

# New parameters in iron metabolism and functional iron deficiency in patients on maintenance hemodialysis

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## KEY WORDS

cardiovascular system, hemodialysis, hepcidin, inflammation, iron deficiency

## ABSTRACT

**INTRODUCTION** Iron metabolism has been studied for many years. New substances involved in iron metabolism continue to be described. Functional iron deficiency (FID) is characterized by the presence of adequate iron stores (as defined by standard criteria) but insufficient iron mobilization required for erythropoiesis during administration of erythropoiesis-stimulating agents.

**OBJECTIVES** The aim of the study was to evaluate new parameters of iron metabolism and the prevalence of FID as well as to assess potential correlations in patients on hemodialysis (HD).

**PATIENTS AND METHODS** The study included 98 patients on maintenance HD. Standard laboratory methods were used to measure the iron status, complete blood count, creatinine, calcium, phosphorus, albumin, intact parathyroid hormone, and lipids. Commercially available kits were used to measure high-sensitivity C-reactive protein (hsCRP), interleukin 6 (IL-6), tumor necrosis factor- $\alpha$ , N-terminal pro-B-type natriuretic peptide (NT-proBNP), growth differentiation factor (GDF15), bone morphogenetic protein (BMP6), hemojuvelin, and hepcidin.

**RESULTS** FID was present in 23% of the patients on HD and was associated with significantly higher serum ferritin, IL-6, hsCRP, hepcidin, and NT-proBNP levels. There were no significant differences in BMP6 and GDF15 levels between patients with and without FID. Patients on HD had increased prevalence of hypertension, diabetes, and left ventricular hypertrophy and required slightly, but insignificantly, higher erythropoietin doses. Predictors of FID included serum iron levels and residual renal function.

**CONCLUSIONS** FID is present in a substantial proportion of patients on HD, who thus should be screened for reversible causes of inflammation. New parameters in iron metabolism do not seem to be related to FID in patients on HD.

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**INTRODUCTION** Iron is a paradoxical element. On one hand, it is essential to any form of life. It is required for catalytic enzymes and proteins involved in DNA synthesis as well as for the transport of oxygen in hemoglobin and myoglobin, transport of electrons, cell respiration, oxidative phosphorylation, tricarboxylic acid cycle, and numerous other biochemical pathways. On the other hand, it is also toxic due to its capacity to produce oxygen free radicals. Living organisms developed many proteins to convey iron in biological fluids or through cellular membranes and to store it in

a nontoxic and easily mobilizable form.<sup>1,2</sup> Our understanding of iron metabolism greatly improved after the discovery of hepcidin in the 21st century.<sup>3,4</sup> Evidence from transgenic mouse models indicates that hepcidin is the predominant negative regulator of iron absorption in the small intestine, iron transport across the placenta, and iron release from macrophages.<sup>5</sup> Moreover, it is an acute-phase protein with antimicrobial activity.<sup>6</sup> In recent years, many new players in iron metabolism have emerged,<sup>7</sup> such as hemojuvelin (cofactor for hepcidin)<sup>8</sup> and bone morphogenetic protein 6

(BMP6) – a cytokine produced in iron overload and responsible for the main pathway of hepcidin activation.<sup>9</sup> In-vitro studies have demonstrated a suppressive effect of growth differentiation factor 15 (GDF15) on hepcidin expression.<sup>10</sup> Iron metabolism in chronic kidney disease (CKD) has not been fully elucidated and is still being studied. The majority of studies concern the effects of iron supplementation on anemia treatment in CKD and dialysis. An important issue in the diagnosis of iron deficiency in patients on chronic hemodialysis (HD) is the markedly different laboratory criteria compared with those applied in patients with relatively normal renal function. It is now recognized that functional iron deficiency (FID) may affect patients with renal failure. FID is characterized by the presence of adequate iron stores, as defined by the standard criteria, but, on the other hand, by insufficient mobilization of iron to adequately support erythropoiesis during the administration of erythropoiesis-stimulating agents.<sup>11</sup> In this setting, an inadequate amount of iron is released from the liver and other storage sites.

The aim of the study was to assess the levels of new parameters of iron metabolism and the prevalence of FID in stable patients on HD and to identify the biochemical and structural heart changes in patients with FID compared with those without FID.

