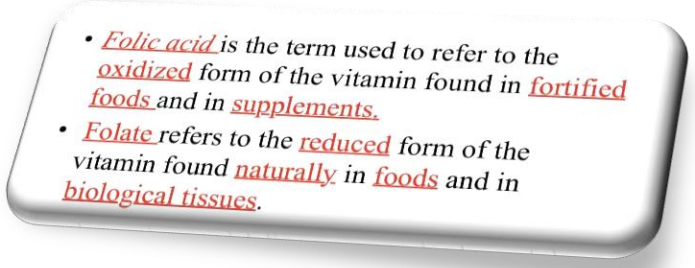
g- Vitamin B_9

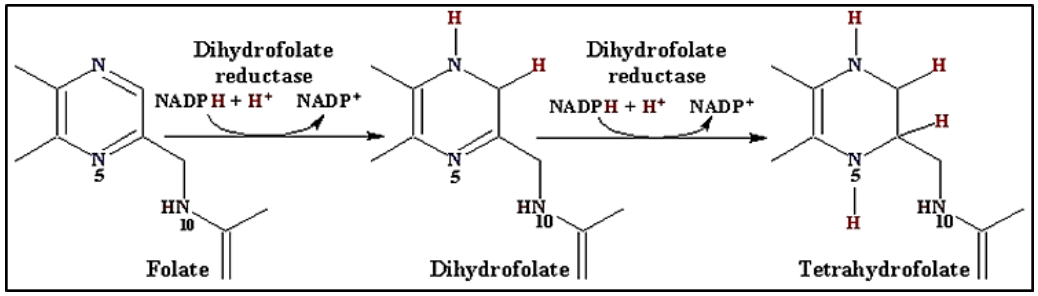
(Folic acid)

Vitamin B_9

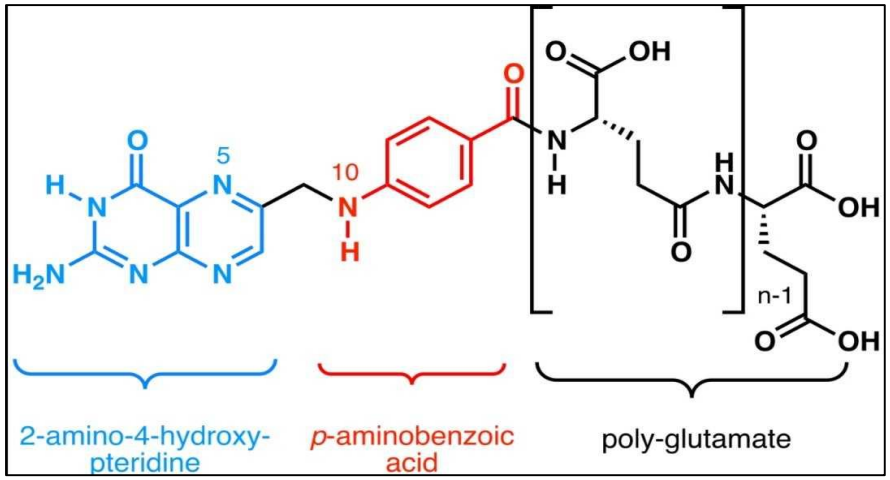
- Folate is the generic descriptor for folic acid and related compounds exhibiting the biological activity of folic acid.
- The term folic acids and folates are used only as general terms for this group of compounds based on the N-[(6-pteridinyl)methyl]-*p*-aminobenzoic acid skeleton conjugated with one or more L-glutamic acid residues.
- Tetrahydrofolic acid is the reduce form of folic acid.



- **Folic acid is itself not biologically active**, but its biological importance is due to **tetrahydrofolate** and other derivatives after its conversion to **dihydrofolic acid** in the liver.



