Series Editors: T.S. Dharmarajan, M.D. and C.S. Pitchumoni, M.D.

Anemia of Gastrointestinal Origin in the Elderly

by T.S. Dharmarajan, May Luz F. Bullecer, and C.S. Pitchumoni

Physiological alterations in the gastrointestinal (GI) system in older individuals may predispose to development of anemia. In more than half the cases an underlying cause can be established. The increased prevalence of gastric hypochlorhydria in the elderly as a result of disease or medications affects bioavailability of several micronutrients predominantly iron, folate and cobalamin. Though GI blood loss is by far the commonest cause of iron deficiency anemia, poor dietary intake, coupled with impaired absorption contributes to deficiency and anemia. Evaluation identifies an etiological basis for anemia and an opportunity for correction.

INTRODUCTION

Anemia is common in the older population. By itself anemia is not a diagnosis, rather it signifies the presence of an underlying pathology. In a well defined population, the incidence of anemia was found to be four to six times higher than clinically suspected (1); anemia increases with age and affects males more than females (1,2). Of note is the observation that affluent healthy elderly have a lower prevalence of anemia; epidemiologic surveys suggest that underdeveloped countries and those of low socioeconomic status (with nutritional deficiencies) have a higher prevalence (2). A study performed on healthy free living subjects revealed the prevalence of anemia to be about 5% when adequate iron intake was possible; nevertheless in these subjects, vitamin B_{12} (cobalamin) and folate deficiencies were common (3). In the global population, the estimated prevalence of iron deficiency with or without anemia is 60%–80% with the number supposedly affected approximately 3.5–5 million (4). Iron deficiency is the commonest nutritional basis for anemia; less common causes include folate, B_{12} (cobalamin) and copper deficiencies. Anemia is associated with decreased survival, oftentimes as a result of associated comorbidity (1).

T.S. Dharmarajan, MD, FACP, AGSF, Associate Professor of Medicine, New York Medical College, Chief, Division of Geriatrics, Director Geriatric Medicine fellowship Program, Our Lady of Mercy Medical Center, Bronx, New York, University Affiliate of New York Medical College. May Luz F. Bullecer, MD, Fellow, Geriatric Medicine, Our Lady of Mercy Medical Center, Bronx, New York, University Affiliate of New York Medical College. C.S. Pitchumoni, MD, MPH, FACP, MACG, Professor of Medicine / Community and Preventive Medicine, New York Medical College, Director, Department of Medicine, Chief, Division of Gastroenterology and Nutrition, Our Lady of Mercy Medical Center, Bronx, New York.

GASTROINTESTINAL (GI) ABSORPTION OF NUTRIENTS

Age related gastrointestinal changes may affect absorption of micronutrients (5,6,7). While gastric acid secretion generally remains intact with aging, the preponderance of atrophic gastritis, *Helicobacter pylori (H. pylori)*

infections and the widespread use of acid lowering agents have the potential to reduce gastric acidity. Consequently, folate and cobalamin absorption as well as the conversion of the less bioavailable ferric iron to the soluble ferrous form are impaired (7) (Table 1). Atrophic gastritis occurs in 11% to 50% of older adults in the US, with the less common Type A atrophic gastritis predominantly affecting the body of the stomach, and the more common Type B gastritis involving the antrum (7). Pernicious anemia is a classic example of Type A atrophic gastritis, while *H. pylori* is a common etiology of Type B chronic atrophic gastritis. There is also slowing of liquid (vagally mediated) and mixed liquid-solid gastric emptying which leads to decreased bioavailability of vitamins and minerals (7). Solid food (antrally determined) emptying is preserved (5,6,7). In the small intestine, there is a decline in lactase activity resulting in variable degrees of lactose intolerance; it is therefore not unusual for the elderly to refrain from consuming milk and other dairy products, sources of calcium, phosphorus and vitamin D (the last through fortification) (7). An additional consequence of decreased acid secretion (hypochorhydria/achlorhydria) and atrophic gastritis is small bowel intestinal bacterial overgrowth (SIBO), a disorder prevalent in the elderly. Conditions affecting intestinal motility (diabetes, scleroderma, prior intestinal surgery etc.), jejunal diverticulosis and immune deficient states are additional causes of SIBO (5,6,7). All these disorders can also be grouped under blind loop syndromes although some of the above may not be associated with an anatomic blind loop. The upper GI tract is normally sterile, with $<10^3$ bacteria/mL an acceptable limit; bacterial overgrowth leads to malabsorption of fat soluble vitamins by bacterial deconjugation of bile salts and alters utilization of vitamin B_{12} as bacteria take up or bind cobalamin (7) . Deficiency of conjugated bile acids also causes steatorrhea. On the other hand, interestingly, serum folate levels are normal or even elevated as a result of bacterial synthesis (7).

