Factitious Biochemical Measurements Resulting From Hematologic Conditions

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**Key Words:** Artifact; Factitious; Hyperkalemia; Myeloma; Paraprotein

**Abstract**

Factitious laboratory results often lead to unnecessary testing or treatment. This brief review of factitious biochemical results due to preexisting hematologic conditions focuses on the mechanisms underlying the factitious results and suggests ways to prevent them. An observant pathologist identifies these errors, intervenes in a timely fashion, investigates the sources of error diligently, and institutes measures to prevent their recurrence.

A significant number of laboratory results and reports are factitious or misinterpreted by clinicians and other laboratory clients. Such mishaps may lead to unnecessary diagnostic evaluation and/or unwarranted therapeutic interventions. On the other hand, an astute observer may identify the factitious nature of a result and investigate it to diagnose an underlying serious condition.

The sources of factitious laboratory results may be preanalytical, analytical, or postanalytical factors. The preanalytical factors are in vivo causes, such as preexisting disease conditions and medications, and in vitro causes, such as problems with sample collection, type of sample tube, anticoagulant and ambient conditions, and duration of storage and transport. Recent fiscally driven efforts at centralization of laboratory facilities mean longer transportation times, while the batching of laboratory tests leads to longer storage times. The analytical factors are instrument and method-related issues, specifically the advanced automation of clinical laboratories and the lack of human intervention before the results are released. Lastly, the postanalytical factors are human errors in transcription of results and comprehension and interpretation of reports.

Larger clinical laboratories are conventionally subdivided into hematology, chemistry, microbiology, anatomic pathology, and so on. The testing is done by specialized technologists who are competent in identifying and correcting errors in their own subspecialties but not outside their field of expertise. This article bridges that gap by reviewing the factitious biochemical measurements that arise as a result of hematologic conditions and factors. The artifacts are classified by hematologic conditions and their mechanisms and prevention are discussed.
Hematologic Conditions Associated With Factitious Biochemical Results

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G6PD, glucose-6-phosphate dehydrogenase; Hb, hemoglobin; HDL, high-density lipoprotein; HPLC, high-performance liquid chromatography; IVIG, intravenous immunoglobin.

Paraproteins and Polyclonal Hyperimmunoglobulinemias

Paraproteins can interfere with many laboratory measurements (Table 1) such as glucose, bilirubin, high-density lipoprotein (HDL), chloride, phosphate, calcium, urate, thyraxine, C-reactive protein (CRP), antistreptolysin-O (ASO), urea, creatinine, and albumin. As a general rule, all laboratory results in a patient with a paraprotein should be reviewed for possible error, especially results that are clinically inconsistent. The immunoglobulins associated with factitious results are usually monoclonal but can be polyclonal. Among the paraproteins, IgM is more often the culprit because its higher molecular weight yields heavier precipitates and causes more interference. In some cases, investigation of clinically “out of place” factitious biochemical results leads to identification of a paraprotein and subsequent diagnosis of an underlying lymphoplasmacytic neoplasm.

The frequency of immunoglobulin-induced laboratory errors is variable and probably underreported. The testing for up to half of patients with monoclonal immunoglobulinemia...
showed interference in phosphate assay. Large reviews of patients with paraproteinemia show that the immunoglobulin concentration in patients with factitious results did not differ from patients without the interference. When the interference occurred, however, the degree of interference was proportional to the immunoglobulin levels.

Immunoglobulins can induce factitious results in one or more of the following ways: (1) Immunoglobulins may precipitate or flocculate due to chemical interaction with the test reagents or to their inherent chemical structure, eg, cryoglobulinemia. The opaque precipitates interfere with automated nephelometric, turbidimetric, colorimetric, and light-scatter-based autoanalyzers. (2) Immunoglobulins may chemically inactivate the test reagents. (3) Immunoglobulins increase the colloid phase of plasma and relatively decrease the aqueous phase, thereby reducing the amount of water-soluble molecules. (4) Immunoglobulins may act as antigens and bind to reagents or the analyte and interfere with immunologic measurements.