#### **PATIENTS AND METHODS** Study population

The study included 98 prevalent patients on maintenance HD. The inclusion criteria were as follows: stable clinical state, no thrombosis or inflammation (C-reactive protein [CRP] within the normal range, i.e., below 6 mg/l using the low-sensitivity method), absence of acute cardiovascular complications (including uncontrolled hypertension, acute coronary syndrome, acute heart failure). Patients with renal graft failure and those on immunosuppressive therapy were excluded. Median time on HD was 39 months (range, 3–278 months). All patients were treated with regular HD for 4 to 5 hours 3 times a week. The blood flow was between 180 and 280 ml/min with the dialysate flow of 500 ml/min. Ultrafiltration varied according to the patients' actual weight. All patients were dialyzed using low-flux polysulphone membranes (Fresenius, Bad Homburg, Germany) and low-flux modified cellulose membranes (Terumo, Japan; Nipro, Japan; Althin, Japan; Gambro, Sweden; Braun, Germany) with a bicarbonate-buffered dialysate. The mean kinetic of urea modeling (Kt/V) was  $1.17 \pm 0.22$ . The causes of renal failure included chronic glomerulonephritis ( $n = 29$ ), diabetic nephropathy ( $n = 21$ ), chronic interstitial nephritis ( $n = 14$ ), polycystic kidney disease ( $n = 12$ ), and amyloidosis ( $n = 7$ ). The cause was unknown in 15 patients. Our study population included 46 patients who participated also in our previous studies, in which we assessed the levels of hemojuvelin and neutrophil gelatinase-associated lipocalin (NGAL).<sup>12,13</sup> Recombinant human

erythropoietin (EPO) was administered in 75 patients and antihypertensive drugs in 69. FID was defined as ferritin above 200 ng/ml with transferrin saturation (TSAT) below 20%.<sup>14</sup>

**Laboratory measurements** Blood was drawn in all patients between 8.00 and 9.00 a.m. prior to the midweek dialysis session and before heparin administration. Blood for urea and creatinine measurements for the Kt/V calculation was taken after HD from the arterial line of the HD system, immediately before discontinuation of the extracorporeal circulation. Enoxaparin (Clexane, Sanofi-Aventis, France) was used as an anticoagulant during HD and was given as a single intravenous injection at the beginning of each dialysis session. Blood samples were centrifuged at 2500 g for 15 minutes at room temperature to serum. Samples were aliquoted and stored at  $-70^{\circ}\text{C}$  before the assays.

High-sensitivity CRP (hsCRP) was measured using the kits from American Diagnostica (Greenwich, Connecticut, United States). Soluble transferrin receptor (sTfR), interleukin 6 (IL-6), tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), and GDF15 were measured using the kits from R&D (Abington, United Kingdom). Hepcidin was measured by an assay from Bachem (United Kingdom), while N-terminal pro-B-type natriuretic peptide (NT-proBNP), BMP6, and hemojuvelin using the kits from Usbn Life Science (Wuhan, China). NGAL was measured using the assays from Bioport (Gentofte, Denmark). Hemoglobin, total protein, serum lipids, albumin, CRP (for screening purposes), serum iron, TSAT, ferritin, calcium, phosphate, creatinine, urea, and parathyroid hormone were measured by standard laboratory methods in a central laboratory. Echocardiography was performed in all patients by a cardiologist.

**Statistical analysis** The data were analyzed using the Statistica 9.0 computer software. If possible, data were logarithmically transformed to achieve normal distribution. Normality of variable distribution was tested using the Shapiro-Wilk test. Normally distributed data are reported as means  $\pm$  standard deviation and nonnormally distributed data as median and interquartile ranges. The analysis of variance (ANOVA; with post-hoc Tukey test for unequal groups) or the Kruskal-Wallis ANOVA (the difference between the mean of 2 variables was calculated by the Mann-Whitney  $U$  test) were used in the statistical analysis to compare the differences between the groups with a  $P$ -value less than 0.05 considered statistically significant, when appropriate. A linear regression analysis employed Pearson or Spearman coefficients as appropriate. A multiple regression analysis was used to determine independent factors affecting the dependent variable.

