar University Hospital for four decades. 125 patients have been chosen for the study and regularly observed throughout 18 months, and the relation between the serum iron level and the complication incidence, especially infection, observed. During the research 2 patients died, whereas three were excluded from the programme since they had not been regularly observed. As the indicator of iron supply level in the organism, the serum ferritin level was chosen, and the serum ferritin concentration of 500 μg/L was taken as the borderline between a normal serum level and iron overload of the organism. The relation between the serum ferritin level and sepses, as well as the relation between the serum ferritin level and vascular access infection, were observed separately. The observation purpose was to establish the aforementioned relations, as well as to determine the primary point of infection from which the general infection, in the sense of bacteraemia, was developed. Other complications, apart from infection, which can put the vascular access and life of a dialysed patient in danger, were also taken into the observation process. The serum ferritin level, erythrocytes level and haemoglobin level in the blood were also observed.

An arteriovenous fistula for vascular access was set up in all patients. The patients who, at the time of agreeing to take part in the study who did not display any signs of a local infection or sepses, nor displaying any of the possible complications that might threaten the vascular access and the patient's life, were chosen. The patients who, for any reason, had blood or a blood derivates transfusion in the last six months, were not taken into

consideration for the study. Moreover, dialysed patients younger than 10 years of age were also excluded from the research.

Descriptive statistics have been used in the basic evaluation of the numerical data in order to determine the mean values, the standard deviation and span. Categorical data has been shown by the frequency of appearance as well as their proportion, that is, their percentage. In the statistical analysis we have used the χ^2-test. The statistical significance has been regarded on the level of importance $p<0.05$ that is with 95% of relevance threshold. For the analysis of the collected data we have used the application program Statistics version 8.0 whereas the graphic presentation has been made in Excel.

Results

Table 1 shows the distribution of patients according to age and sex, whereas Table 2 lists the pathological conditions that caused end-stage renal disease (ESRD). As can be viewed from Table 2, hypertensive nephrosclerosis is the most frequent cause of kidney failure by far, which represents a distinct difference in relation to other authors' reports regarding kidney function failure and complete anuria. This remains to be processed. Table 3 illustrates the incidence of concomitant diseases, out of which some can be an independent risk factor in the complications occurrence, especially diabetes.

Table 4 shows the incidence of local infection of vascular access and the infection of organic system, listed according to frequency, which then became the primary

TABLE 1
DISTRIBUTION OF EXAMINEES ACCORDING TO AGE AND SEX

Age (year)	Male	Female	Total
0–10	–	–	–
11–20	–	1	1
21–30	3	–	3
31–40	8	6	14
41–50	10	7	17
51–60	23	13	36
61–70	10	7	17
71–80	15	13	28
81–90	–	3	3
91–100	1	–	1
Total	70	50	120

TABLE 2
PATOLOGICAL CONDITION WHICH CAUSED END-STAGE RENAL DISEASE (ESRD)

Cause of renal insufficiency	Total of patients
Hypertensive nephrosclerosis	35
Interstitial nephritis	27
Glomerulonephritis	21
Diabetic nephropathy	12
Chronic pyelonephritis	11
Polycystic kidney	6
Obstructive nephropathy	5
Unknown	3
Total	120

TABLE 3
THE INCIDENCE OF CONCOMITANT DISEASE

Comorbidity	Number of patients	%
Cardiovascular disease	51	42.5
Diabetes	12	10.0
Carcinoma	5	4.2
Others	2	1.7

TABLE 4
THE ILLUSTRATION OF THE PRIMARY SPOT OF INFECTION AND THE TYPES OF ISOLATED MICROORGANISMS IN IRON OVERLOAD DIALYSED PATIENTS

Primary spot of infection	Number of patients	Isolated microorganisms	Number of patients with microorganisms	%
Vascular access	15	*Staphylococcus epidermidis*	4	26.6
		Streptococcus aureus	6	40.0
Infection of respiratory system	16	*Streptococcus pneumoniae*	1	6.2
		Klebsiella pneumoniae	2	12.4
Infection of urinary system	9	*Escherichia coli*	3	33.3
		Enterococcus species	2	22.2
Infection of skin and soft tissues	4	*Streptococcus pyogenes*	1	25.0
		Streptococcus aureus	2	50.0
		Staphylococcus epidermidis	1	25.0
Endocarditis	2	*Staphylococcus epidermidis*	2	100.0
Others	2	–	–	–
Total	48		24	

point of the bacteraemia occurrence. The patients who displayed the general symptoms and the laboratory results confirmed bacteraemia were treated and recorded as patients with sepses. Table 4 illustrates that out of 120 observed haemodialysis uremic patients, 48 (40.0%) of them displayed the symptoms of a local and systematic infection, and from those 48 patients with infection, 40 (83.3%) of them had symptoms and laboratory results which indicated that it was bacteraemia, hence, the appropriate treatment to the displayed septic condition was implemented.