The paraprotein interference in laboratory testing is intermittent; it is seen in some patients and not others and at one time in a patient and not at another time. Also, since the

### Table: Solution to Paraprotein Interference

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<tr>
<td>blood</td>
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<tr>
<td>Use anticoagulants containing fluoride or oxalate</td>
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<tr>
<td>3</td>
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reagents are frequently modified by the manufacturers, these laboratory errors are difficult to anticipate.

Paraprotein-associated factitious results can be minimized or avoided by one or more of the following measures: (1) diluting the sample to reduce the precipitates; (2) “deproteination” of the sample to eliminate the paraprotein; (3) using a saline or water blank instead of plasma (IgM, but not IgG or IgA, interferes with the reading of blank cuvettes in some instruments, eg, Olympus AU800 [Olympus, Center Valley, PA]) instruments using the Trinder method to measure hydrogen peroxide. This can be avoided by replacing saline with water; and (4) setting up manual flags that identify higher baseline absorbance or a sudden change in absorbance when the interacting reagent is added; such manual flags are, however, discouraged by instrument manufacturers.

**Factitious Hyperbilirubinemia**

Total and indirect bilirubin levels of more than 30 mg/dL (513.1 µmol/L), but normal levels of direct bilirubin, may be seen in patients with paraproteins. These factitious results are seen in serum and plasma. They are seen with the liquid end point chromogenic Roche assay using the Hitachi 917 analyzer (Roche Diagnostics, Indianapolis, IN) but not with the Vitros 950 (Johnson & Johnson, Langhorne, PA). However, this artifact is unlikely to be restricted to this platform because most automated analyzers use similar routines. The interference is rare, and the testing for 100 patients with paraproteins and 13 with polyclonal hypergammaglobulinemia did not show any interference. Dilution of the sample only partially corrected the artifact. The samples consistently produced a spike in absorbance when reagent 2 (Roche Diagnostics) was added, and designing a flag for this spike identified the factitious result consistently, without any false-positive results.

**Factitious Hypolipidemia and Normolipidemia**

Falsely low or undetectable levels of HDL by the homogeneous colorimetric Roche HDL-C Plus assay (Roche Diagnostics) may be seen in up to 25% of patients with paraproteins. Reanalysis on other instruments such as the Vitros and Beckman LX-20 (Beckman-Coulter, Fullerton, CA) instruments yielded normal results. Unlike the late interference with reagent 2 in the Roche bilirubin assay, the interference in Roche HDL-C assay is at an early stage owing to precipitation of the paraprotein by reagent 1 (Roche Diagnostics) and can be flagged by monitoring for high baseline absorbance. Another report described similar artifacts using a liquid-based enzymatic reaction, but a non–liquid-based technique provided normal levels.

**Factitious Hyperphosphatemia and Hypophosphatemia**

Paraproteins exert biphasic interference on serum phosphate levels, usually resulting in factitious hyperphosphatemia but occasionally in hypophosphatemia. Pseudohyperphosphatemia may be seen in patients with IgM, IgA, or IgG paraproteins and results in unwarranted investigations of renal dysfunction and changes in treatment plans. In addition, hypophosphatemic patients showing falsely “high” levels of phosphate may be labeled as pseudonormophosphatemic, and this may be just as clinically relevant as pseudohyperphosphatemia. This interference is seen with the liquid colorimetric assay on the Bayer Advia 1650 (Bayer, Pittsburgh, PA) but not with slide-based, solid-state colorimetric assays on the Vitros 950. In a prospective study, only 1 of 27 samples with paraprotein had clinically significant pseudohyperphosphatemia. Deproteination completely corrected this artifact, suggesting the causative role of precipitation of paraprotein in an acid pH or binding to the inorganic phosphorus.

On the other hand, pseudohypophosphatemia was seen in 2 patients with monoclonal gammopathy of undetermined significance and multiple myeloma, respectively, using non-deproteinized samples but not in deproteinized samples.

