FERRİTİN

Diagnostic reagent for determination of Ferritin concentration.
Liquid. Dual reagents. Store at +2/+8°C. For in Vitro Diagnostic Use (IVD). **Do not freeze.**

Ref No	Pack
MH-372	75 mL
MH-373	50 mL

Changes made in the instructions for use are marked as grey.

INTENDED USE

This test is used for the quantitative determination of ferritin in human serum and plasma.

GENERAL INFORMATION

Ferritin is a protein first isolated from the spleen of a horse in 1937 by French scientist Laufberger.[1] It was later found that ferritin is a highly conserved, widely available protein that can accommodate up to 4500 iron atoms. In humans, ferritin is a heteropolymer of 24 subunits of two types, heavy/heart (H) and light/liver (L), which combine to form a hollow spherical shell containing Fe atoms stored as ferric oxyhydroxide phosphate.[2,3] The ferroxidase activity of H-ferritin converts Fe^{+2} to Fe^{+3}, which is required for Fe to accumulate in the nanocage. L-ferritin induces Fe nucleation. L-ferritin is predominant in Fe-storing tissues (liver, reticuloendothelial), while H-ferritin is preferentially expressed in cells with a significant antioxidant activity (brain, heart).[3] Fe^{+2} is delivered to ferritin by cytoplasmic chaperones.[4] The release of Fe from ferritin is facilitated by multiple mechanisms, including autophagy and lysosomal degradation of ferritin.[5,6] Ferritin is present in almost all cells and provides a readily available Fe reserve for the formation of Hb and other heme proteins. Fe bound to ferritin is protected from body fluids and thus cannot cause oxidative damage as in the free ionic form. Ferritin expression is tightly regulated at the transcriptional and post-transcriptional level by various factors including Fe, cytokines, hormones and oxidative stress.[3,7]

Approximately 1 µg/L serum ferritin corresponds to approximately 8 to 10 mg stored Fe.[8-10] Serum ferritin differs from tissue ferritin in that it is glycosylated, contains mostly L chains and is Fe-poor (mostly apoferritin).[11] Serum ferritin reflects both reticuloendothelial and parenchymal Fe stores.[10] Moreover, despite its long-term use in the assessment of body Fe stores, the source of the serum ferritin molecule in cells and its elaborate secretion pathway are poorly understood.

However, animal studies suggest that macrophages contribute significantly to serum ferritin concentrations.[12] Furthermore, receptor interactions with serum ferritin and cellular effects are unclear and are topics of active debate.[11]

Ferritin is a stable marker. It has a non-crucial diurnal rhythm, reaching peak levels around noon. The day to day variation ranges from 5.9% in a recent study compared to the older studies of around 14%. The cause of this day to day variation is unknown, but it is likely to reflect fluctuations in intracellular protein synthesis and leakage of intracellularly stored ferritin, as occurs in fasting, heavy exercise and inflammation.[10,13-15]

Serum ferritin concentration roughly reflects body Fe content. Very early in the development of iron deficiency, serum ferritin concentration decreases long before changes in blood Hb concentration, erythrocyte size, or serum Fe concentration are observed. Plasma ferritin concentration increases in patients with Fe overload in the body for any reason and is used to measure the efficiency of Fe chelation therapy with phlebotomy treatment. Ferritin also serves as a positive acute phase reactant in various inflammatory conditions.[16-18] As a result, hyperferritinemia is not synonymous with Fe overload, and many disorders can cause an increased serum ferritin concentration that is not always associated with an increase in body Fe content.[10,19-22] High serum ferritin levels are not always associated with increases in liver iron content, and serum ferritin levels do not indicate whether iron is stored in parenchymal cells or reticuloendothelial macrophages.[2,10] Ferritin concentrations are higher in conditions in which iron is distributed to the reticuloendothelial system (such as patients receiving transfusions or patients with chronic inflammatory diseases) than in diseases in which iron accumulates in parenchymal cells (hepatocytes) due to excessive absorption (such as hereditary hemochromatosis, some non-transfusion-dependent sideroblastic anemias and b-thalassemia intermedia).[23]