Table 5 illustrates maximum, minimum and middle values, as well as the standard deviation of the observed variables of the serum level. Table 6 illustrates the distribution of patients according to the serum ferritin level. In this table it can be seen that 21 (17.5%) had a serum ferritin concentration above 500 μg/L, and this particular level was perceived throughout the study as the threshold of iron overload dialysed patients, that is, patients with a serum ferritin level above this level were considered, throughout the treatment in progress, as iron overload patients. Therefore, in the observed clinical material, 17.5% patients had iron overload. It can also be noticed in Table 6 that 50 (41.67%) of the patients had a ferritin level below 200 μg/L, which means that they had a certain level of iron deficiency since this serum ferritin level is normally perceived as a lower serum value.

Table 7 shows the distribution of patients according to the erythrocytes number, and Table 8 according to the haemoglobin level in the blood. From the tables aforementioned, it is evident that 87.5% of the patients had a blood haemoglobin concentration below 4,0 million, and 79.2% had a haemoglobin level below 4.0 g/L, which means that former were at a higher and the latter at a lower level of insufficiency. A point of interest that needs pointing out, one patients actually displayed an erythrocytes value below 2 million/L.

Table 9 shows the complications which endanger vascular access and consequently the life of the patient in the programme of chronic haemodialysis. 59 patients exhibited one of the listed complications. It can be viewed that of the 120 patients (100.0%), infection was the most common complication and it was exhibited in 48 (81.0%) patients. This number is comprised of the patients with a local infection of the vascular approach, as well as the patients with an infection of some of the organ systems, which then developed into sepses. The table also illus-

TABLE 5
THE ILLUSTRATION OF MINIMUM, MAXIMUM AND MIDDLE VALUES, AS WELL AS THE STANDARD DEVIATION OF MONITORED VARIABLES OF SERUM LEVELS

Variable	Min	Max	$\overline{X}$	SD
Serum proteins g/L	30.6	85.1	63.46	6.93
Serum albumins g/L	20.2	50.1	36.6	3.8
C-reactive proteins mg/L	0.1	191.8	12.31	21.05
Serum ferritin μg/L	4.43	1119	169.05	206.58
Hemoglobin g/L	59	160	102.61	17.83
Urea prior to dialysis mmol/L	5.2	44	21.3	5.16
Serum Calcium mmol/L	5.24	13.12	8.94	0.84

TABLE 6
DISTRIBUTION OF EXAMINEES ACCORDING TO SERUM FERRITIN CONCENTRATION

	Serum ferritin level (μg/L)	Number of patients	%	
	<100	31	31.3	
	101–200	19	19.2	
	201–300	28	28.3	99 82.5%
	301–400	12	12.1	
	401–500	9	9.1	
Iron overload	501–600	5	23.8	
	601–700	1	4.8	
	701–800	2	9.5	21 17.5%
	801–900	7	33.3	
	901–1000	6	28.6	
	Total	120 (100.0%)		

TABLE 7
DISTRIBUTION OF EXAMINEES ACCORDING TO THE ERYTHROCYTES CONCENTRATION IN BLOOD

Erythrocytes number(10^6/L)	Number of patients	%	
< 2.0	1	0.83	
2.0–2.5	5	4.17	
2.5–3.0	17	14.17	105 87.5%
3.0–3.5	49	40.83	
3.5–4.0	33	27.50	
4.0–4.5	9	7.50	
4.5–5.0	6	5.00	12 12.5%
> 5.0	–	–	
Total	120	100.00	

TABLE 8
DISTRIBUTION OF EXAMINEES ACCORDING TO THE HEMOGLOBIN LEVEL IN BLOOD

Hemoglobin level in serum (g/L)	Number of patients	%	
<7.0	–	–	
7.0–8.0	3	2.50	
8.0–9.0	10	8.33	95 79.2%
9.0–10.0	42	35.00	
10.0–11.0	40	33.33	
11.0–12.0	16	13.33	
12.0–13.0	6	5.00	25 20.8%
13.0–14.0	3	2.50	
Total	120	100.00	