Table 1
Common Sites of Hematinic Micronutrient Absorption (8, 11)

Stomach
- Gastric acid promotes conversion of ferric to ferrous iron
- Facilitates release of cobalamin from dietary protein
- Secretion of intrinsic factor

Small intestine
- Iron: absorbed in the duodenum > jejunum > ileum
- Copper small intestine, jejunum and ileum
- Zinc: small intestine, no preferred site
- Cobalamin: mainly absorbed in the ileum
- Folate: mostly absorbed in the jejunum

MICRONUTRIENT DEFICIENCIES AND ANEMIA

Iron

Dietary Sources

There are several sources of organic iron in our diet. Sources of iron may be heme or non heme. Hemoglobin and myoglobin, basically animal sources derived from meat, poultry, and fish, comprise heme iron, while non heme iron is present in fruits, vegetables and cereals (8,11). Based on the "iron: calories ratios" (amount of iron in a given source per calorie), green vegetables and legumes are the highest sources of iron (8). Although high in calories, liver, kidney, beef and oysters are rich sources of iron (12); the bioavailability of animal sources of iron is superior (11) (Table 2). Dietary iron is reduced by gastric acid to the ferrous form which is soluble and easily absorbed. While iron absorption occurs anywhere in the small intestine, it occurs predominantly in the duodenum. Several factors affect absorption of iron. Phosphates, phytates, tannins, antacids, zinc supplements, alkaline pH, and malabsorption syndromes in general interfere with iron absorption. On the other hand, ascorbic acid improves iron absorption; iron from digested meat or poultry (through release of cysteine or cysteine containing polypeptides) is better absorbed (8). In healthy individuals without iron deficiency, approximately 5%–10% of dietary iron is absorbed; the presence of iron deficiency enhances absorption by 20%–40%.

Transferrin and lactoferrin are iron transport proteins. Transferrin is a plasma glycoprotein that binds two atoms of iron. Transferrin bound iron is disseminated throughout the body, but mainly in red blood cell

Table 2
Dietary Sources of Iron (8,9,10,12)

Food	*Rich*	*Moderate*	*Poor*
Meat[1]	Liver, roast beef, hamburger	Chicken, turkey	Pork chop, egg, sausage
Fruits[2]	Dried peaches	Raisins, strawberries	Apricots, apple, figs
Vegetables[3]	Lentils, tofu, chickpeas artichoke, broccoli	Beans, potato, spinach	Cabbage, beets, corn
Beverages[4]	None	None	Milk, wine, soda, juices
Snacks[5]	None	None	Popcorn, potato chips, pretzel

[1]serving size: 3 oz. or one slice; [2]serving size: 1/2 cup or medium slice; [3]serving size: 1/2 to 1 cup ; [4]serving size: 1/2 cup or 240 mL; [5]serving size: 1 oz. Rich source: 2–3 mg iron/serving. Moderate: 1–2 mg iron/serving. Poor source: <1 mg iron/serving.

precursors in the bone marrow for erythropoiesis. Normal transferrin saturation ranges from 20% to 45%. Lactoferrins are found in milk, semen and cytosol of granulocytes and act as an intracellular iron trap protecting the cytosol from possible superoxide injury brought about by ferrous form of iron (8).