**Factitious Hyponatremia/Hypochloridemia**

Pseudohyponatremia, pseudohypochloridemia, and reduced anion gap were seen in a patient when using the indirect ion-specific electrode method, Hitachi 917, but not with the direct electrode method, ABL 725 (Radiometer, Westlake, OH). Serum potassium was normal with both methods. This artifact is due to a water exclusion effect, ie, increased colloid phase decreases the aqueous phase per volume of sample, and, thus, the plasma has lower levels of electrolytes per volume of sample. Pseudohyponatremia is seen with the indirect method because it involves dilution of the sample, which exaggerates this aqueous phase deficit. There is no dilution step in the direct method. The patient described had recently received 40 g of intravenous immunoglobulin, which may have further increased the serum protein levels.

**Factitious Hypercalcemia**

Pseudohypercalcemia due to an IgM paraprotein was seen in 2 patients when using the Arsenazo dye method on the Beckman CX7 analyzer (Beckman-Coulter). The precipitation and turbidity interfered with reading the test. In both cases, this interference led to extensive diagnostic evaluation for parathyroid function and other causes, and parathyroid surgery was considered for 1 patient as well. Measurement using atomic absorption spectrometry and O-cresolphthalein complexone assay provided the correct readings.

**Factitious Hypoglycemia**

Consistent pseudohypoglycemia in hexokinase methods, but not in glucose oxidase methods, was seen in a diabetic patient. Subsequent investigations revealed an IgM-κ paraprotein. In another patient, a low level IgM paraprotein (60
mg/dL [600 mg/L]) in a patient with small lymphocytic lymphoma/chronic lymphocytic leukemia was associated with extremely low blood glucose measurements by the hexokinase method (Roche/Hitachi), while the glucose dehydrogenase strips (glucometer) consistently showed expected levels. This was possibly due to antibody activity of the monoclonal protein against an antigen in the hexokinase reagents.

**Factitious Hypouricemia and Normouricemia**

Increased IgM, but not increased IgA or IgG, led to a marked underestimation of uric acid levels by the Trinder reaction in the Olympus AU800. This phenomenon is likely due to high absorbance in the blank cuvette owing to protein precipitation but was not corrected by deproteination with 20% trichloroacetic acid. Replacing the saline with water in the blank position completely corrected the anomalous results without affecting the results in patients without myeloma.

**Factitious Hypoalbuminemia**

Artifactualy low serum albumin levels were seen in 1 of 16 patients with an IgM paraprotein. The paraprotein interfered with albumin measurements by slowing the bromocresol green reaction so that the 10 second reading was artificially low. The interference was not immunological, ie, the IgM did not act as antialbumin.

**Factiously High CRP Levels**

Artificually high levels of CRP have been described in a patient who was subsequently diagnosed to have low level IgM-λ monoclonal gammopathy of undetermined significance, in another patient with an IgM-κ paraprotein, and 1 with polyclonal increase in IgM. There was no clinical suspicion of systemic inflammation in either patient. The phenomenon was ascribed to binding of the paraprotein to anti-CRP–antibody coated latex particles in a Behring II nephelometer (Siemens, Deerfield, IL) and was abolished by deproteination of the sample or using a manual kit method.

**Falsely High Ferritin Levels**

When a latex-enhanced immunoassay was used, spuriously high serum ferritin levels were seen in a patient with polyclonal IgM hypergammaglobulinemia in absence of clinical infection or malignancy. Methods not using latex enhancement provided normal results.

**Falsely High ASO Levels**

Artificially high levels of the ASO titer were seen in a patient with an IgM-κ paraprotein due to coating of the ASO antigen–laden latex particles by the paraprotein in a Behring II nephelometer. The ASO titer was normal using the Rantz-Randall method that uses human group O erythrocytes.

**Falsely Low Urea Levels**

Falsely low blood urea levels and discordance with creatinine levels may be seen in patients with an IgM paraprotein when using the o-phthalaldehyde method or the Astra 8 (Beckman-Coulter) or Synchron CX3 analyzer (Beckman-Coulter). The creatinine levels are unaffected by the paraprotein, truly reflecting the renal status. It seems that the paraprotein coats the sensing electrode and interferes with the reading. Using an enzymatic method with Olympus AU5000 analyzer (Olympus) avoids the artifact.