Pteridine derivative
Variable degree of hydrogenation of pteridine nucleus
Single-carbon units bind nitrogen at position 5 and/or 10
One or more glutamyl residues linked via peptide bonds

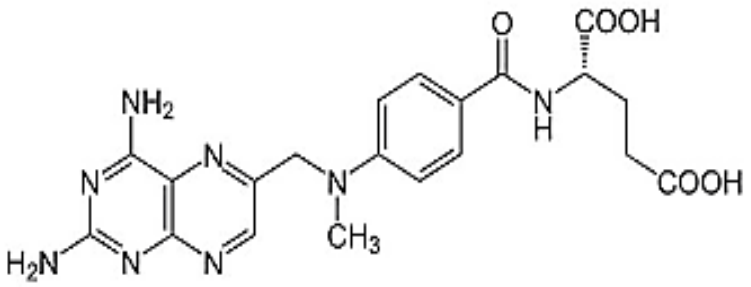


Folate antagonists

1- Aminopterin (4-aminofolic acid) is rodenticide

2- Methotrexate (4-amino-N^{10}-methylfolic acid) is antineoplastic agent.

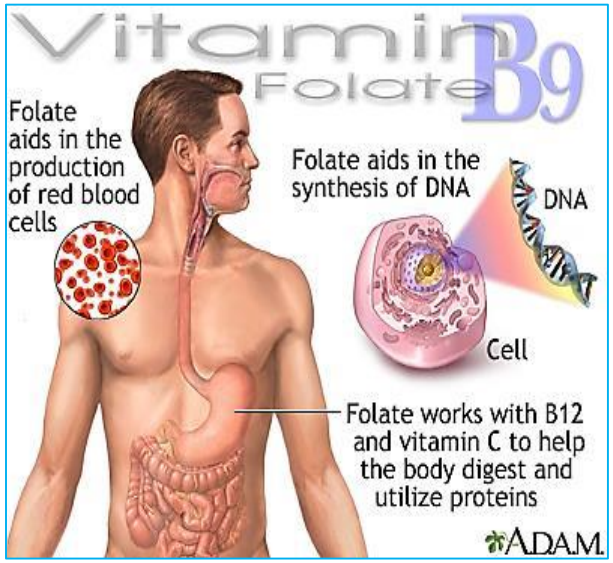
Aminopterin



MTX

Significance of the vitamin

- It is important for normal metabolism and to the etiology of homocysteinemia and birth defects.
- Deficiency of the vitamin is prevalent in poverty and malnutrition population causing anemia.
- High doses of folate may maske the macrocytic anemia of vitamin B_{12} deficiency.



