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СОДЕРЖАНИЕ ГЕМОГЛОБИНА В РЕТИКУЛОЦИТАХ: НОВОСТИ 2020

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Содержание гемоглобина в ретикулоцитах (Hb-ret) является эффективным индикатором состояния синтеза гемоглобина в реальном времени, который позволяет диагностировать и контролировать дефицит железа и железодефицитную анемию во всех возрастных группах с сопутствующими заболеваниями или без них, включая бета-талассемию. Анализ Hb-ret – менее инвазивный метод, чем исследование железа костного мозга, менее дорогой, чем биохимический анализ показателей обмена железа, и может быть доступен даже в местных лабораториях. Этот обзор посвящен материалам, опубликованным, в основном в 2020 г., и некоторым исследованиям клинического применения Hb-ret измеренного на гематологических анализаторах Sysmex.

Ключевые слова: *содержание ретикулоцитарного гемоглобина; дефицит железа; железодефицитная анемия; талассемия.*

RETICULOCYTE HAEMOGLOBIN CONTENT: 2020 UPDATE

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The hemoglobin content of reticulocytes (Hb-ret) is an effective real-time hemoglobin synthesis status indicator that permits diagnosis and monitoring of iron deficiency and iron deficiency anemia in all age groups with or without underlying diseases, including beta thalassemia. Hb-ret is less invasive than bone iron examination, less expensive than iron biochemical tests and might be available even in local laboratories. This review covers reports published mainly in 2020 and some other studies dedicated to clinical application of Hb-ret measured by Sysmex hematology analyzers.

Keywords: *reticulocyte hemoglobin content; iron deficiency; iron deficiency anemia; thalassemia*.

Reticulocytes are immature red blood cells released into the blood two to three days following hematopoiesis and become mature red blood cells one to two days later. In the bone marrow, iron is taken up from the blood during hematopoiesis and then binds to heme protein to form hemoglobin (Hb). The hemoglobin content of reticulocytes (Hb-ret) is considered to reflect Hb synthesis potential and the iron levels used in hematopoiesis [1].

At the beginning of 2020, an excellent review about Hb-ret was published by Chie Ogawa, et al. [2]. The review covered iron metabolism in the body, hematopoiesis in the erythroid system, and the measurement principle and characteristics of Hb-ret and its

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application in clinical studies mainly dedicated to commercial H*3 and ADVIA hematology analyzers. This paper aimed to analyze more recent studies about Hb-ret and some not previously included reports, such as clinical applications of Hb-ret parameters measured by Sysmex hematology analyzers.

Diagnosis of iron deficiency and iron-deficiency anemia

Anemia is a significant worldwide health problem. Approximately one-third of the world's population suffers from anemia, half of which is iron deficiency (ID) [3,4]. Traditional indices of body iron, such as *serum ferritin* (SF), *serum iron*, *total iron-binding capacity*, and *transferrin saturation* (TSAT), are affected by other factors (inflammatory state, diurnal variation, diet/malnutrition, decreased liver function) and iron metabolism. Differently, Hb-ret is not affected by any factors other than those participating in iron metabolism, as long as there is no abnormality in Hb synthesis [2]. However, a study of 405 healthy adolescents (subjects with a hematological or systemic disease, present or previous infectious or febrile disease, or C-reactive protein >0.5 mg/dL excluded) found that higher body weight was associated with slightly, but significantly lower, Hb-ret with no ID associated [5].

The Hb-ret level was significantly lower in non-ID anemia than in healthy controls but significantly higher than in ID [6]. The areas under the curve (AUC) resulting from receiver operating characteristic curve analysis for the diagnosis of absolute iron-deficiency anemia (IDA) were reported to be 0.69-0.89 and 0.64-0.84 for SF and TSAT, respectively, in contrast to 0.74-0.93 for Hb-ret [2,3]. The variability of AUC for Hb-ret could also be explained by the different cutoff values applied: 27.2 pg to 30.5 pg [2,7].

The Hb-ret is proposed for IDA detection in infants who have difficulties with blood draws [8]. An American retrospective records review of 190 paired ferritin and Hb-ret measurements in neonates showed that the Hb-ret makes a more accurate ID diagnosis than ferritin [9]. A study of 274 samples from infants hospitalized in intensive care units confirmed that Hb-ret levels at birth are higher than any other day of a healthy life, in accordance with a relatively high level of erythropoietin before birth. In term infants (more than 37 weeks of gestation), the later Hb-ret decrease was less compared with preterm infants (before 37 weeks of gestation), which is partly explained by the minor incidence of conditions related to hospitalization [10].