Hemoglobin synthesis in normal adults utilizes approximately 20–25 mg of iron per day, increased several fold during erythropoiesis. Excess iron is stored as ferritin (rapid exchanging pool) and hemosiderin (slow exchanging pool). Ferritin is the intracellular storage of iron that exists in multiple isomeric states. Worth mentioning are the H and L monomers. H monomers are relatively more acidic, contain more iron and are found mostly in the heart, while L monomers are relatively basic, with little iron and found in the liver. In the presence of malignancies such as breast cancer and lymphomas, H type ferritin is increased in the serum (8). Normal ferritin value ranges from 50–150 µg/L. Hemosiderin is the storage form of iron, present in the reticuloendothelial system of the liver, spleen, bone marrow and other organs. It contains more iron than ferritin. In the presence of increased demand for iron during erythropoiesis, both forms can be mobilized.

Stages of Iron Deficiency

The initial stage of deficiency is termed as *iron storage depletion* wherein the ferritin level is less than 20 µg/L, while other ferrokinetic parameters (iron, total iron binding capacity, transferrin saturation, hematocrit and cell morphology) are still normal. *Iron deficient erythropoiesis* occurs when ferritin is less than 15 µg/L, with abnormal ferrokinetics (decreased serum iron and increased total iron binding capacity) but red blood cell morphology remains normal. *Iron deficiency anemia* manifests with microcytic, hypochromic, aniso-poikilocytic cells; here decreased serum iron (< 30 µg/L) and increased total iron binding capacity (400 µg/L), along with low transferrin saturation (below < 20%) are observed (13).

While iron deficiency is multifactorial, it commonly results from GI blood loss. In fact, iron deficiency anemia in older adults warrants evaluation for a gastrointestinal etiology. In the presence of iron deficiency, it should be presumed that occult GI bleeding is likely. More than two-thirds of adults with iron deficiency anemia are found to have a GI lesion (2,15). In the geriatric age group, chronic GI blood loss may be due to medications, neoplasms or other causes (16,17) (Table 3). The use of non steroidal anti-inflammatory agents (NSAIDS) and aspirin (prescribed or over the counter) is common in the elderly and results in erosive gastritis. Anticoagulant use is frequently associated with guaic positive stools, but a GI pathological basis is found in most cases (14,18). Non GI blood loss and frequent blood withdrawal for laboratory tests in hospitalized elderly can contribute to anemia (16). Celiac disease once considered to be a disease of chil-

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Table 3
Iron Deficiency Anemia from GI Bleeding in the Elderly (16,17)

Upper GI Bleed	*Lower GI Bleed*
Gastric ulcer	Diverticulosis
Duodenal ulcer	Angiomatous malformations
Gastritis	Neoplasm (benign, malignant)
Esophagitis	Ischemic enteritis and colitis
Esophageal varices	Radiation colitis
Neoplasm (benign or malignant)	Inflammatory bowel disease
Vascular malformations	Hemorrhoids
Medications *	Medications*

*Examples: aspirin, NSAIDS, anticoagulants, corticosteroids

dren and young adults, can manifest practically at any age solely as iron deficiency anemia. Iron deficiency exclusively from dietary basis is rare, although as described above, gastric hypo or achlorhydria predisposes to decreased iron absorption (19).

Diagnosis and Management

Iron deficiency is diagnosed based on ferrokinetic parameters. Levels of serum iron, iron binding capacity and ferrritin fluctuate in the presence of disease. Besides, serum iron can be (falsely) low even in the absence of true iron deficiency (19). In healthy elderly, a serum ferritin value of less than 18 µg/L is diagnostic, while 50 µg/L in the presence of inflammatory disease may be suggestive (16,20,21). The response to iron therapy further supports the diagnosis (16). It is worth emphasizing that iron deficiency anemia should be investigated for an underlying etiology. It appears as though some degree of "physiological" blood loss occurs even in normal subjects, with an upper limit of 1.5 mL blood loss per day (14). Approximately 2 mL/day of GI blood loss equals 1 mg of daily iron loss; a chronic loss of 10 mL/day results in iron deficiency (14).

Iron replacement may be oral or parenteral. Oral iron therapy in high doses is often poorly tolerated due to GI side effects (nausea, vomiting, taste disturbances, constipation, and diarrhea). Therefore, it is prudent to initiate oral iron with low doses, typically once daily ferrous sulfate 300 mg (60 mg elemental iron), titrating to two and three times daily over weeks as tolerated (16). Once daily iron dosing in older individuals may result in better compliance; too often, multidosing results in side effects and stoppage of therapy altogether. Iron is better absorbed from an empty stomach; however, it is usually prescribed with meals to minimize side effects. Elixir forms are available for those with dysphagia or on tube feeding. Although anemia may be corrected in six weeks, iron therapy is continued for three to six months to replace storage iron (16) (Table 4) .