Source of the vitamin

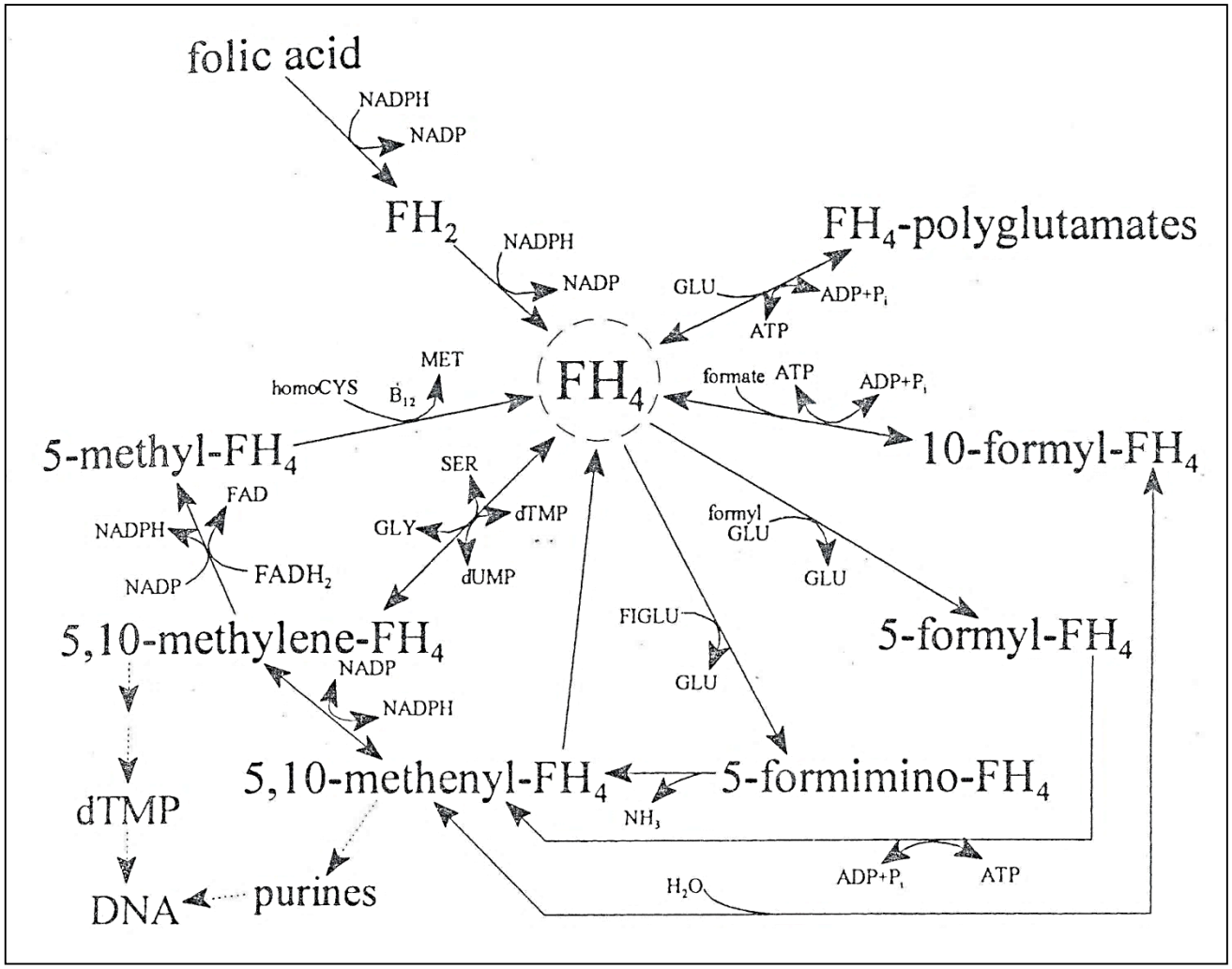
- Liver, mushrooms and green leafy vegetables are rich sources of the vitamin.
- It is available in the reduced form FH_4 as 5-methyl-FH_4 and 10-formyl-FH_4.
- Most of folates are easily oxidized in the presence of light and heat even to inactive forms in the acid environment of normal gastric juice.
- In case of pernicious anemia (gastric anacidosis), isomerization will not occur.
- Presence of conjugase inhibitors reduce the bioavailability of folate.