The diagnostic sensitivity of low ferritin levels in detecting Fe deficiency is low in the presence of comorbidities. High ferritin concentrations observed in various diseases are not always associated with body iron stores. These disorders include infection (including COVID-19), inflammatory disorders, hemophagocytotic lymphohistiocytosis and related macrophage activation syndromes, Gaucher disease, adult-onset Still's disease, hereditary hyperferritinemia-cataract syndrome, hyperthyroidism, tumors, liver and kidney failure, cell necrosis, chronic alcohol consumption, non-alcoholic fatty liver disease and/or metabolic syndrome.[24-31]

Serum ferritin test is also used to monitor iron overload in patients with chronic kidney disease, which may result from excessive iron supplementation to optimize hemoglobin content and minimize the dose and cost of EPO therapy. However, serum ferritin in these patients is not always related to the iron content of the liver.[32,33]

Some studies have reported that increased plasma ferritin

levels may be a strong predictor of premature death.[34] Moderately to dramatically increased ferritin concentrations have been reported to predict myocardial infarction, carotid plaques and early death in a level-dependent manner.[34-36]

Nevertheless, further prospective controlled studies are needed to assess if the risk associated with hyperferritinemia represents only a predictor of risk or if it is in fact a risk factor. Serum ferritin is often used to assess iron overload and monitor iron chelation therapy in patients with iron overload anemia, such as thalassemia syndromes and sickle cell anemia. Serum ferritin in these diseases is usually associated with liver iron concentrations.[23,37]

TEST PRINCIPLE

Immunoturbidimetric measurement

Serum ferritin molecules cause precipitation of latex particles coated with anti-human antibodies present in the reagent. The turbidity resulting from precipitation is determined turbidimetrically from the absorbance reading at a wavelength of 540 nm and is directly proportional to the ferritin concentration in the sample.

REAGENT COMPONENTS

Reagent 1:

Glycine buffer	:≤ 185 mmol/L
Sodium chloride	:≤ 125 mmol/L
Sodium azide	:≤ %0.1

Reagent 2:

A solution of latex particles coated with anti-human ferritin antibodies

Sodium azide	:≤ %0.1

REAGENT PREPARATION

Reagents are ready for use.

REAGENT STABILITY AND STORAGE

Reagents are stable at +2/+8˚C till the expiration date stated on the label which is only for closed vials.

Once opened vials are stable for 30 days at +2/+8°C in optimum conditions. On board stability is strongly related to auto analyzers' cooling specification and carry-over values.

Reagent stability and storage data have been verified by using Clinical and Laboratory Standards Institute (CLSI) EP25-A protocol.[38]

SAMPLE REQUIREMENTS

Serum can be used and is collected according to the standard procedures. For plasma, sample collection tubes with Li heparin and K_3-EDTA should be preferred.

Ferritin activity stability in serum:

8 hours at +20/+25ºC,
7 days at +2/+8ºC,
1 year at -20ºC.

CALIBRATION AND QUALITY CONTROL

Calibration: The assay requires the use of a Ferritin Calibrator or Protein Calibrator.

Ferritin Calibrator (Liquid)
Ref.No: VT-011

Protein Calibrator (Lyophilized)
Ref.No: VT-012

Calibration stability depends on the application characteristics and cooling capacity of the autoanalyzer used. Calibration stability is 30 days.

Traceability is provided by Biological Reference Material 94/572 (World Health Organization).

Control: Commercially available control material with established values determined by this method can be used. We recommend:

Ferritin Control Level 1 (Liquid)
Ref.No: VT-041

Ferritin Control Level 2 (Liquid)
Ref.No: VT-042

Protein Control Level 1 (Lyophilized)
Ref.No: VT-013

Protein Control Level 2 (Lyophilized)
Ref.No: VT-014

At least two level controls must be run once in every 24 hours. Each laboratory should determine its own quality control scheme and procedures. If quality control results are not within acceptable limits, calibration is required.