Hb-ret permits differentiation between IDA, ID without anemia, and normal state in children and adolescents [2]. In a study conducted on 207 Indonesian children, Hb-ret was significantly different between ID without anemia (normal Hb according to age and one of two criteria: TSAT <15% and/or SF<15 mg/L) and normal state, but not between iron depletion (IDep) (normal Hb according to age, normal TSAT, and SF<15 mg/L) and normal state [11]. In this study, all venous blood samples were analyzed at two different laboratories using ADVIA 2120 and Sysmex ST 2000i. It is unclear whether the results between equipment systems were compared. Comparing results produced by different analytical systems and the small sample number could explain the absence of the difference between the normal state and IDep.

A recent Spanish study reported that Hb-ret, in addition to the serum transferrin receptor (sTfR, the conventional analytic parameter was not influenced by proinflammatory states), increased the sensitivity of ID assessment from 9.1% to 12.1% in adolescents [4].

The possibility of a quick ID/IDA diagnosis and the test availability in a local laboratory is crucial, especially for children, pregnant women, and older people [12-14], which is another important benefit of Hb-ret use. This biomarker is currently available on many hematology analyzers, being determined simultaneously with the other hematological parameters and decreasing the economic burden of ID/IDA diagnosis and monitoring [14,15]. These reasons also made Hb-ret be suggested as a preoperative marker

of latent anemia within the Patient Blood Management program. Identifying and treating patients with ID proactively enhanced recovery after surgery concept helped to prevent complications and extended hospital stays [16]. Hb-ret can be used as a routine screening test to detect latent ID in blood donors, providing an opportunity to make appropriate and timely interventions, like dietary changes or drug supplementation, to prevent overt IDA development [17].

Thalassemia

Microcytosis and hypochromia can be falsely interpreted as ID/IDA in individuals with thalassemia. Beta-thalassemia trait (BTT) is an autosomal dominant disorder that results in defective production of beta globulin chains, which are Hb-constitutive proteins. BTT is ubiquitous in African populations. It also shows a significant prevalence in the Mediterranean, Middle East, Transcaucasus, Central Asia, Indian subcontinent, and the Far East. The reported BTT incidence is 14% and 12% in Cyprus and Sardinia, respectively. However, BTT due to population migration is now also common in Northern Europe, North, and South America, in the Caribbean, and Australia. Since this disease has a powerful socio-economic impact and diagnosis is usually based on specific expensive tests, there is a need for rapid, simple, and low-cost screening tests [18].

Based on a study of 293 samples from Italian children, a discrimination index (DI) for BTT screening (DI-BTT) was developed. The DI-BTT can be calculated using the following formula:

$$(RBC \times MCHC \times 50/MCV)/CHr,$$

RBC – red blood cell, MCHC – mean cellular hemoglobin concentration, MCV – mean cellular volume, and CHr – mean reticulocyte hemoglobin. The evaluation of this index permitted identifying patients with BTT. DI-BTT was significantly higher in BTT patients (6.93±1.64) and clearly separated them from normal controls (3.43±0.39) and IDA patients (3.71±0.39) with $p<0.001$. The authors state that the utility of this promising and low-cost method requires furthers confirmation in a larger number of cases [18].

ID screening in patients with thalassemia

As explained above, efforts have been made to differentiate IDA from thalassemia. Still, a bigger challenge is to find a simple indicator for identifying ID in thalassemia prevalent geographic areas [19]. Hb-ret combined with red blood cell distribution width (RDW) standard deviation (RDW-SD) was powerful in differentiating thalassemia from IDA [20]. A recent study of 304 female university students with an age range of 18 to 30 years, all of whom resided in northeast Thailand, revealed that 25% had ID and 50% carried the thalassemia gene. Additional formulas derived from the Hb-ret and other parameters were also established and tested for predicting ID. Performance with an AUC of 0.874 was shown by the following formula:

$$(Hb\text{-}ret/RDW\text{-}SD) \times 10,$$

which was the best predictor for identifying ID among participants: with an optimal cutoff value less than 6.1, at least 80% of individuals with and without ID were correctly identified (80% sensitivity and 86.5% specificity) [21].