**RESULTS** FID was present in 23% of all HD patients. The clinical and biochemical parameters of HD patients with and without FID are presented

**TABLE** Clinical and biochemical characteristics of hemodialysis patients with and without functional iron deficiency

	FID (–) n = 75	FID (+) n = 23
age, y	58.25 ± 14.24	61.09 ± 12.46
RRF, ml	900 (0.185)	410 (0.65) <sup>a</sup>
time on HD, mo	38 (18–68)	24 (15–52) <sup>a</sup>
Kt/V	1.18 ± 0.22	1.05 ± 0.21 <sup>a</sup>
hemoglobin, g/dl	11.96 ± 1.34	11.16 ± 1.08 <sup>a</sup>
total cholesterol, mg/dl	179.04 ± 49.62	178.61 ± 42.09
HDL-C, mg/dl	42.32 ± 11.20	45.26 ± 15.36
LDL-C, mg/dl	107.67 ± 38.04	102.43 ± 34.15
triglycerides, mg/dl	161.91 ± 72.81	154.26 ± 64.04
total protein, g/dl	6.71 ± 0.56	6.36 ± 0.83 <sup>a</sup>
albumin, g/dl	4.06 ± 0.46	3.75 ± 0.37 <sup>a</sup>
fibrinogen, mg/dl	350.08 ± 82.03	383.49 ± 108.67
pre-HD creatinine, mg/dl	9.19 ± 2.59	6.96 ± 2.74 <sup>c</sup>
post-HD creatinine, mg/dl	4.27 ± 1.18	3.51 ± 1.32
urea, mg/dl	159.03 ± 37.63	147.35 ± 37.54
calcium, mg/dl	9.04 ± 1.16	8.85 ± 0.94
phosphate, mg/dl	6.28 ± 2.30	5.23 ± 2.19
PTH, pg/ml	133 (57–326)	198 (100–656) <sup>a</sup>
alkaline phosphatase, U/l	145.50 (91–223)	179.00 (125–230)
EPO dose, IU/wk	3000 (2000–6000)	4000 (3000–5000)
hsCRP, mg/l	5.32 (2.07–11.53)	7.11 (0.2–15.86) <sup>b</sup>
interleukin 6, pg/ml	7.66 (6.68–12.48)	9.72 (7.44–12.62) <sup>a</sup>
iron, µg/dl	93.01 ± 39.34	43.43 ± 16.85 <sup>c</sup>
TSAT (%)	38.12 ± 15.24	15.94 ± 3.19 <sup>c</sup>
ferritin, ng/ml	578.05 ± 339.35	630.74 ± 282.13
sTfR, nmol/l	33.56 ± 16.48	35.40 ± 18.89
hepcidin, ng/ml	22.54 ± 13.22	39.67 ± 14.40 <sup>a</sup>
BMP6, ng/ml	74.69 ± 52.16	57.42 ± 56.56
TNF-α, pg/ml	19.40 (9.30–27.20)	22.60 (13.00–32.40)
GDF15, pg/ml	5218 (3437–6273)	5026 (3883–6195)

Data are presented as means ± standard deviation or median and interquartile range.

**a**  $P < 0.05$ , **b**  $P < 0.01$ , **c**  $P < 0.001$

Abbreviations: BMP6 – bone morphogenetic protein 6, EPO – erythropoietin, FID – functional iron deficiency, GDF15 – growth differentiation factor 15, HD – hemodialysis, HDL-C – high-density lipoprotein cholesterol, hsCRP – high-sensitivity C-reactive protein, Kt/V – kinetic of urea modeling, LDL-C – low-density lipoprotein cholesterol, PTH – parathyroid hormone, RRF – residual renal function, sTfR – soluble transferrin receptor, TNF-α – tumor necrosis factor-α, TSAT – transferrin saturation

in the **TABLE**. The levels of new parameters in iron metabolism (GDF15, BMP6, hemojuvelin) were similar, independently of the iron status. FID was associated with significantly higher serum levels of ferritin, IL-6, hsCRP, and hepcidin. It was also related to significantly lower levels of serum albumin, iron, TSAT, predialysis creatinine levels, lower hemoglobin levels, decreased residual renal function (RRF), and lower Kt/V. An EPO dose was nonsignificantly higher in patients with FID. These patients also had significantly higher left ventricular internal end-diastolic dimension and higher left ventricular internal end-systolic dimension (54.35 ± 9.29 mm vs. 48.64 ± 8.74 mm,