REFERENCE INTERVALS / MEDICAL DECISION LEVELS

Serum and Plasma

Children	: 7-140 µg/L
Men	: 20 - 250 µg/L
Women	: 20 - 200 µg/L

Note 1: There is a problem of standardization in the interpretation and comparability of ferritin results because different laboratories evaluate different ferritin isoforms and use different antibodies and standards in immunoassays. The diversity and development of measurement techniques and the limited use of WHO reference materials is another problem.[39,40]

Note 2: Race/ethnicity factors (Native Africans, African Americans and Asians in particular) also have higher mean

serum ferritin concentrations than those typical of the white race, but the basis for this phenomenon is not fully understood.[41]

Note 3: In general, reference limits vary and depend on age and gender. Serum ferritin concentrations are normally in the range of 12 to 300 µg/L and are lower in children (especially after 6 months) than in adults. Mean values are lower in pre-menopausal women than in men, reflecting women's low Fe stores due to losses during menstruation and pregnancy. Changes in serum ferritin concentration during development from birth to old age reflect changes in the amount of Fe stored in tissues.[39]

Threshold values for Fe deficiency and Fe loading:

- Most publications agree that ferritin concentrations below 12 to 30 µg/L define absolute Fe deficiency. In populations exposed to infections and in patients with renal failure, inflammatory bowel disease, chronic heart failure or other (low-grade) inflammatory diseases, thresholds indicating Fe deficiency are generally considered to be higher than in those without these diseases. In these cases, concentrations above 100 µg/L usually exclude absolute Fe deficiency and other parameters are needed to diagnose Fe deficiency at concentrations between 30 and 100 µg/L.

- To define Fe overload, thresholds of 150 to 200 and 200 to 300 µg/L for pre-menopausal women and men/post-menopausal women are often used as reference values, respectively.[39]

Each laboratory should investigate the transferability of the expected values to its own patient population and if necessary, determine its own reference range.

Reference interval data have been verified by using CLSI EP28-A3c protocol.[42]

PERFORMANCE CHARACTERISTICS

Measuring Interval

According to CLSI EP34-ED1:2018, “Measuring Interval” refers to the interval where the analyte concentration is measured with intended accuracy in terms of medical and laboratory requirements without dilution, concentrating or any kind of pre-treatment that is between the analyte’s lower limit of quantitation (LLoQ) and upper limit of quantitation (ULoQ).[43]

The determined analytic measuring interval for Ferritin is 4-500 µg/L.

Detection Capability

Limit of Detection (LoD): 2 µg/L

Limit of Quantitation (LoQ): 4 µg/L

Note: LoQ values are based on Coefficient of Variation Percentage (CV) ≤ 20%.

LoD and LoQ values have been verified by using CLSI EP17-A2:2012 protocol.[44]

Linearity

This method shows measurement linearity in the activities up to 500 µg/L. Autoanaylzer’s auto-dilution system can be used if the concentrations have higher values. See device manual for further information.

For the manual dilution procedure, dilute the sample 1:10 using 0.90% isotonic. After this process, multiply the result of the reworked sample by the dilution factor. Do not report the sample result after dilution if it is marked as lower than the linear lower limit. Rerun with a suitable dilution.

Linearity Studies data have been verified by using CLSI EP06-A:2003 protocol.[45]

Precision

Running system has been developed according to 20x2x2 “The Single Site” protocol. Repeatability and Within-Laboratory Precision/Within-Device values have been obtained according to the running results.

According to the protocol in use, 2 separate runs per day have been made for 20 days (no obligation for being consecutive days). This protocol has been applied to each low and high samples separately and 80 results have been obtained for each one. Statistically, the results have been obtained using 2-factor Nested-ANOVA model.[46]

Repeatability (Within Run) and Repeatability (Day to Day) CV% values of Ferritin have been given in the table 1 and 2 respectively.