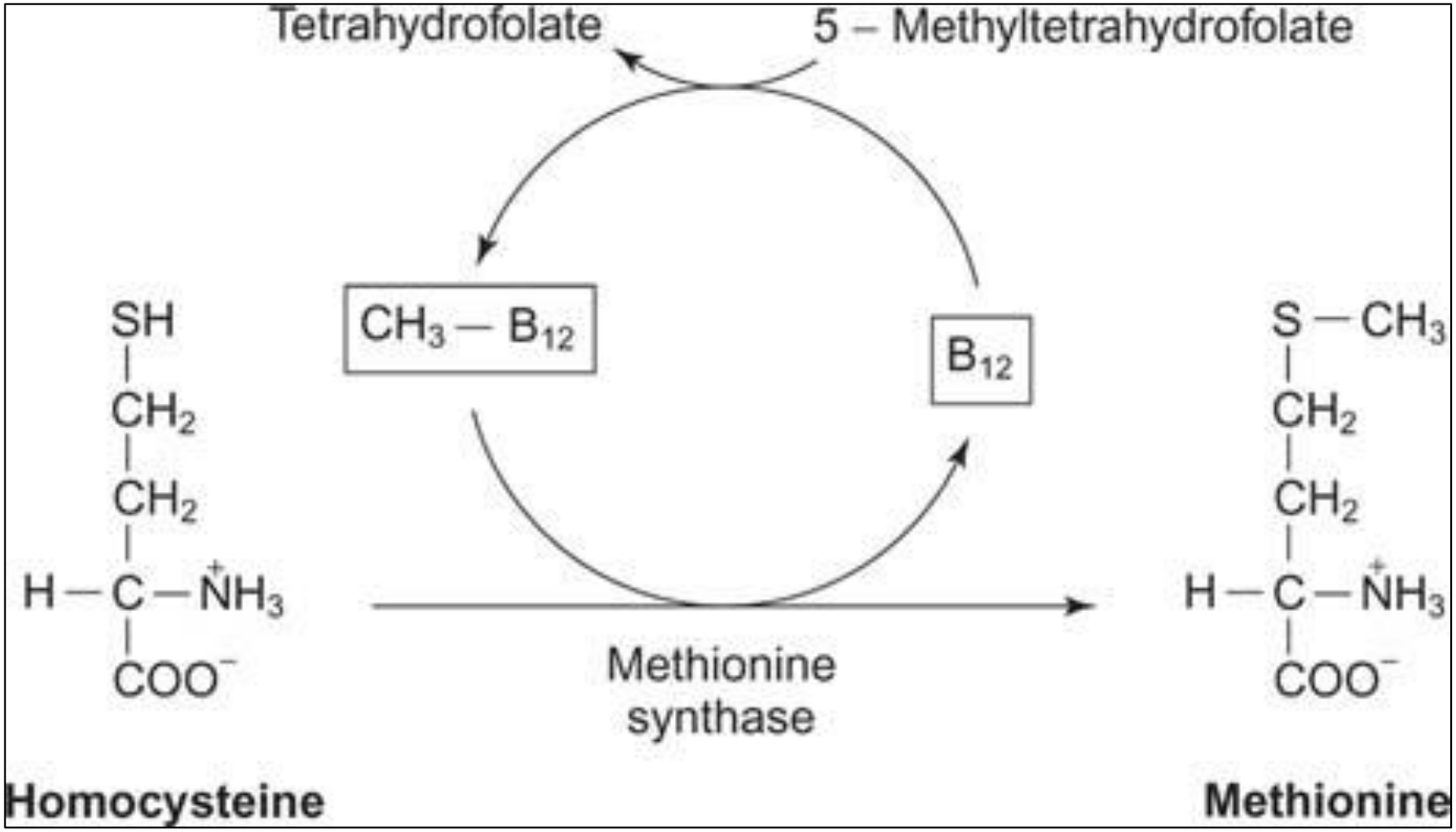
Supplement		Metabolic Pathway
Folic acid	→	Dihydrofolate (DHF)
		↓
Folinic acid (folinate salts)	→	Tetrahydrofolate (THF)
		↓
		5,10-Methylenetetrahydrofolate (5-10 MTHF)
		↓
Levomefolic acid (levomefolate salts)	→ (=)	5-Methyltetrahydrofolate (L-5-MTHF or levomefolate)