**Falsely Low Creatinine Levels**

Of 18 patients with IgG myeloma, 3 showed artificially low levels of serum creatinine on several instruments that determine creatinine by the Jaffé reaction but expected results using an enzymatic method. Acid precipitation or dithiothreitol preincubation abolished the artifact.

**Falsely Low Thyroxine Levels**

Three patients with myeloma had undetectable levels of thyroxine by a homogeneous enzyme immunoassay (EMIT) but normal results with competitive protein-binding radioassay on small, reusable Sephadex columns. The interference was due to turbidity of the paraproteins in the EMIT reaction mixture, resulting in an increased absorbance and a marked underestimation of hormone concentration.

**Increased Blood Cell Counts**

Factitious biochemical results that can be seen in patients with increased numbers of WBCs, RBCs, or platelets include pseudohyperkalemia, pseudohypokalemia, pseudohypoglycemia, and falsely increased serum cobalamin levels. These artifacts are due to release of cellular constituents during clotting or storage, eg, potassium, or to the metabolic activity of the cells consuming nutrients and oxygen from plasma before the sample is analyzed.

**Factitious Hyperkalemia and Hypokalemia**

Hyperkalemia is a common and often life-threatening condition, seen most often in patients with renal failure and sometimes in patients taking drugs such as angiotensin converting-enzyme inhibitors, potassium-sparring diuretics, laxatives, trimethoprim, corticosteroids, β-blockers, and nonsteroidal anti-inflammatory agents. Pseudohyperkalemia is a common laboratory artifact and may lead to unnecessary treatment or emergency referral and hospital admission. The artifact is due to leaching of potassium from the cytosol during clotting or prolonged storage of the sample. It is usually seen in serum but not plasma, a fact that can be gainfully used in the differentiation of true hyperkalemia from
Pseudohyperkalemia is seen in patients with acute leukemia; chronic myeloproliferative disorders such as chronic myeloid leukemia, polycythemia vera, and essential thrombocythemia; chronic lymphocytic leukemia; and in some patients with reactive thrombocytosis.

In 1 review of the data for 435 patients with a reactive or neoplastic increase in blood cell counts, thrombocytosis was associated with higher levels of pseudohyperkalemia, erythrocytosis was associated with a mild increase in potassium levels, but no pseudohyperkalemia was seen with isolated leukocytosis. Approximately 75% of patients with essential thrombocythemia and polycythemia had factitious elevation of the serum potassium level above the reference range compared with a third of patients with reactive thrombocytosis. There is only a weak correlation between the degree of pseudohyperkalemia and the platelet count. In 1 study, the serum potassium level was found to increase at the rate of 0.07 to 0.15 mEq/L (0.07-0.15 mmol/L) for every 100 × 10^8/L (100 × 10^5/L) increase in the platelet count. However, the authors concluded that the correlation was very weak, a finding later confirmed by others.

Preanalytical conditions that induce in vitro hemolysis or clotting of the sample result in pseudohyperkalemia or exacerbate the pseudohyperkalemia due to increased numbers of blood cells. Conditions that induce in vitro hemolysis include fist clenching during phlebotomy, blood drawing into an evacuated tube, use of small-gauge needles, use of tourniquets, cold storage, delay in sample processing, and the mechanical trauma during shaking or hard centrifugation of the sample or pneumatic tube transport. A leukemic patient with pseudohyperkalemia in serum and plasma due to traumatic cell lysis during pneumatic tube transport was treated with unnecessary dialysis until its artifactual nature was suspected following the failure of normalization of serum potassium levels when dialyzed against a potassium-free dialysate. A similar phenomenon was not seen in samples with a normal WBC count.

Factitious hyperkalemia can be minimized by prompt analysis of the sample. However, astute clinical determination of absence of symptoms of hyperkalemia is the only way to avoid unnecessary diagnostic workup or treatment.

Factitious hypokalemia may be seen in patients with a high WBC count (>100,000/µL [100 × 10^9/L]) in acute leukemia when the blood samples have been allowed to stand at room temperature. This phenomenon is related to transcellular potassium shift into the leukemic cells. Pseudohypokalemia should not be confused with true hypokalemia, which may be seen in patients with acute myeloid leukemia, especially with monocytic differentiation. The mechanism in this case is related to lysozymuria, which promotes renal tubular excretion of potassium.