Table 1. Ferritin Repeatability (Within Run) results obtained from samples in two different concentrations

Mean Concentration	SD*	%CV	n
61 µg/L	1.34	2.20	80
145 µg/L	2.32	1.60	80

Note: This working system has been named “Within-Run Precision” in the previous CLSI - EP05-A2 manual.[47]

Table 2. Ferritin Repeatability (Day to Day) results obtained from samples in two different concentrations

Mean Concentration	SD*	%CV	n
61 µg/L	2.26	3.70	80
145 µg/L	3.05	2.10	80

Note: This working system has been named “Total Precision” in the previous CLSI - EP05-A2 manual.[47]

Prozone Effect: No prozone effect has been observed up to 30.000 µg/L tested for Ferritin.

Interference

Endogenous interferant and analyte concentrations that have been used in the Ferritin scanning tests has been determined

according to “CLSI EP37-ED1:2018” and “CLSI EP07-ED3:2018” manuals.[48,49]

The total acceptable error rate, which is going to be used to detect whether the observed differential value obtained from Ferritin interference scanning test is appropriate, is determined as ±10%.[50]

In Ferritin test results, no significant interaction has been observed in the determined endogenous interferant and analyte concentrations or between interferants and analyte.

Hemoglobin	: 300 mg/dL
Lipemia	: 1000 mg/dL
Bilirubin	: 62 mg/dL
Rheumatoid factors	: 520 IU/mL

It should be noted that endogenous interferants, as well as various medicines and metabolites, anticoagulants (e.g. Heparin, EDTA, citrate, oxalate) and preservatives (e.g. sodium floride, iodoacetate, hydrochloride acide) such as additives, materials that may contact with samples during collection and processing (serum separator devices, sample collection containers and contents, catheters, catheter wash solutions, skin disinfectants, hand cleaners and lotions, glass washing detergents, powder gloves), dietary substances known to affect some specific tests (caffeine, beta-carotene, poppy seeds, etc.), or some substances present in a sample that cause foreign proteins (heterophilic antibodies, etc.), autoimmune response (autoantibodies, etc.), or due to malignancy (for example, interference by paraproteins with phosphate testing and indirect ion selective electrode methods) may show some negative effects that will cause various attempts and some misjudgements.[49]

These performance characteristics have been obtained using an autoanalyzer. Results may vary slightly when using different equipment or manual procedures.

WARNINGS AND PRECAUTIONS

IVD**:** For in Vitro Diagnostic use only.
Do not use expired reagents.
Reagents with two different lot numbers should not be interchanged.
For professional use.
Follow Good Laboratory Practice (GLP) guidelines.
Contains sodium azide.

CAUTION: Human source samples are processed with this product. All human source samples must be treated as potentially infectious materials and must be handled in accordance with OSHA standards.

Danger

EUH032	:Releases a very toxic gas if contacts with acid.
H317	:May cause allergic skin reaction.

Precaution

P280 / mask.	:Use protective gloves / clothes / glasses
P264	:Wash your hands properly after using.
P272	:Contaminated work clothes should not be allowed to be used outside of the workplace.

Intervention

P302+P352	:Wash with plenty of water and soap if it contacts with skin.
P333+P313	:Seek medical help if it irritates your skin or develops rash.
P362+P364	:Remove contaminated clothes and wash properly before using.

Disposal

P501	:Dispose the vials and contents according to the local regulations.

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SYMBOLS

IVD	In Vitro Diagnostic Medical Device
LOT	Lot Number
R1	Reagent 1
R2	Reagent 2
GTIN	Global Trade Item Number
REF	Reference Number
GLP	Good Laboratory Practices
FOR USE WITH	Identifies Products to Be Used Together
PRODUCT OF TURKEY	Product of Turkey
	Manufacturer
	Expiration Date
	Temperature Limits
	Consult Instructions for Use
	Caution
	Number of Tests