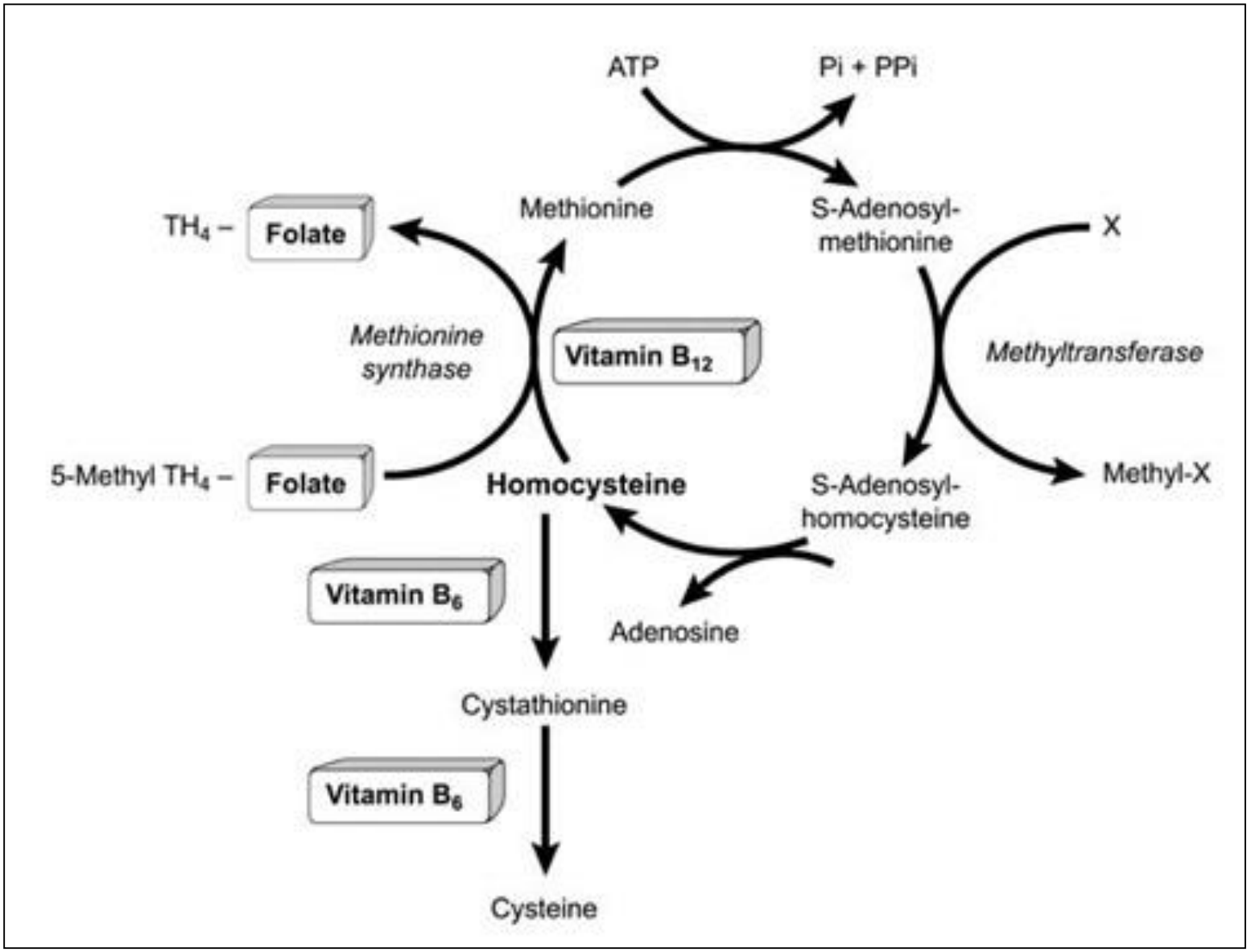
Metabolic functions of folate

- It acts as a coenzyme in many reactions of the metabolism of amino acid and nucleotides.
- It serves as an acceptor or donor of a single-carbon unit in the biosynthesis of DNA and methionine.
- Methionine is essential amino acid for the synthesis of proteins.

- The N5,N10-methylene-tetrahydrofolate can either donate its single-carbon group directly, be oxidized by NADP to the methenyl form, or be reduced by NADH to the *methyl* form. Depending on the biosynthetic pathway involved, any of these species can donate the 1-carbon group to an acceptor. The methylene form donates its methyl group during the biosynthesis of thymidine nucleotides for DNA synthesis, the methenyl form donates its group as a formyl group during purine biosynthesis, and the methyl form is the donor of the methyl group to sulfur during methionine formation.


folic acid
NADPH
NADP
FH2
NADPH
NADP
FH4-polyglutamates
GLU
ADP+Pi
ATP
MET
homoCYS
B12
FH4
formate
ATP
ADP+Pi
5-methyl-FH4
10-formyl-FH4
SER
FAD
NADPH
GLY
dTMP
formyl GLU
GLU
NADP
FADH2
dUMP
FIGLU
5,10-methylene-FH4
5-formyl-FH4
GLU
NADP
NADPH
5,10-methenyl-FH4
5-formimino-FH4
NH3
dTMP
ADP+Pi
ATP
H2O
DNA
purines