$P < 0.05$ , and 38.59 ± 7.06 mm vs. 31.58 ± 4.44 mm,  $P < 0.05$ , respectively). These structural heart changes were also accompanied by significantly higher NT-proBNP levels (19,550 ± 10,170 pg/ml vs. 13,760 ± 8550 pg/ml,  $P < 0.05$ ) in patients with FID. The prevalence of diabetes was higher in HD patients with FID (26% vs. 8%,  $P < 0.05$ ). The prevalence of stroke was also significantly higher in these patients (24% vs. 9%,  $P < 0.05$ ).

In patients with FID, hepcidin was related in a univariate analysis to dialysis vintage ( $r = 0.38$ ,  $P < 0.05$ ), cholesterol ( $r = 0.43$ ,  $P < 0.05$ ), RRF ( $r = 0.62$ ,  $P < 0.01$ ), and ferritin ( $r = 0.46$ ,  $P < 0.01$ ). In patients without FID, hepcidin was related in a univariate analysis to sTfR ( $r = -0.23$ ,  $P < 0.05$ ), IL-6 ( $r = 0.29$ ,  $P < 0.05$ ), BMP6 ( $r = -0.39$ ,  $P < 0.05$ ,  $n = 42$ ), ferritin ( $r = 0.29$ ,  $P < 0.01$ ), and ejection fraction ( $r = 0.22$ ,  $P < 0.05$ ). In patients with FID, GDF15 was related in a univariate analysis to serum iron ( $r = -0.61$ ,  $P < 0.05$ ) and TSAT ( $r = -0.66$ ,  $P < 0.05$ ). In patients without FID, GDF15 was related to hsCRP ( $r = 0.29$ ,  $P < 0.05$ ) and NGAL ( $r = 0.39$ ,  $P < 0.05$ ). In patients with FID, BMP6 was related in a univariate analysis to serum creatinine before HD ( $r = -0.61$ ,  $P < 0.05$ ), hemoglobin ( $r = -0.63$ ,  $P < 0.05$ ), hematocrit ( $r = -0.79$ ,  $P < 0.01$ ), fibrinogen ( $r = -0.57$ ,  $P < 0.05$ ), alkaline phosphatase ( $r = -0.55$ ,  $P < 0.05$ ). In patients without FID, BMP6 was related to hepcidin ( $r = -0.39$ ,  $P < 0.05$ ) and fibrinogen ( $r = -0.33$ ,  $P < 0.05$ ). However, those associations were not significant in a multivariate analysis in both groups.

In a univariate analysis, FID was related to serum albumin ( $r = -0.28$ ,  $P < 0.05$ ), creatinine before HD ( $r = 0.23$ ,  $P < 0.05$ ), RRF ( $r = -0.33$ ,  $P < 0.05$ ), Kt/V ( $r = 0.23$ ,  $P < 0.05$ ), serum iron ( $r = -0.59$ ,  $P < 0.001$ ), TSAT ( $r = -0.64$ ,  $P < 0.001$ ), ferritin ( $r = 0.23$ ,  $P < 0.05$ ), sTfR ( $r = -0.25$ ,  $P < 0.05$ ), NT-proBNP ( $r = -0.26$ ,  $P < 0.05$ ), and hepcidin ( $r = -0.23$ ,  $P < 0.05$ ). In a stepwise forward multivariate analysis in the model with serum iron, the predictors of FID included serum iron ( $\beta$  value =  $-0.51$ ,  $P = 0.000475$ ) and RRF ( $\beta$  value =  $0.25$ ,  $P = 0.049$ ) accounting for 33% of the variations, followed by hepcidin and TSAT ( $P = 0.12$  and  $P = 0.16$ , respectively). When iron was excluded from the model, creatinine before HD as a predictor reached statistical significance ( $\beta$  value =  $0.33$ ,  $P = 0.024$ ) followed by hepcidin ( $P = 0.12$ ), hemoglobin ( $P = 0.18$ ), and Kt/v ( $P = 0.24$ ), accounting for 21% of the variations.