TABLE 9
RELATION BETWEEN THE SERUM FERRITIN LEVEL AND COMPLICATION INCIDENCE

Serum ferritin (μg/L)	Infection	Thrombosis	»Steal« syndrome	Monomyelic neuropathy	Pseudoaneurism	Bleeding seroma	Total	
<100	11	3	–	–	–	1	15	
101–200	4	3	–	–	–	1	8	
201–300	7	–	–	–	–	–	7	35 72.9%
301–400	7	1	–	–	1	–	9	
401–500	6	1	–	–	–	–	7	
501–600	3	–	–	–	–	–	3	
601–700	1	–	–	–	–	–	1	
701–800	2	–	–	–	–	–	2	13 27.1%
801–900	4	–	–	–	–	–	4	
901–1000	3	–	–	–	–	–	3	
Total	48 (81.3%)	8 (13.56%)	0 –	0 –	1 (1.69%)	2 (3.39%)	59 (100%)	

Serrum ferritin level μg/L	Number of patients with complications	Number of patients without complication	χ^2	p
<500	35	53	2.532	0.11
>500	13	8		

trates that 13 (27.08%) patients out of 48 (100.0%) had a serum ferritin level above 500 μg/L and they were, according to the set criteria (500 μg/L) in this study, iron overloaded. Other possible complications, apart from thrombosis, were displayed in a statistically insignificant proportion. It can also been viewed from Table 9 that there is no significant difference regarding the serum ferritin level according to the number of patients with complications (χ^2=2.532, p=0.11).

Table 10 illustrates the relation between the serum ferritin level and sepses incidence. It can be seen from the table that in the group of patients with sepses, 13 (32.5%) out of 40 (100.0%) of them had a serum level above 500 μg/L and 27 (67.5%) below the mentioned

TABLE 10
THE RELATION BETWEEN THE SERUM FERRITIN LEVEL AND SEPSES

		Patients			
% With sepses	Ferritin serum Level (μg/L)	With sepses	Without sepses	Total	% Without sepses
	<100	6	25	31	
	101–200	4	15	19	
27 67.5%	201–300	6	22	28	72% 90.0%
	301–400	5	7	12	
	401–500	6	3	9	
	501–600	3	2	5	
	601–700	1	–	1	
13 32.5%	701–800	2	–	2	8 10.0%
	801–900	4	3	7	
	901–1000	3	3	6	
	Total	40	80	120 (100.0%)	
40	<500 μg/L=27=67.5%	80.0–35.0=45.0	80	<500 μg/L=72=90.0%	
	>500 μg/L=13=32.5%			>500 μg/L=8=10.0%	

Serum ferritin level (μg/L)	Number of patients with sepses	Number of patients without sepses	χ^2	p
<500	27	72	7.857	0.005
>500	13	8		

TABLE 11
THE RELATION BETWEEN THE SERUM FERRITIN LEVEL AND VASCULAR ACCESS INFECTION INCIDENCE

Patients					
% With infection	Serum ferritin level (μg/L)	With vascular approach infection	Without vascular approach infection	Total	% Without infection
	<100	–	31	31	
	101–200	–	19	19	
5 33.33%	201–300	1	27	28	93 88.57%
	301–400	3	9	12	
	401–500	1	7	9	
	501–600	2	3	5	
	601–700	1	–	1	
13 66.67%	701–800	2	–	2	12 11.42%
	801–900	4	4	8	
	901–1000	1	5	6	
	Total	15 (13.25)	105 (86.75)	120 (100.0%)	
Serum ferritin level (μg/L)	With vascular approach infection	Without vascular approach infection	χ^2		p
<500	5	93	23.86		<0.001
>500	10	12			

level. The difference between these two determined levels is 35.0%, and it expresses the infection incidence ratio in relation to the serum ferritin level within the group of patients with sepses.

Among patients without sepses, 8 (10.0%) of them out of 80 (100.0%) had a serum ferritin level above 500 μg/L, and 72 (90.0%) of them below this value. The difference between these two determined values is 80.0% expressed in percentages, and it expresses the infection incidence ratio in relation to the serum ferritin level within the group of patients without sepses.

If the two values determined in each group of patients are compared, that is, 80.0% and 35.0%, the difference is 50.0% and it is statistically significant (χ^2=7.857, p=0.005). This difference in particular addresses the level of association between the sepses incidence and iron overload (500 μg/L) in haemodialysis uremic patients. The infection incidence, if expressed in percentages, is significantly higher among the observed patients with a serum ferritin level above 500 μg/L than among those patients with lower values.

