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Iron Deficiency, Introduction to a Diagnostic Problem in a County Hospital

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Abstract

Aim: Focus of this study was set for investigation of a potential diagnostic role of serum-iron-content in case of iron deficiency, thus, its measurements were compared to the simultaneously detected other parameters of iron metabolism and to the hemoglobin values of reticulocytes.

Results: Amongst of 644,558 clinical records of patients, a remarkable number of 30,830 iron measurements have been analyzed. Insufficient serum iron level (SeFe <11 µmol/L) was proven in case of 9169 (29.74%) patients with a gender ratio of 6760/2409, females versus males. Resulting the concurrently performed 1,671 tests for transferrin saturation, ferritin level and reticulocyte-hemoglobin-content, iron deficiency got proven in 1,487 (88.9%) patients.

Serum-iron level higher than 11 µmol/l (SeFe>11 µmol/L) was found in 24,070 patients, meanwhile, 1,884 studies performed for transferrin saturation, ferritin level and reticulocyte-hemoglobin-content concluded iron deficiency in 412 (21.9%) cases. The diagnostic value of SeFe<11 µmol/L was found with 88.90% of sensitivity and 78.13% specificity, for both females and males.

Discussion: Based on our patient cohort studied for iron deficiency, the parameter of SeFe level <11 µmol/L was satisfactory for ID screening. For wider studies on iron-metabolism we suggest measuring ferritin level, reticulocyte-hemoglobin-contents, CRP level and the transferrin saturation, considering that the last one is the most reliable.

Introduction

Iron is a well-known essential mineral for humans, due to its' central role in oxygenation of the body. Several reasons may lead to iron deficiency (ID), such as low dietary intake, malabsorption, increased demand, or loss of blood. Iron deficiency affects 6-8% of the population in the wealthy countries and around 40-45% in the third world. Iron deficiency anemia (IDA) develops in 30-40% of all iron deficiencies [1-3]. Diagnostic approaches for IDA may be misled by a quite frequently appearing form of the disease, the functional iron deficiency.

Reportedly, the most important laboratory parameters of ID are the serum iron level, the transferrin volume (Trf), the transferrin saturation (Trfsat) and the serum ferritin level.

Some may conclude the low level of ferritin is the best diagnostic parameter for ID, but the clinical evaluation can be biased by its acute-phase-nature, or its usual co-appearance with liver cell damage, and even more its frequent co-existence with tumors. Considering the facts above, the Trfsat is the most useful diagnostic parameter for our clinical practice [4].

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The reticulocyte-hemoglobin-content has also been reported for a meaningful parameter of ID [5-8]. Our previous publication highlighted the importance of another complete blood count parameter, the MCH [9,10].

The uncertainties of the diagnostic role of serum-iron measurement in ID resulted us to study it in a wide patient cohort.

Comparisons between serum-iron (SeFe) measurements and other commonly tested ID variables were taken in consideration as main study targets for present publication.

Patients and methods

644,556 samples were tested for complete blood count (CBC) in our county hospital over a period of 5-years (2013-2017) which were used for data collection for this study. We excluded the patients who were either under 18 years or had received hemodialysis therapy from this investigation.

All patients were Caucasian by race with no cases of Thalassemia in their clinical records.

Diagnosis of iron deficiency got established by measurements of the transferrin saturation (Trfsat), the reticulocyte-hemoglobin-content (Ret-Hgb) and the serum ferritin level, which were respectively equal to or lower than 20%, 28 pg and 30-20 µg/L (in both males and females). The CBC tests were run on the Sysmex XN-2100i (Hoffmann-LaRoche) machine, the hemoglobin level measurements were performed by sodium lauryl sulfate (SLS)-method, the red blood cell counting was done with impedance test and the reticulocyte quantification was conducted by flow cytometry.

Iron parameters were tested by COBAS 8000 c502-es (Roche) immunochemistry analyzer.

Serum iron levels were measured with the FerroZine method at 552 nm and the results were given in µmol/l. The first threshold set for SeFe was 6.6 µmol/L for females and 11 µmol/L for males, but it has been revised for females also to 11 µmol/L.

Ferritin levels were measured by electrochemiluminescence immunoassay – ECLIA, and transferrin levels with immunoturbidimetry.

Transferrin saturation was calculated by the following formula: the serum iron level divided by the transferrin volume and multiplied with a factor of 3.98. We expressed the results in percentage, and values lower than, or equal to 20% got considered as abnormal ones.

Diagnostic criterion of anemia was the hemoglobin level lower than or equal to 130 g/L in males, and 120 g/L in females [11].