Monitoring of ID/IDA therapy

Hb-ret is useful for the early measurement of the response to iron therapy, increasing on the second day after initiating iron therapy [22]. It helps to monitor intravenous and oral iron therapy in adults [6,23], children [24], and infants [25,26].

A recent study dedicated to evaluating a low monthly dose of intravenous iron sucrose in patients on peritoneal dialysis. No difference was between Hb-ret levels determined at baseline, after one month, and after three months of treatment timepoints [27]. The study included a very small sample number of 18 patients, leading to high SD values. It is unclear whether it was possible to stratify patients and see the difference (as the Hb level increased significantly) or if the stability the Hb-ret levels was due to measuring long periods after iron supplementation.

During oral iron therapy, only a small proportion of ingested iron is absorbed,

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necessitating higher intake, which may result in adverse side effects, reduced compliance, and inefficient repletion of iron stores through hepcidin activation. Increasing the absorption of iron could be a strategy for solving these problems.

A study in female iron-deficient athletes showed that group with a daily intake of 10^{10} colony-forming units of the probiotic strain *Lactobacillus plantarum* 299v (Lp299v, LP299V®) in addition to iron (LpFe) showed a tendency toward higher ferritin levels after the first four weeks compared with iron intake alone. Over the 12-week study, both groups increased their iron status, as demonstrated by a 70% increase in plasma ferritin after intake of Lp299v with 20 mg of iron compared with 42% after 20 mg of iron alone. However, the difference between groups did not reach statistical significance. LpFe use led to the same increase in Hb-ret as iron alone after the first four weeks but showed a tendency toward higher Hb-ret levels over the 8- and 12-week study with p=0.275 and p=0.083, respectively [28].

Iron supplements and erythropoiesis-stimulating agents (ESAs) are used to treat anemia in the majority of patients undergoing hemodialysis (HD). The effective use of ESAs strictly demands preventing both ID and iron excess. Thus, maintaining optimum iron levels is a critical challenge. A study of 181 patients undergoing maintenance HD and were administered recombinant human erythropoietin indicated that Hb-ret values allow finding optimal SF levels, as Hb-ret showed a dependence on in vivo iron levels up to a certain level and remained unaffected at levels above these [1].

Hb-ret in patients with other underlying pathologic conditions

A frequent extra-intestinal manifestation of inflammatory bowel disease (IBD) is IDA, which is associated with a poorer outcome. IDA in IBD patients is linked to impaired iron absorption due to chronic inflammation, bowel resection (especially in Crohn's disease), malnutrition, and chronic blood loss. ID diagnosis and further management of these patients is difficult because of ferritin elevation related to inflammation and the possibility of chronic disease anemia. The examinations of 123 anemic patients with IBD showed that, among different biomarkers, Hb-ret has the best performance in ID diagnosis, considering a cutoff of 30.0 pg with an AUC of 0.858, a sensitivity of 76.8%, and a specificity of 99.8% [29].

The assessment of Hb-ret to detect ID was recently proposed in patients with chronic hepatitis C [30] and patients with *Helicobacter pylori* infection [31].

Hb-ret is recommended as an easy and affordable tool to assess IDA in childhood cancer during chemotherapy treatment. The cutoff level of 28 pg was suggested after a prospective study included 100 pediatric patients [32].

Pneumonia

An exciting application of Hb-ret was suggested by Schoorl and co-authors based on Hb-ret being a sensitive indicator of monitoring short-term deteriorations in functional iron supply for erythropoiesis [33,34]. In anemia of inflammation, a protective mechanism activates iron retention from the blood circulation as an essential pathogenic growth factor while increasing the efficacy of cell-mediated immunity. Results of a study of 75 subjects with community-acquired pneumonia demonstrated a temporary impairment of Hb-ret with a decline from 3% to 8% within the time period elapsing from hospital admission until day four and a significantly increasing trend toward values within the reference range at day 14. These alterations were registered all together with a temporary increase of cytokine-stimulated serum hepcidin-25 (studied in 25 patients), a hepato-cellular peptide hormone that regulates iron redistribution during inflammation [34].

Conclusions

Hb-ret is an effective and widely available Hb synthesis status indicator that permits ID/IDA diagnosis and monitoring in all age groups with or without underlying diseases, including beta-thalassemia. The local study of cutoff values might be helpful

for accurate diagnosis resulting in the perspective of raising the life quality and reducing the cost of patient care. The possibility of Hb-ret use as a biomarker while monitoring anemia of inflammation and predicting pneumonia prognosis has to be studied.

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