The relation between the vascular access local infection and the serum ferritin concentration is illustrated in Table 11. It is evident from that table that 15 (12.5%) out of 120 (100.0%) patients displayed a local infection of the vascular access. From those 15 (100.0%) patients with an infection of the vascular access, 10 (66.66%) of them had a serum ferritin level above 500 μg/L, and 5 (33.33%) of them below this value. The difference between these two determined values, expressed in percentage is 33.33%, and it indicates the relation between the patients with a vascular access infection and the iron overload ratio, that is, the infection incidence and iron overload relation.

Among the patients without a vascular access local infection, 12 (11.42%) out of 105 (100.0%) of them had a serum ferritin level above 500 μg/L and 93 (88.57%) of them below this value. The difference between these two values expressed in percentage is 77.15%, and states the iron overload ratio among the patients without local infection of vascular access.

If two the values determined in both formed groups of patients are compared, that is, 77.15% and 33.33%, the difference is 43.82% which is statistically significant (χ^2=23.186, p=0.001). This difference addresses the association level between the vascular access infection incidence and iron overload (above 500 μg/L) in haemodialysis uremic patients. The incidence of vascular access local infections expressed in percentages is significantly higher in those with a serum ferritin level above 500 μg/L, than in those with a serum concentration below this value.

Discussion

High therapeutic dosages of iron preparations can lead to the state where the amount of orally or parenterally intake or iron surpasses the capacity of the transferrin to bind iron ions[5]. Under normal circumstances, all the ions brought into the organism are bound to transferrin, and thus become inactive for other systems[5,13]. Bound in such a way, they are not accessible even to bacteria[14]. Iron ions not bound to transferrin are free in the serum, and they become catalysts for the development of hydrophilic (oxidative) radicals, which disturb the phagocytes function and the chemotaxis of polymorphonuclear granulocytes[13,16,17], and they are also at the

bacteria's disposal supporting their growth and virulentia[18]. It can be concluded that the threshold of binding capacity of the transferrin for iron ions can be easily crossed.

Professional reports mention different data regarding the frequency of infection in haemodialysis uremic patients. When the iron overload determined by the serum ferritin concentration is compared to the frequency of bacterial infection, we gain an insight into the significance of an iron overload in dialysed patients[8,17,23,24]. There is an increased bacteria infection risk in dialysed patients with iron overload[25]. Tielemans et al.[7] claim that just a serum iron increase, regardless of the genesis, strengthens the growth and bacteria virility in vitro and in vivo. Boelaert et al.[8,23] determined that the infection risk is up to three times higher in patients with a serum ferritin level above 1000 μg/L, than in those patients with lower values. It has also been mentioned that there are numerous factors influencing the risk of developing bacteria infections in dialysed patients with an iron overload in the serum[5,19,26].

The intake of iron preparations into the organism of dialysed patients, especially the sodium ferric gluconate complex, together with erythropoietin, reduces the bacteria infection risk[3,10,27]. Due to the accompanying effects of the bacterial infection incidence, Michael et al.[3] are of the belief that the routine practise of a too liberal intake of iron preparations into the organism of this population should be abolished. On the other hand, the oral intake of iron preparations cannot in such organisms maintain a secure balance of stored iron[27,28]. Therefore, in order to maintain the balance of iron concentration in the serum as far as possible, a parenteral intake is being applied more frequently with a cautious dosage[26,29,30]. Hörl et al.[31] consider that high doses of therapeutic iron develop various conditions, from an inclination to bacterial infection, to cardiovascular complications to carcinomas.

There have been numerous discussions held through medical journals regarding: 1. How big the incidence of iron overload is in dialysed patients, 2. What the ratio of iron overload of the organism is in the incidence of morbidity and mortality of this population of patients, 3. What the upper physiological threshold of the serum ferritin level is, 4. What is the most appropriate and the most effective way of applying iron preparations in the anaemia treatment[5,26,27,32] of such patients. It is widely accepted that the criteria for the overload of the serum ferritin level is above 500 μg/L[9,11,12,19,32]. In various studies, data regarding the ferritin level in the serum has been mentioned, in other words, regarding the iron overload of this population of patients and the incidence is generally ranging between 10.0% and 15.0%. Patruta et al.[12], as well as Kaufman et al.[33] determined that in more than 10% of their patients, the serum ferritin level was above 650 μg/L, and the transferrin saturation below 20%, Boelaert al.[23] determined the aforementioned value in 14.3% of their patients, whereas Tielemansa et al.[7] as well as Rotellara et al.[34] findings also range within these limits.