Factitious Hypoxemia

Pseudohypoxemia^3,53-59,86 is seen in patients with marked leukocytosis, thrombocytosis, and, very rarely, in patients with reticulocytosis. Pseudohypoxemia can lead to suspicion of serious clinical conditions such as pulmonary leukostasis, pulmonary embolism, or pneumonia. It is more pronounced in patients with immature leukocytes and higher leukocyte counts. It disappears as the leukemic burden diminishes with treatment. Pseudohypoxemia is seen only in arterial blood samples used in conventional arterial blood gas analyzers and not in the capillary blood samples used in pulse oximeters. Pseudohypoxemia is due to rapid consumption of the oxygen dissolved in the plasma by a large number of metabolically active cells. Another possible mechanism is coating of the sensing electrode by large numbers of leukemic cells that interfere with the reading. However, that does not explain why pseudohypoxemia is more pronounced with blasts than with mature cells.

Pseudohypoxemia can be prevented or minimized by running the sample without delay, eg, by using continuous arterial blood gas sampling, by placing the sample immediately on ice, by adding potassium cyanide or sodium fluoride, or by using plasma instead of whole blood. However, most of these methods are expensive, and the results are not consistent. The only way to consistently prevent factitious hypoxemia due to increased numbers of blood cells is to use pulse oximetry, which measures capillary oxygen tension.

Factitious Hypoglycemia

Pseudohypoglycemia has been reported with leukemias with high WBC counts,^3,52,59 in myeloproliferative disorders, and in patients receiving hematopoietic cytokines with rapidly rising counts. The artifact is due to glucose consumption by the metabolically active cells and can be prevented by using anticoagulants containing sodium fluoride or potassium oxalate.

Factitiously High Cobalamin Levels

Factitiously high levels of cobalamin have been seen in patients with myeloproliferative disorders with high leukocyte counts. A true cobalamin deficiency can be masked. A similar artifact has also been seen with plasma cell neoplasms.

Hemolysis

Hemolysis can occur in vivo and in vitro. In vitro hemolysis can occur during sample collection owing to a difficult venipuncture; sampling through narrow-gauge needles or intravenous catheters (especially in small infants); extreme tourniquet pressure; and prolonged fist clenching, and during
transport and storage owing to extremely high or low temperatures. In vivo hemolysis is seen in hemolytic anemia. In vitro hemolysis results in factitiously high levels of serum potassium and folate, whereas in vivo hemolysis results in masking of glucose-6-phosphate dehydrogenase (G6PD) deficiency and in low levels of hemoglobin (HbA1c).

**Factitious Hyperkalemia**

In vitro hemolysis results in pseudohyperkalemia due to potassium release from erythrocyte cytosol. The increase in potassium levels is directly proportional to the plasma Hb concentration, and a correction factor of 0.00319 × plasma Hb (mg/dL) has been devised to derive the actual potassium level.

**Misleadingly Low HbA1c Levels**

Because of the shortened RBC life span, in vivo hemolytic conditions, eg, hereditary spherocytosis, lead to an estimated glycated hemoglobin, or HbA1c, that is correct but clinically misleading. In HIV+ patients, HbA1c underestimated the glucose levels by 12.3% compared with the 3-month average fasting blood glucose levels. The authors also found that the patients had low haptoglobin levels, indicating hemolysis, probably induced by nucleoside analog drugs. The mechanism for lowered HbA1c in hemolysis is that the HbA1c levels increase during the life of erythrocytes, and determination of its reference range presumes a normal erythrocyte lifespan of 120 days. In conditions of hemolysis, and following massive hemorrhage, the average age of erythrocytes is less than 120 days, and, consequently, HbA1c levels are factitiously low. HbA1c estimations are also correct but clinically misleading in patients who have had a recent blood transfusion.

**Misleading Normalization of G6PD**

G6PD levels may be increased to normal and clinically misleading shortly after a hemolytic crisis. The younger erythrocytes and reticulocytes replacing the older RBCs have higher levels of G6PD, which may mask a hemizygous G6PD deficiency.