**DISCUSSION** Since it is clinically important to diagnose FID, we focused on the associations between FID and novel parameters in iron metabolism. The first reports on FID date back to 1989<sup>15,16</sup>; however, no generally accepted definition has been introduced so far. It is widely acknowledged that FID is associated with lower TSAT and elevated ferritin.<sup>17</sup> The diagnosis of iron deficiency or FID is particularly challenging in patients with acute or chronic inflammatory conditions, because most of the biochemical markers of iron metabolism are affected by

the acute-phase reaction. Serum iron and ferritin are laboratory tests commonly used for the detection of iron deficiency but their values may be false in complex cases.<sup>17,18</sup> There is also no consensus in the nephrology community on the upper level of ferritin.<sup>19</sup>

It was reported that serum ferritin remains a reliable marker of bone marrow iron stores in HD patients.<sup>20</sup> Although, the number of iron-stained cells in the bone marrow is the gold standard for iron stores, these patients may have decreased serum iron levels and thus limited iron available for erythropoiesis. Moreover, this is a complicated, costly, and invasive method of determining iron stores in the bone marrow. FID usually responds to iron therapy, whereas inflammatory iron block is resistant to such treatment. Unfortunately, with both FID and inflammatory iron block, TSAT is less than 20% and the ferritin level is elevated (between 100 and 800 ng/ml). The response to EPO or parenteral iron may help distinguish between these 2 possibilities. With EPO administration, ferritin levels may decrease in patients with FID but not with inflammatory iron block. Inflammatory iron block is also most likely present if the administration of intravenous iron is associated with a progressive increase in ferritin concentration rather than with increased erythropoiesis.

We found that FID was related to serum iron and its derivatives, i.e., TSAT, but also to RRF. FID was not associated with other parameters of iron metabolism, including the new ones – BMP6, GDF15, and hemojuvelin. However, in a stepwise multivariate regression analysis, hepcidin was relatively close to be the predictor of FID. Until now, none of the published studies focused on FID, hepcidin, and other iron players in HD population. However, we should be cautious in the interpretation of these results because intraindividual variability of serum hepcidin-25 in HD patients has recently been reported.<sup>21</sup> Inflammation and the use of iron did not affect the degree of variability, and hepcidin levels were higher after an interdialytic period of 3 vs. 2 days. Therefore, we conducted our study before a midweek dialysis. Hpcidin has a dual role – of a ferrostat and of defensin. It may also represent an acute-phase reactant.<sup>22</sup> Deteriorating renal function may enhance the overall inflammatory response due to decreased renal clearance of the factors that are directly or indirectly involved in inflammation. The same applies to the relation between RRF and inflammation<sup>12</sup> because we demonstrated that hepcidin was affected by RRF.<sup>23</sup>

So far, no biomarkers considered as the gold standard for iron store or availability have been defined, so the search continues. The sTfR concentration can reflect the functional iron status while ferritin – iron storage.<sup>24,25</sup> However, some data have demonstrated that sTfR offers little advantage over conventional laboratory indicators of the iron status.<sup>26</sup> That is why, sTfR has not been introduced as a regular indicator of the iron status.

Lack of the difference in serum sTfR between our study groups might be caused by low sensitivity and specificity of this marker in the assessment of the iron status in HD population.

Our study has been the first to assess the novel markers of iron metabolism, namely, BMP6 and GDF15, in patients on HD. We found that BMP6 levels were below the detection limit for the assay in one-third of the patients. We did not observe any differences in BMP6 levels between patients with and without FID. There are no data available on BMP6 in patients with CKD or even in healthy volunteers. None of the new parameters evaluated in our study was included in the definition of FID and proved their usefulness in the assessment of iron status in dialysis patients. Unfortunately, none of these parameters met our expectations, and iron metabolism not only in CKD but also in HD still remains an unsolved mystery. Therefore, clinical assessment of the effects of iron and erythropoiesis-stimulating agents on hemoglobin levels is the most important<sup>27,28</sup> to diagnose FID. Interestingly, in a recent paper by Ghoti et al.,<sup>29</sup> EPO was reported to utilize excess iron in patients on long-term HD with high ferritin levels (>1000 ng/ml) 1 year after withholding intravenous iron treatment. In addition, in 11 of 12 patients, CRP was elevated but no data were provided at 1 year whether inflammation subsided after iron utilization, predominantly from the liver and spleen. Hemoglobin remained stable during the study and was between 10 and 13 g/dl. However, in some patients, TSAT was above 50% suggesting secondary iron overload or even hemochromatosis.