In addition, scientific reports mention various data regarding the frequency of infection in haemodialysis uremic patients. The infection incidence in these patients varies in different medical surroundings, thus, reports mention the incidence to range from 12.0% to 35.0%[9]. In recent times, the incidence is expressed by the number of infection episodes throughout 100 patients' months[9,19,21]. As a result, the infection incidence in the materials of Tokarsa et al.[21] was 2.2 episodes *per* 100 patients months in one analysis, and 3.5[21] in the other report, whereas Hoen et al.[19] had a lower incidence, which was 0.93, and in Kessler et al.[9] it was 2.4. According to the findings of Tokarsa et al.[21], in a third of the patients with bacterial infection, the infection's point of entrance was the vascular access, and according to Kessleru et al.[11], in half of them. Albers[35], on the other hand, indicates that infections constitute 20% of all vascular access complications, and Butterly and Schwab[36] had the same finding. It has been mentioned that infection[37,38] is the cause of death in 12% to 38% of this population of patients. Himmelfarb and Hakim[39] conducted a study summarising the numerous published reports, from which it was evident that the infection, as referred to in the reports in case, was the cause of death in the range of 13.1% and 35.7% of deceased dialysed patients.

The state of decreased bacterial infection risk[3,27] is developed by a controlled intake of iron preparations into the organism of dialysed patients. Due to accompanying effects of the bacterial infection incidence, Michael et al.[3] are of the belief that the routine practise of a too liberal intake of iron preparations into the organism of this population should be abolished. On the other hand, the peroral intake of iron preparations cannot be maintained in such organisms, as neither tissue storage nor the serum secure a balance in the iron concentration[27,40]. Therefore, the parenteral intake has been applied with an increasingly more cautious dosage[11,26,29,30]. The intake of high doses of therapeutic iron into the organism of dialysed patients, as considered by Hörl et al.[31], develops conditions, apart from an inclination to bacterial infection, to cardiovascular complications as well as carcinomas. Contrary to this, Hoen et al.[19] consider that after the introduction of erythropoietin therapy, the iron overload of dialysed patients does not represent a risk factor, whereas Powe et al.[20] claim that in spite of the knowledge gained regarding the pathophysiological processes, the septicaemia risk factors have not been marked sufficiently yet.

Furthermore, there is no consent regarding the criteria for establishing and treating of iron deficiency in the serum and tissue storage[11,41–43] nor concerning the manner of iron preparations intake[26] into the organism[26], and there is no uniformity regarding the views on the upper differentiation level between the normal and the increased serum ferritin concentration[11,32] nor the optimal level of haemoglobin concentration[44–46]. Therefore, Fishbane[32,47], Auerbach et al.[48], Madore et al.[49] as well as Lee et al.[50] consider that these problems have not yet been studied or discussed sufficiently, neither in professional

literature adequately accentuated, hence, according to them, the aforementioned subject matter should be researched and discussed in greater depth and consequently, apart from all other things mentioned, to reach a decision regarding the upper limit of serum ferritin concentration without iron overload risk. In the same token, Kalantar-Zadeh et al.[51], as well as Katoditrou et al.[52] believe that these are professional problems which primarily demand scientific and professional analysis, and then agree on the consensus, as each and every patient should be exposed to the least risk regarding the inadequate application of iron preparations during anaemia treatment, and subsequently from the possibility of developing an iron overload.

The aforementioned view is especially emphasised in an analysis and recommendation of the USA NKF K/DOQI, 2006[53], which then influenced our research in the field of the issue addressed above. We are putting forward our results for the purpose of scientifically processing and interpreting them. We have conducted a research regarding the iron overload of dialysed patients and the relation between this overload and infection incidence. It is apparent that the establishing of iron deficiency, correction of such an insufficiency, the possibility of a consecutive iron overload with side effects and dangerous consequences, has not been either completely scientifically analysed or has a consensus been achieved regarding the issue, as it has been already pointed out. Every research regarding the subject matter serves as an addition to the maturity in realising the necessity of the overall scientific analysis of the issue, since numerous publications publish and instigate various debates, put forward different approaches and individual assessments regarding the matter, which do not result in a consensus of the vital propositions concerning many issues outlined[32,41,42,48,52,54–56].