Parenteral therapy (iron dextran, iron sucrose, ferric gluconate) is reserved for those unable to tolerate oral administration, presence of conditions that interfere with iron absorption and for chronic non compliance. Precautions are recommended for parenteral therapy; side effects include anaphylaxis, hypotension, myalgias, fever and urticaria. Blood transfusion is indicated for acute blood loss and compromised organ function states, particularly in the elderly. Each mL of packed red blood cell contains 1 mg of iron (16).

VITAMIN B_{12} (COBALAMIN)

Cobalamin is present only in animal proteins (e.g. liver, red meat, poultry, fish, eggs and dairy products) (22,23) (Table 5). Fruits and vegetable do not contain

Table 4
Iron Availability and Stores (7,8,16)

- Iron absorption decreased with hypochlorhydria
- Dietary iron deficiency is rare
- Overwhelmingly, iron deficiency is from GI blood loss
- Heme iron (animal sources) more bioavailable than non heme iron
- Ferrous form better absorbed than ferric iron
- Dairy products and pizza are poor sources
- Recommended daily allowance 10 mg/day
- Serum ferritin, a non-invasive test, reliably reflects storage iron
- Ferritin value <18 µg/L suggests iron deficiency, values elevated in inflammation
- Body iron compartments:
  - Hemoglobin iron: 2 gms
  - Storage iron (ferritin, hemosiderin) : 1 gm
  - Transport (transferrin, lactoferrin): 3 mg

Table 5
Dietary Sources of Vitamin B_{12} and Folic acid (12)

Food	*Size*	*Vitamin B_{12} (µg)*	*Folate (µg)*
Chicken liver	3 oz	16.5	654
Pork liver	3 oz	15.8	139
Sardines	3 oz	7.7	21
Porkchop	3 oz	0.9	5
Eggs	1 whole	0.5	23
Yogurt	1 cup	1.4	28
Milk	1 cup	0.9	13
Orange juice	1 cup	none	136
Spinach	1/2 cup	none	108
Broccoli	1 cup	none	62
Grapenut cereal	1/4 cup	none	101

the vitamin, as only bacteria and protozoa synthesize cobalamin (11). Bacteria present in the GI tract, synthesize cobalamin primarily in the colon (23,24), however this is not absorbed. The predominant site of absorption is the ileum (24).

Vitamin B_{12} absorption is a complex process. Several reviews including a recent one in this journal detail the process (22,23,24,25,26,27). In brief, absorption entails the initial separation of cobalamin from food bound protein by peptic acid activity, and the binding of B_{12} to R protein. The next step, beyond the stomach, involves the separation of B_{12} from R binder in an alkaline medium and coupling of the vitamin to intrinsic factor (IF). The IF—cobalamin complex migrates to the terminal ileum where B_{12} is absorbed in the presence of calcium. Body cobalamin stores usually range from 2–10 mg. Approximately 2-5 µg is lost daily, however more than 75% of this cobalamin excreted via the bile is reabsorbed, thanks to an excellent enterohepatic recirculatory pathway, in the absence of intake, deficiency occurs only after several years. The current recommended dietary allowance is 2.4 µg/day (23) but only a smaller amount needs to be absorbed to prevent deficiency.

Food—cobalamin malabsorption indicates the inability to separate cobalamin from food protein; it is usually due to gastric dysfunction and is the most common cause of deficiency in older adults. Conditions predisposing to deficiency in older adults include pernicious anemia, gastrectomy, achlorhydria, pancreatic disease, small bowel intestinal bacterial overgrowth, malabsorption, veganism, acid lowering drugs (e.g. histamine receptor blockers, proton pump inhibitors) and other medications (cholestyramine, metformin, nitrous oxide, colchicine etc.) (22,23,24,25,26). Pernicious anemia, an autoimmune disorder formerly considered the most common cause, only accounts for 10%–15% of deficiency (Tables 5,6).