The iron status of an individual may play an important role in cardiovascular health. Moreover, iron deficiency has been shown to cause ventricular hypertrophy.<sup>30</sup> Anemia and iron deficiency are common in chronic heart failure,<sup>31</sup> another frequent complication in CKD.<sup>32</sup> We observed more advanced left ventricular hypertrophy and more advanced CHF in patients with FID. So far, there have been no reports on the possible correlations between iron deficiency and heart function and morphology in HD patients, despite the evidence of various disturbances in LV geometry in patients with HD.<sup>33</sup> In our previous study including patients on peritoneal dialysis, the presence of cardiorenal anemia syndrome was associated with worse survival.<sup>34</sup>

Since inflammation is associated with worse response to erythropoietin-stimulating agents and worse outcome, the most important therapeutic approach should be the search for potentially reversible and treatable causes of inflammation. All measures that could help maintain RRF as long as possible should also be considered (i.e., avoidance of nephrotoxic drugs or of hypotension episodes, etc). Optimization of HD treatment to achieve appropriate Kt/V might be another possible option.

In conclusion, new players in iron metabolism seem to be unrelated to FID, which is observed in

a marked number of patients on HD. FID in these patients is associated mainly with their chronic inflammatory state, which should be promptly diagnosed and treated.

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# Nowe parametry w metabolizmie żelaza oraz jego funkcjonalny niedobór u pacjentów przewlekłe hemodializowanych

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## SŁOWA KLUCZOWE

hemodializa,  
hepcydyna, niedobór  
żelaza, stan zapalny,  
układ sercowo-  
-naczyniowy

## STRESZCZENIE

**WPROWADZENIE** Metabolizm żelaza jest od lat przedmiotem wielu badań. Wciąż opisuje się kolejne nowe substancje biorące w nim udział. Funkcjonalny niedobór żelaza (*functional iron deficiency* – FID) charakteryzuje się obecnością adekwatnych zasobów żelaza (definiowanych za pomocą standardowych kryteriów) oraz nieadekwatną mobilizacją żelaza do erytropoezy podczas stosowania leków stymulujących erytropoezę.

**CELE** Celem badania była ocena stężenia nowych markerów metabolizmu żelaza i częstości występowania FID oraz ocena ich ewentualnych korelacji w grupie chorych hemodializowanych.

**PACJENCI I METODY** W badaniu wzięło udział 98 pacjentów przewlekłe hemodializowanych. Za pomocą metod standardowych oceniano parametry gospodarki żelaza, morfologię krwi obwodowej oraz stężenia: kreatyniny, wapnia, fosforanów, albuminy, iPTH (*intact parathyroid hormone*) i lipidów. Białko C-reaktywne oznaczone metodą o dużej czułości (*high-sensitivity C-reactive protein* – hsCRP), interleukinę 6 (IL-6), czynnik martwicy nowotworów  $\alpha$ , peptyd natriuretyczny NT-proBNP (*N-terminal pro-B-type natriuretic peptide*), czynnik różnicowania wzrostu 15 (*growth differentiation factor 15* – GDF15), BMP6 (*bone morphogenic protein 6*) oraz hemojuwelinę i hepcydynę oceniano za pomocą zestawów komercyjnych.

**WYNIKI** FID występował u 23% pacjentów hemodializowanych i wiązał się z większymi stężeniami ferrytyny, IL-6, hsCRP, hepcydyny oraz NT-proBNP. Nie stwierdzono istotnych różnic pod względem stężeń GDF15 i BMP6 między osobami z FID a osobami bez tego niedoboru. U pacjentów hemodializowanych częściej występowało nadciśnienie tętnicze, cukrzyca i przerost lewej komory serca, wymagali oni również nieco, ale niezamiennie, większych dawek erytropoetyny. Predyktorami FID były stężenie żelaza i resztkowa czynność nerek.

**WNIOSKI** FID występuje w znaczącej części populacji chorych hemodializowanych, którą powinno się badać pod kątem odwracalnych przyczyn stanu zapalnego. Jak się wydaje, nowe markery metabolizmu żelaza nie są związane z FID u pacjentów hemodializowanych.

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