**Factitiously High Serum Folate Levels**

Falsely higher levels of serum folate may be seen in hemolyzed samples owing to the release of large amounts of folate from erythrocyte cytosol.

**Erythrocyte Membrane Abnormalities**

Certain rare, dominantly transmitted hereditary abnormalities of erythrocyte cell membranes result in pseudohyperkalemia. This group has been termed hereditary stomatocytosis and related disorders and includes hereditary dehydrated stomatocytosis (also known as xeroctytosis), hereditary overhydrated stomatocytosis, hereditary cryohydrocytosis, and familial hyperkalemia. The presence of stomatocyte morphologic features is a sensitive marker but not specific for this group of conditions. Stomatocytes are frequently seen in liver disease, in which there is no cation leak across the membrane and no pseudohyperkalemia. Also, some cases of frank stomatocytic hemolytic anemias do not show pseudohyperkalemia.

The cation leak in hereditary stomatocytosis is due to an abnormality of temperature-dependent membrane electrolyte pumps. The pseudohyperkalemia develops on cooling of the sample and can be seen as soon as 1 hour after collection. The plasma and serum values are abnormal. The artifact can be prevented by keeping the sample at 37°C and by analyzing promptly after collection.

**Abnormal Hemoglobins**

HbA1c values reflect long-term glycemic control in patients with diabetes. However, HbA1c measurement by high-performance liquid chromatography (HPLC)-based assays is inaccurate in the presence of some structurally abnormal hemoglobins. The extent of interference varies with the specific commercial HPLC method used and the type of abnormal hemoglobin.

Some hemoglobin variants result in underestimation of HbA1c, eg, Hb Takamatsu, HbS Suzhu, HbC, HBS, Hbo Padova, HbH Meurut, Hb Riyadh, Hb Camden, HbJ Lome, Hb Ube-2, Hb Etobicoke, Hb Görwihl, and Hb Rambam. Other variants result in overestimation of HbA1c, eg, Hb Raleigh, Hb Okayama, Hb Graz, HbK Woolwich, Hb Osu-Christiansborg, Hb Sherwood Forest, Hb South Florida, and Hb Niigata. Increased HbF, eg, in hereditary persistence of fetal hemoglobin or the rise of HbF during pregnancy may also yield factitiously higher results for HbA1c because of coelution.

Hb variants interfere with the measurement of HbA1c in a variety of ways. HbA1c overestimation is due to coelution of the native Hb variant with HbA1c or its separation from HbA so that the denominator is small. HbA1c underestimation is due to separation of the glycated hemoglobin variant from HbA1c so that it is not considered in the HbA1c calculations. Interference of Hb variants with HbA1c measurements can often be eliminated by changing the assay method. Failing that, regular blood glucose monitoring by a point-of-care device should be advised.
Transfusion of Blood Products

Pseudohyponatremia

Therapeutic hypergammaglobulinemia produced by infusion of intravenous immunoglobulins can lead to pseudohyponatremia.33,81,82 This artifact results from increased colloid (immunoglobulin) phase in plasma, reducing the sodium-carrying aqueous phase. This is an in vivo artifact that, unlike pseudohyperkalemia, produces clinical symptoms, eg, neurologic deterioration,33 and may even lead to death.82

Misleading Normalization of G6PD

G6PD levels may be higher after transfusion of 1 or more units of packed RBCs,65 masking a hemizygous G6PD deficiency. Repeated testing after 8 to 12 weeks provides correct values.

Misleading Normal RBC Folate and Serum Cobalamin

RBC folate and serum cobalamin levels may be misleadingly normal after transfusion due to correction by transfused RBCs and plasma. Repeated testing after 12 weeks provides correct values.

Summary

Factitious laboratory results often lead to unnecessary testing or treatment. This brief review of factitious biochemical results due to preexistent hematologic conditions focuses on the mechanisms underlying the factitious results and suggests ways to prevent them. Observant pathologists identify these errors, intervene in a timely manner, investigate the sources of error diligently, and institute measures to prevent their recurrence.

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