FOLIC ACID

Folic acid (pteroylglutamate) is present in most natural foods (12,28). (Table 5). Extended food cooking decreases folate content by 50%–90% from oxidation. Folate absorption occurs via the entire length of the small intestine, primarily in the jejunum by hydrolysis at the brush border membrane (29). Transport of folate is through a specific carrier-mediated, sodium dependent process active at acid pH (29). Folates undergo reduction in the gut lumen and are methylated and formylated. Methyltetrahydrofolate, the predominant form is found to be more efficiently transported across the intestinal cells to the body cells (bone marrow, reticulocytes, liver, renal tubular cells and cerebrospinal fluid) (28). Normal body folate stores range from 5–10 mg, partly maintained by a folate enterohepatic circulation. About 100 µg of biologically active folate is excreted in the bile daily. The recommended dietary allowance for normal healthy persons is 3.1µg/kg body weight (approximately 0.2 mg/day). Higher intake is recommended for those with increased demand (e.g. infection, hyperthyroidism, etc.) or increased cell turnover (e.g. malignancy, hemolysis, etc.). Folate deficiency may occur from insufficient ingestion or absorption, increased utilization or augmented requirement, excretion and destruction. (Table 5). A number of medications and alcohol interfere with the absorption of dietary folate; prominent among them is dilantin, a commonly used drug in older subjects.

Individuals with folate and B_{12} deficiency may be asymptomatic or present with fatigue, weakness, hematologic and neuropsychiatric manifestations (the last notable with B_{12} deficiency) from defective DNA synthesis. Elevated homocysteine from either vitamin deficiency is a risk factor for coronary artery and cere-

Table 6
Common Mechanisms of Vitamin B_{12} and Folic Acid Deficiency in the Elderly *(12,28)

Mechanism	*Vitamin B_{12}*	*Folate*
Insufficient ingestion	veganism, alcoholism, poverty	overcooked foods, alcohol
Insufficient absorption	pernicious anemia, gastrectomy atrophic gastritis, drugs, SIBO[1]	GI malabsorption medications
Augmented demand	hyperthyroidism, malignancy	hemolytic anemia, malignancy,
Increased excretion	liver, renal disease	renal dialysis, exfoliative dermatitis
Increased destruction	excessive antioxidants	excessive antioxidants

*For illustration only and not all inclusive; [1]Small bowel intestinal overgrowth

brovascular disease, vascular thrombosis and development of cognitive deficits in the elderly (30).

Diagnostic evaluation includes a thorough history (associated systemic conditions, medications, prior surgery and dietary intake), physical examination and select laboratory studies. In asymptomatic individuals who are at risk for deficiency and older individuals (age >50 years old), screening for B_{12} deficiency is suggested (22,24,25). Folate deficiency may be verified by serum folate and red blood cell (RBC) folate levels. Serum folate is an indicator of folate balance, not stores; it is influenced by dietary intake and decreases after just three weeks of folate deprivation. RBC folate decreases only after several months of folate deprivation. (31). Elevated homocysteine levels may suggest deficient folate or B_{12} status (amongst other causes) (31).

Replacement for vitamin B_{12} deficiency may be parenteral, oral, intranasal or sublingual (22,25). Oral supplementation in doses even as low as 50 µg daily is found to significantly increase levels in those without prior gastric surgery or symptoms of malabsorption (32). Higher oral doses (500–2000 µg daily) are effective in pernicious anemia. Oral folate replacement entails using 1 mg daily for four to six months; it may be discontinued once dietary intake contains at least one fresh fruit or fresh vegetable daily with avoidance of alcohol (16,28).

COPPER

Copper is an essential micronutrient, found in animal products except, for milk which is a poor source (33). Rich sources of copper include animal liver, oysters, nuts, seeds, and lesser amounts in whole grain and legumes, fruits and vegetables (34). The copper content of the whole body ranges from 50–120 mg with the highest concentration in liver, brain, kidney and heart (34). The recommended daily requirement is 1.5–3 mg /day. Copper is absorbed in the small intestine by facilitated diffusion through the mucosal surface and exits by active transport through the basolateral membrane. Much of copper in serum is incorporated into ceruloplasmin (an α_2 glycoprotein with six atoms of copper per molecule) and approximately 10% is bound to albumin, other proteins and amino acids. In blood, copper bound to albumin acts as a temporary storage site, while in the liver, copper bound to metallothionein is the storage form (33). Zinc and other ions competitively bind to metallothionein, which explains the occurrence of copper deficiency in those on zinc supplementation (150 mg/day) (33) The data on effects of phytate and fiber on copper absorption appear inconsistent (11,34).

