Today topics: nutritional requirements for hematopoiesis

Vitamin B12
Folic acid
Iron
Deficiencies of these requirements
Facts regarding Vitamin B12 (Cyanocobalamin)**

- Water soluble vitamin
- Vit B12 in diet can be destroyed by digestive enzyme. It is protected by intrinsic factor
- Prolonged deficiency leads to irreversible neurological damage
- Its absorption from gastrointestinal tract (terminal ileum) needs presence of intrinsic factor
- It is absorbed from terminal ileum with intrinsic factor by pinocytosis.
Absorption of vitamin $B_{12}$

Vitamin B12 binds a glycoprotein (intrinsic factor) in stomach. I.F. is secreted by the parietal cells.

Vitamin-intrinsic factor complex recognises surface receptors of mucosal cells in ileum and is absorbed there.

It is stored mainly in the liver in amounts (3-5mg) sufficient to last a couple of years.

Increased need in pregnancy, lactation, growth
Sources of Vitamin B$_{12}$

1. Fish
2. Eggs
3. Meat and liver
4. Dairy Products

** Dietary deficiency is rare except in vegetarians
FOLIC ACID (FOLATE)

- **Dietary sources**
  - Present in animal and vegetable products
    - Green leafy vegetables: Asparagus, broccoli, spinach, lettuce
    - nuts and whole grain cereals.
    - Liver, yeast, mushrooms, oranges
    - Cooking depletes food of folate

- **Metabolism**
  - Absorbed most actively in the jejunum and upper ileum

- **Body stores are 5-10 mg (liver)**
  - Requirement of the body for folic acid is increased in pregnancy and lactation
    - Folate deficiency can lead to birth defects (neural tube defects)
Role of vitamin B12 and folic acid in synthesis of cellular DNA**

**Bone marrow cellular elements are among the most rapidly dividing cells in the body (because of continuous needed for RBCs and WBCs).

Dividing cells needs continuous formation of DNA. Both vit B12 and folic acid are needed for formation of THYMINE (one of four nitrogen bases that form the DNA).
Role of vitamin B12 and folic acid in synthesis of cellular DNA (cont.)**

**Because both Vitamin B12 and folic acid are needed for normal formation of DNA, therefore nuclear maturation and cell division of bone marrow cells (hematopoiesis) is not rapid and this leads to larger cells (macrocytes).

The macrocytes have irregular, oversized (large than normal) and oval shape with fragile cell membrane.

Macrocytes are red cells with an increased size, 9-12µm in diameter

Abnormal cell membrane of RBCs leads to short life of RBCs.
Megaloblastic anemia**

Both vitamin B12 and folate deficiency cause an identical megaloblastic anemia.

Pernicious anemia is due to primary deficiency of vitamin B12 secondary to failure of vitamin B12 absorption from gastrointestinal tract. This absorption failure is due to absence of intrinsic factor (atrophic gastric mucosa).

Normal RBCs vs. macrocytes.
Megaloblastic anemia due to Deficiency of vitamin $B_{12}$

Causes of vitamin $B_{12}$ deficiency:

1. Impaired absorption
   a. Gastric atrophy: Auto immune disease can destroys the parietal cells that secrete the I.F. required for absorption of vit. B12.
   b. Gastrectomy
   c. Intestinal disease like ileal resection
   d. Infestation with Fish tapeworm (*Diphyllobothrium latum*)

in these cases treatment is life long injections of vitamin B12 (oral administration wouldn't be much use!)

2. Less vitamin B12 intake- rare seen in vegetarian
Megaloblastic anaemia and folic acid deficiency

Folic acid deficiency reduces the capacity of the body to make DNA which affects the rapidly dividing bone marrow cells associated with red blood cell production. So folic acid deficiency produces megaloblastic anemia.

Importance of folic acid during early pregnancy:
Closure of the neural tube occurs very early in pregnancy. This closure may not occur in Cases of deficiency of folic acid.

Incidence of neural tube defects (like spina bifida) can be prevented by using folic acid supplements in women intending to become pregnant.
Neurological abnormalities in Vit B12 deficiency

- Vit B12 is needed for normal formation of neuronal membrane and therefore deficiency leads to abnormalities in neuronal membrane synthesis.
  - Neurologic defects seen with B12 deficiency
    - Peripheral neuropathy
    - Demyelination of neuron axons in spinal cord

- Also Vit B12 is needed for normal function of the central nervous system.

Megaloblastic anaemia could be due to folic acid deficiency or vitamin B12 deficiency. In either case folic acid would cure the anaemia but if the true underlying deficiency involved vitamin B12 the patient would still go on to develop the irreversible neurological disorders. For this reason such patients are always given folic acid and vitamin B12 supplements until the true cause of the anaemia is identified.