Tetrahydrofolate
5 – Methyltetrahydrofolate
CH3 — B12
B12
Methionine synthase
Homocysteine
Methionine

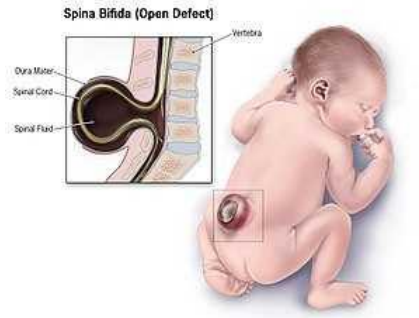

ATP
Pi + PPi
Methionine
S-Adenosyl-
methionine
X
TH4 –
Folate
Methionine
synthase
Vitamin B12
Methyltransferase
5-Methyl TH4 –
Folate
Homocysteine
S-Adenosyl-
homocysteine
Methyl-X
Vitamin B6
Adenosine
Cystathionine
Vitamin B6
Cysteine

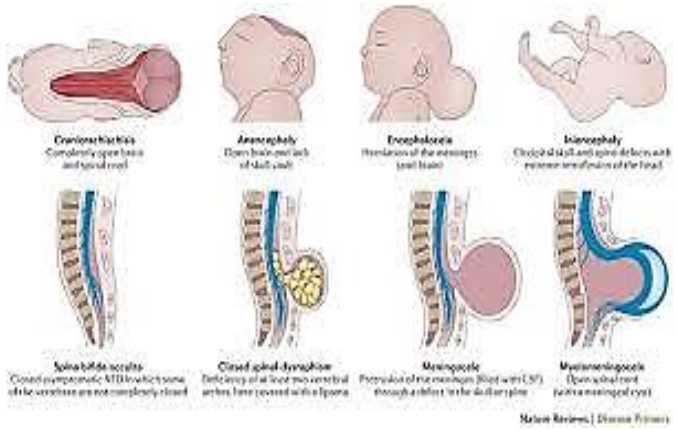
Recommended Daily Allowance (RDA)

- 400 µg/day for men and women 9 years of age and above.
- 600 µg/day for pregnant women.

Folate deficiency

- It results in impairment of DNA biosynthesis, which is manifested clinically as anemia, weakness and depression.
- In pregnant women, it may lead to birth defects as Neural tube defect (NTD).
- Neural tube defects are birth defects caused by abnormal development of the neural tube, a structure that give rise to the brain and spinal cord.





- Homocysteinemia, which through experimental studies, may be associated with increase in heart diseases.

Folate uses

- In case of folate deficiency.
- Patients with homocysteinemia.
- Pregnant women.

Folate toxicity

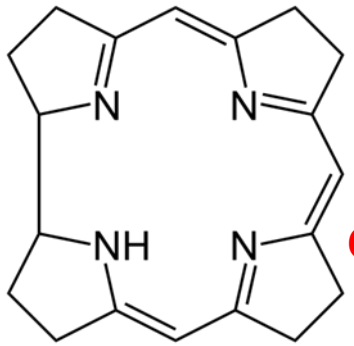
- It is low.
- Inconsistent results have been reported concerning the effect of high folate doses (1-10 mg) on human epileptics.
- Some patients may show increase in the frequency or severity of seizures and reduced anticonvulsant effectiveness.