The results of our research contribute to the scientific approach in processing the issue with the necessity of bringing clear and practical instructions as well as suggestions regarding the possible reduction of complications, and consequently to the reduction of the morbidity and mortality of haemodialysis uremic patients. In the research conducted, the 500-μg/L threshold of the serum ferritin level as a differentiation level between the presupposed physiological and non-physiological level of the iron supply of the dialysed patients was determined. The research results of the relation between these two values and the complication incidence, especially infection, achieved by this study, provide scientific confirmation concerning the association of the two observed parameters, that is, an iron overload of the organism and the infection incidence. By analysing and observation the process of 120 haemodialysis uremic patients throughout a period of 18 months, the achieved research results can be summarised as follows:

1. 41. 67%of the patients had an iron deficiency,
2. 17. 5% of the patients had an iron overload, that is, a serum ferritin level above 500 μg/L,
3. 40. 0% of the patients had at least one infection episode, and 33% of them had at least one septic infection episode,
4. 12.5% of the patients had a local infection of the vascular access, and in 31,13% of the cases, the entry point of the infection in the organism was the vascular access,
5. the sepses incidence is significantly higher in the patients with a serum ferritin level above 500 μg/L, than in those patients with a lower serum ferritin level than the mentioned value (χ^2=7.857, p=0.005),
6. the incidence of local infection of the vascular access is significantly higher in the patients with a serum ferritin level above 500 μg/L, than in those patients with a lower serum ferritin level than the stated value (χ^2=23.186, p=0.001),
7. the overall infection incidence is 3.8 on 100 patients months.

The illustrated results indicate that an iron overload represents an independent risk factor in the development of conditions for increasing risk of infection. Moreover, an iron overload is seen as a »modifiable factor« which can be influenced, and in this way it may reduce the possibility of developing a local infection of the vascular access and sepses in the organism of haemodialysis uremic patients. As it has already been mentioned, the morbidity and mortality of this population of patients can be decreased in such a way. The research findings of the relation between infection as a complication and an iron overload of the observed patients' organism, shows a positive correlation between these two observed variables. Since infection is one of the most influential factors of morbidity and mortality of dialysed uremic patients, the decreasing of morbidity and mortality of this population of patients can be influenced by a meaningful organised observation process, as well as an appropriately chosen therapeutic approach. It is to be expected that the results of this research will contribute to a more studious scientific approach to this issue, which would then, subsequently, represent a scientific and professional addition to this study.

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ETIOLOŠKI ODNOS SERUMSKE RAZINE ŽELJEZA I INCIDENCIJE INFEKCIJE U BOLESNIKA LIJEČENIH KRONIČNOM HEMODIJALIZOM

S A Ž E T A K

Tijekom liječenja anemije u dijaliziranih bolesnika dio jona željeza ostaje u serumu slobodan tako da je na raspolaganju bakterijama za rast i jačanje njihove virulencije. Sve se više ukazuje u dijaliziranih bolesnika na linearni odnos povišene razine željeza u serumu i tkivnim depoima s jedne i incidencije upale s druge strane. U stručnom se tisku sve glasnije ukazuje na potrebu jasnog određivanja gornjeg praga limita serumske koncentracije željeza, a dosljedno tome i na određivanje preciznijih stručnih uputa za liječenje anemije. U nakani da se uključimo u te stručne i znanstvene rasprave promatrali smo u 120 naših bolesnika liječenih kroničnom hemodijalizom odnos opterećenosti organizma željezom i incidencije komplikacija, a posebno infekcije. Utvrđeno je da je incidencija sepse značajno viša u ispitanika sa serumskom razinom feritina iznad 500 μg/L, nego u onih s razinom feritina nižom od navedene vrijednosti (χ^2=7,857, p=0,005). Incidencija infekcije vaskularnog pristupa isto je tako značajno viša u ispitanika sa serumskom razinom feritina iznad 500 μg/L, nego u onih s razinom feritina nižom od navedene vrijednosti (χ^2=23,186, p=0,001). Incidencija sveukupne infekcije u svih ispitanika iznosi 3,8 epizoda na 100 bolesnikovih mjeseci i kreće se unutar referiranih vrijednosti drugih autora. Zaključak – Rasčlambom postignutih rezultata utvrđeno je da je incidencija infekcije značajno veća u dijaliziranih bolesnika sa serumskom razinom feritina višom od 500 μg/L, nego u onih s nižim vrijednostima.