Important points:
- Although macrocytic anemia due to vit B12 deficiency may respond to folate therapy, neurologic findings will not improve
- Neurologic findings may be permanent if not treated early.
Body iron**

- It is needed for formation of Hb, myoglobin, cytochrome oxidase, peroxidase and catalase.
- Iron is needed to $O_2$ transport
- There are 4.5 grams of iron in human body
  - 65% ........Hb (RBCs). i.e. 2/3 of total body iron is in heme
  - 4%............myoglobin (muscles)
  - 1%............transferrin (plasma)
  - 15-30%.....stored iron (mainly in liver in form of ferritin)
Dietary Iron

- Normally not all of the iron in the diet (fraction of it) is absorbed.
- Most iron in diet is in Ferric (Fe$^3$) form but absorbed in Ferrous (Fe$^2$) form.
- Diets high in iron ...Red meat/ liver kidney
  Diet of average iron ...Beans/ dark green vegetables/ dried fruit/ nuts
  Diet poor in iron ... milk

- Men lose 0.6 mg /day
- Women lose 1.3 mg /day (during menstruation)
Iron requirements

– Each day 20-25 mg of iron is needed for erythropoiesis, most of which is obtained from normal RBC turnover (using iron coming from destructed old RBCs) and hemoglobin catabolism.
  • In an adult male, only about 1 mg/day needs to be newly absorbed from the diet.
  • Menstruating females need to absorb more per day because 30-40 mg is lost per month. Therefore, they need to absorb an additional 1-1.5 mg/day on top of the male requirement of 1 mg/day
  • Iron requirements ↑ during Pregnancy (expansion of blood mass and fetal requirements loss at delivery leads to a requirement of 1000 mg of iron during pregnancy).
Also There is an increased need for iron in infants and children
Absorption of iron

- Iron kept soluble and in ferrous state by gastric acid (low pH converts Fe+++ into Fe++ which more readily absorbed.
- Iron is mostly absorbed in duodenum
- Iron that enters the body from the small intestine is rapidly bound to transferrin, an iron-binding protein of the blood.
- Transferrin delivers iron to red blood cell precursors, that take up iron bound to transferrin via receptor-mediated endocytosis.
Not all iron is absorbed. About 0.6 mg/day is lost in feces.
**BONE MARROW**

Erythroblast have receptors for transferrin. Transferrin is taken by endocytosis inside erythroblast where iron is released from protein and taken by mitochondria where heme is formed.

**HEPATOCELLYTES**

Iron is stored as ferritin. Iron combines with protein called apoferititin forming the FERRITIN.

When iron in the plasma falls, some ferritin is transported to plasma forming transferrin.

****Excess iron is stored in insoluble form called HEMOSIDERIN****
**SUPPLY, TRANSPORT, AND STORAGE OF IRON**

***Stored forms of iron are ferritin and hemosiderin***

***Transport form of iron is transferrin***
BODY IRON CYCLING

Serum

Transferrin-Fe

Hb

Fe

Bone marrow normoblasts

Circulating red cells

Macrophage

Reticuloendothelial system

Spleen + liver

liver
The Iron Cycle

Bilirubin (excreted)

Macrophages

Degrading hemoglobin → Free iron

Hemoglobin

Red Cells

Blood loss—0.7 mg Fe daily in menses

Tissues

Ferritin

Hemosiderin

Heme

Enzymes

Free iron

Transferrin—Fe

Plasma

Fe++ absorbed (small intestine)

Fe excreted—0.6 mg daily
1. Acidic condition helps in more iron absorption
   - pH decreases (\( \downarrow \text{pH} \rightarrow \uparrow \text{absorption} \))
   - Ascorbic acid increases absorption

2. Chelators:
   - Phytic acid (found in seeds), phosphates, oxalates decrease absorption

*** A chelating agent is a molecule that can bond tightly with metal ions
Feedback Control of Iron Absorption

Ferritin Saturation: When there is excess iron, ferritin (which is normally only $\frac{1}{3}$ saturated with iron), becomes fully saturated. This makes it difficult for transferrin to release iron to the tissues.

- Also when there is excess iron, transferrin (also normally $\frac{1}{3}$ saturated with Fe), becomes saturated. Since saturated transferrin cannot accept new iron from the mucosal cells of the intestine, iron builds up in the epithelial cells which subsequently decreases active absorption from the lumen.

Apotransferrin synthesis: When there is excess iron in the body, rate of apotransferrin production by the liver is reduced and this reduces iron absorption.
IRON DEFICIENCY

*** iron deficiency (mostly because of less iron in the diet or less absorption) causes anemia called iron deficiency anemia

- It is Commonest type of anemia
- It Causes of chronic ill health
- It may indicate the presence of important underlying disease eg. blood loss from tumour

LABORATORY DIAGNOSIS: IRON DEFICIENCY
- Microcytic hypochromic anaemia
- Decreased serum iron
- decreased % transferrin saturation

RBC indecies
- MCV < 80 fl
- MCH < 26 ug
- MCHC < 31%
CAUSES OF IRON DEFICIENCY

• Increased physiologic demand eg. pregnancy, lactation, rapid growth
• Blood loss from GI tract, uterus
• Malabsorption
• Diet of low iron content