Statical analysis: In addition to the descriptive statistical method, the chi-square test was used to compare dichotomous variables. Statistical analysis was performed using the open-source R statistical software package, version 3.1.2 (The R Foundation for Statistical Computing); statistical tests were interpreted at a significance level of 5%.

Ethical approval was granted by the Research Ethics Committee of the Somogy County Moritz Kaposi General Hospital. Due to the retrospective performance of this study, written consent of patients was not required.

Results

Over the 5 years of this retrospective study, 644,556 samples were tested for CBC with a gender ratio of 365,271 females versus 279,285 males. The iron parameters listed above were concurrently controlled in 35,398 cases, with a gender ration of 23,321 females versus 12,077 males.

Serum iron levels have also been measured in 30,830 cases (20,867 females/9,963 males), while the transferrin saturation in 2,938 patients (1,972 females/966 males) and the ferritin values in 2,551 subjects (1,680 females/871 males).

Reticulocyte-hemoglobin-content was tested in 5,117 cases (2,835 females/2,282 males).

SeFe in proven of ID: (Table 1)

Testing 20,867 specimens, the SeFe content was found at low level in 2698 (12.92%) female patients by exclusively using cut off value 6.6 µmol/L (Table 1).

Strikingly higher positivity was found by testing for Trfsat, ferritin and Ret-Hgb-content in patient numbers 523 out of 526 (99.4%), 359 out of 491 (73.1%) and 153 out of 184 (83.2%), respectively. Combined analysis of these three parameters resulted 640 positive findings for iron deficiency out of 674 patients (95%).

While the SeFe cut off value 11 µmol/L, used to be applied exclusively for testing of males in our laboratory, in this case it was used for the processing of female data. The results showed low level, so positive SeFe findings, in 6,760 out of 20,867 (32.39%) patients. The concurrently performed Trfsat, ferritin and Ret-Hgb-content studies manifested positive results in patient ratio of 931 out of 982 (94.8%), 504 out of 816 (61.8%) and 191 out of 281 (68.0%), respectively. Combined analysis of data of these three clinical parameters resulted in 1,106 positive ID findings out of 1,233 (89.7%).

The SeFe results in males were low in 2,409 cases, meanwhile the tests for Trfsat, ferritin and Ret-Hgb-content resulted in positive findings for patient numbers 295 out of 350 (84.3%), 100 out of 297 (33.7%) and 77 out of 112 (68.8%) for proving ID. Combined analysis of the last three parameters resulted in 381 positive ID findings out of 438 (86.8%).

Table 1: Proven of ID

		Female n (%)		Male n (%)	Summary n (%)
SeFe all		20,867		9,963	30,830
Cut off level		Fe<6.6	Fe<11	Fe<11	Fe<11
SeFe bellow of cut off level		2,698 (12.9)	6,760 (32.4)	2,409 (24.2)	9,169 (29.7)
Trfsat	n	526	982	350	1,332
	≤20	523 (99.4)	931 (94.8)	295 (84.3)	1,226 (92.0)
Ferritin	n	491	816	297	1,113
	♀ ≤20, ♂ ≤30	359 (73.1)	504 (61.8)	100 (33.7)	604 (54.3)
Ret Hgb	n	184	281	112	393
	≤28	153 (83.2)	191 (68.0)	77 (68.8)	268 (68.2)
Trfsat+ Ferritin+ Ret Hgb	n	674	1233	438	1671
	Trfsat: ≤20, Ferritin: ♀ ≤20, ♂ ≤30, Ret Hgb ≤28	640 (95.0)	1,106 (89.7)	381(86.8)	1,487 (88.9)

SeFe in exclosure of ID: (Table 2)

18,169 test results were found higher than the SeFe cut off value 6.6 µmol/L, exclusively used for females, though Trfsat, ferritin and Ret-Hgb-content tests confirmed ID in cases of 629 out of 1445 (43.5%), 275 out of 1111 (24.8%) and 59 out of 291 (20.3%). Despite the negative findings by SeFe measurements, the Trfsat, ferritin and Ret-Hgb-content tests used in combination, proved ID in cases of 684 out of1445 (47.3%). Therefore, it can be concluded that, almost half of the ID patients were not identified by screening performed only with SeFe testing.

However, the SeFe cut off value 11 µmol/L is used to be applied for testing of males in our laboratory, now it was used for processing of data of females and provided higher negative results in cases of 14,107/20,867 women. The concurrently performed Tfs, Sf and Ret-Hgb-content tests showed positive ID findings of 221 out of 989 (22.3%), 130 out of 786 (16.5%) and 21 out of 194 (10.8%) patients, respectively. Inspite of the negative findings with this SeFe cut off value, the Tfs, Sf and Ret-Hgb-content measurements used in combination also convinced us about presence of ID in patient numbers of 322 out of 1268 (25.4%). In conclusion, almost a quarter of patients with ID were not identified by SeFe screening method.