h- Vitamin B_{12}

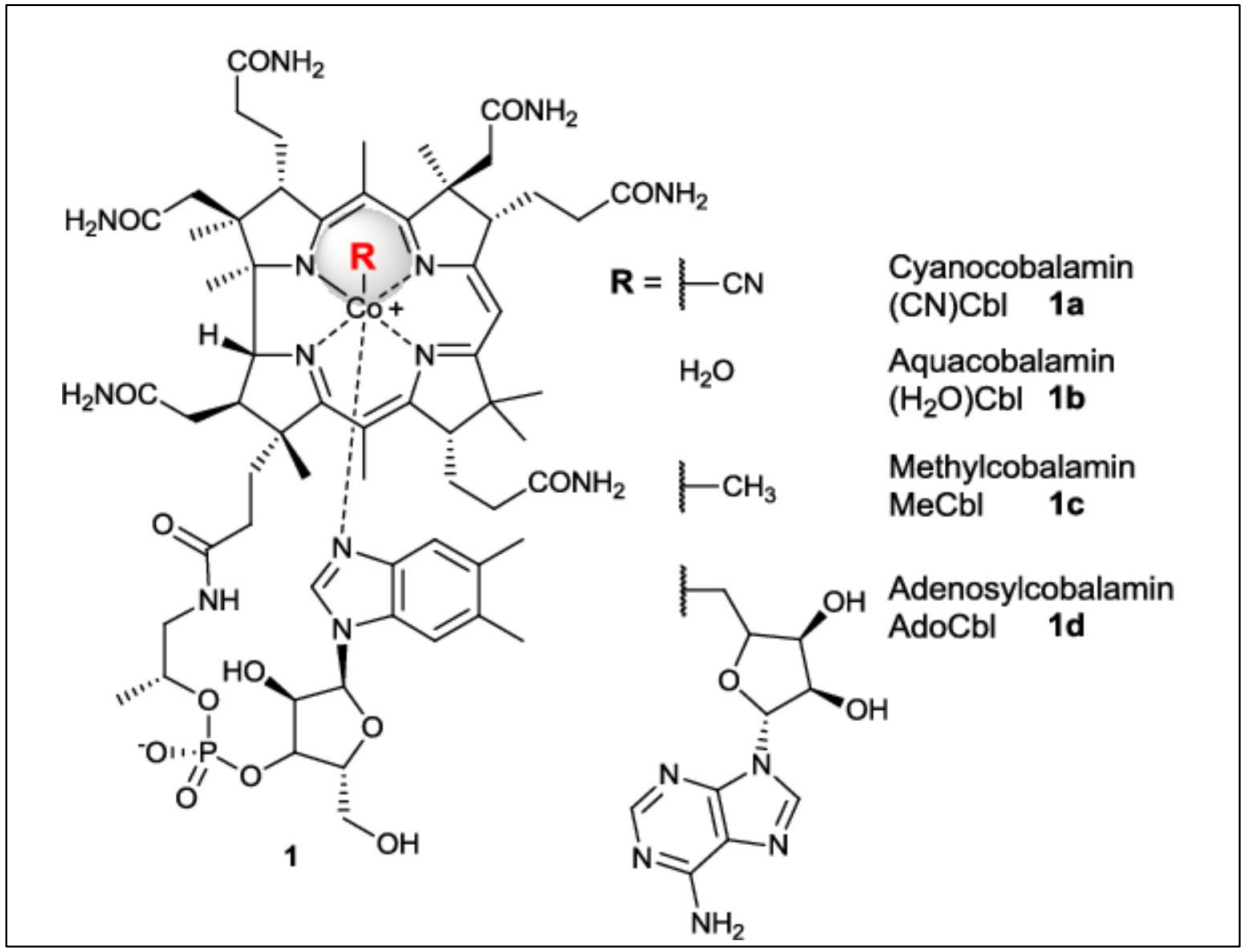
(Cobalamin)

Vitamin B_{12}

- It is the generic descriptor for all corrinoids (compounds containing corrin nucleus) exhibiting the qualitative biological activity of cyanocobalamin.
- Cyanocobalamin is the trivial name of vitamin B_{12} and also called cobalamin.
- Other B_{12} vitamers are methylcobalamin, deoxyadenosylcobalamin, hydroxycobalamin nitrocobalamin and aquacobalamin.
- Cobalamins are unstable to light.