Ceruloplasmin is functionally an enzyme required for iron oxidation. Other essential functions of copper are as constituent of metalloprotein enzymes, cytochrome oxidation system and involvement in hemoglobin synthesis (33,34). Copper deficiency manifests as anemia, neutropenia, bone abnormalities (e.g. osteoporosis), hair and skin depigmentation, and defective elastin formation (33,34). Recent studies have shown the significance of copper in cardiovascular disease based on its role in peroxidation, glycation, alteration of copper

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Table 7
A Comparison of two Essential Trace Elements: Copper and Zinc (11,12,33,40)

	Copper	*Zinc*
Sources	green vegetables, fish	meat, shellfish, cereals, legumes
Daily requirements	1.5–3 mg/day	12–15 mg/day
Absorption		
Phytates and fibers	inhibited (–/+)	inhibited
Effect of other elements	interference by zinc	interference by iron
Site of absorption	distal small intestine (jejunum and ileum)	small intestine
Physiologic role	Component of enzyme systems Mostly bound to ceruloplasmin	co-factor for metalloenzymes
Deficiency	anemia, microcytic dermal changes neutropenia osteoporosis	alopecia dysguesia hypogonadism immune dysfunction scaly, flaky rash

dependent enzymes and nitric oxide metabolism (35).

Conditions of GI origin predisposing to copper deficiency include total parenteral nutrition, chronic diarrhea, malabsorptive disorders (e.g. celiac sprue), prolonged use of antacids and excessive zinc and iron supplementation.

Treatment of deficiency is the use of oral copper sulfate 5 mg/day (36); for those on parenteral nutrition add 0.3 mg/ day (range 0.2–0.45 mg/day) (37) (Table 7).

MICRONUTRIENT—DRUG INTERACTIONS

Several medications interfere with the availability of vitamins and minerals. Mechanisms of malabsorption vary considerably. Cholestyramine binds folate and impairs its absorption (12,39). Colchicine predisposes to intestinal mucosal damage resulting in malabsorption (39). Alcohol and metformin affect folate and vitamin B_{12} absorption. Interaction of alcohol with folate is mainly by inhibition of hydrolysis of dietary folates (29). Competitive inhibition of intestinal folate transport by a metabolic block occurs with sulfazalazine and phenytoin. Increased gastric pH due to chronic use of antacids, histamine$_2$ receptor blockers and proton pump inhibitors decrease the absorption of iron (converted to poorly absorbed trivalent ferric form in alkaline pH) , folate (pH gradient mediated) and cobalamin (failure to release cobalamin from dietary protein) (38,39).

The interactions between zinc, iron and copper, three common micronutrients, is interesting. Zinc is commonly administered for healing of pressure ulcers and more recently has gained favor for use in Age Related Macular Degeneration. Zinc is absorbed mainly in the small intestine and induces formation of copper binding ligands in the mucosa which sequester copper, resulting in deficiency (40). In fact this property is used in Wilson's disease where copper accumulates; large doses of zinc help inhibit copper absorption. Conversely, a high copper intake does not interfere with zinc absorption.

Microcytic anemia due to copper deficiency is unresponsive to iron replacement alone. Oral iron, especially in ferrous form interferes with zinc absorption; both metals appear to compete for the same absorption site. Zinc is present in eggs, chicken, beef, shellfish and whole grain cereals. Mean intake is 8–16 mg/day (40).

SUMMARY

Anemia commonly occurs in older adults on a gastrointestinal basis. Iron deficiency is the most prevalent cause of nutritional anemia; the most common etiology of iron deficiency anemia is blood loss from the gastrointestinal tract. Less common GI causes of anemia of

GI origin include folate and B_{12} deficiencies. Folate fortification of food has been implemented to minimize nutritional folate deficiency and prevent harmful consequences. In light of this, screening the elderly population, especially those at risk, for B_{12} status assumes significance and helps early intervention to reverse potential neurologic and hematologic consequences. ■

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