SeFe testing of males with the routine cut off value of 11 µmol/L, showed higher results negative cases of 7,554/9963 (75.82%), but the Trfsat, ferritin and Ret-Hgb-content tests identified positive cases in patient numbers of 65/617 (10.6%), 23/470 (5.3%) and 14/169 (8.3%). Despite the false negative findings with SeFe test, results of the Trfsat, ferritin and Ret-Hgb-content tests proved ID in patients numbers of 90/616 (14,6%). It can be concluded that, almost fifteen percent of the ID cases were not discovered by testing with SeFe.

Table 2: Exclusion of ID.

		Female n (%)		Male n (%)	Summary n (%)
SeFe All		20,867	20,867	9,963	30,830
Cut off level		Fe>6.6	Fe>11	Fe>11	Fe>11
Se Fe above of cut off level		18,169 (87.1)	14,107 (67.6)	7,554 (75.8)	24,070 (78.1)
Trfsat	n	1,445	989	616	1,605
	≤20	629 (43.5)	221 (22.3)	65 (10.6)	286 (17.8)
Ferritin	n	1,111	786	470	1,256
	♀ ≤20, ♂ ≤30	275 (24.8)	130 (16.5)	23 (5.3)	153 (12.2)
Ret Hgb	n	291	194	169	363
	≤28	59 (20.3)	21 (10.8)	14 (8.3)	35 (9.6)
Trfsat+ Ferritin+ Ret Hgb	n	1,445	1 268	616	1,884
	Trfsat: ≤20, Ferritin: ♀ ≤20, ♂ ≤30, Ret Hgb ≤28	684 (47.3)	322 (25.4)	90 (14.6)	412 (21.9)

Concluding the previous findings in females, the SeFe screening with cut off value 6.6 µmol/L ensures the specificity of SeFe testing in 95.72%, but its sensitivity value drops to the low level of 48.34%. While this screening performed with cut off value of 11 µmol/L, it secures the specificity still at the level of 88.16%, and its sensitivity remarkably increases to 77.45%.

Furthermore, the cut off value 11 µmol/L of SeFe used for screening in males goes with high specificity of 90.22%, and sensitivity of 80.89%.

Overall, for both genders, the cut off value of 11 µmol/L for SeFe screening ensures sensitivity of 88.99% with specificity of 78.13% for ID diagnosis.

Discussion

Our retrospective study reported the transferrin saturation with the highest performance for reliability in comparison to other parameters for ID diagnosis, and it confirmed the previous publications on uncertainties of ferritin as a diagnostic criterion.

Lack of screening explains the frequent findings of high ferritin levels in patients. The functional iron deficiency (FID) tests in patients with several chronic diseases and with frequent inflammatory backgrounds may have modified the results of the tests for ID [3].

In our opinion, the reduced efficiency of the reticulocyte-hemoglobin-content test is probably an artifact of the irregular iron support provided for a few days in the hospital, which may also explain the low ferritin findings in case of detection of a high SeFe value.

The internationally well-known standard deviation of the minimum value of SeFe has also prevailed in our own laboratory, especially in case of women [1-3].

In comparison with the diagnostic value of the low transferrin saturation [12], the SeFe cut off value <11 µmol/L proved its highly reliable value in 92% of iron deficiencies.

In case of males, this value is considered a reliable parameter for investigation of iron deficiency with 90.22% specificity and 80.89% sensitivity. While in females, the cut off value of 6.6 µmol/L can be considered too low with 48.34% sensitivity which indicates its unreliability for ID diagnostic purpose. This is demonstrated by the fact that 47.3% of patients tested with this cut off value had provided negative preliminary findings for ID however they still had iron deficiency with further investigations.

SeFe cut off value 11 µmol/L is more reliable for females too with its specificity (88.16%) and sensitivity (77.45%), although this value still not ruled out ID in cases of 25.4% of patients.

Conclusion

Iron metabolism data from patients treated in our hospital suggest that the bottom levels of SeFe are nearly the same as in men as in women. The value of SeFe <11 µmol/L is suitable for the confirmation of ID, but for diagnostic exclusion it is not recommended, due to the false negative results of almost in 15% of male, and more than 25% of female patients.

The SeFe measurement complemented with the determination of transferrin saturation can be concluded the suitable tests methods for establishment of iron deficiency diagnosis.

Authors' contribution: All authors read and approved the final version of the manuscript

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