Corrin


CONH2
CONH2
CONH2
H2NOC
R
N
N
Co+
H
N
N
H2NOC
CONH2
O
NH
N
N
HO
O
-O
P
O
O
O
OH
1
R =
CN
Cyanocobalamin
(CN)Cbl 1a
H2O
Aquacobalamin
(H2O)Cbl 1b
CH3
Methylcobalamin
MeCbl 1c
OH
O
OH
N
N
N
N
NH2
Adenosylcobalamin
AdoCbl 1d

Significance of B_{12}

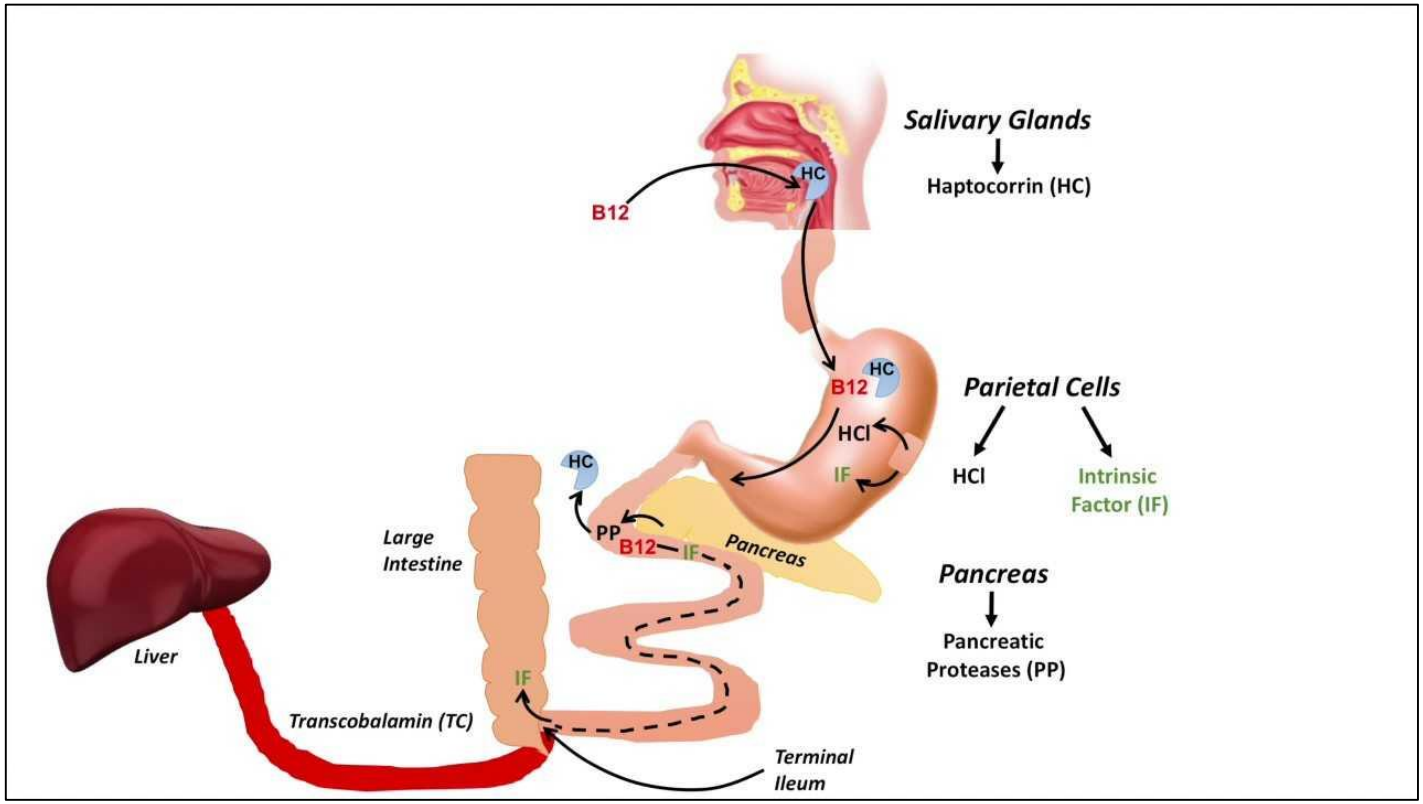
- It is biosynthesized by bacteria.
- The vitamin is seldom found in in foods derived from plants.
- Strict vegans may produce vitamin B_{12} deficiency manifested as anemia and peripheral neuropathy.
- Low B_{12} status is not uncommon among older people.

Sources of B_{12}

- Animal tissues like liver, kidney, and fish are good source of the vitamin.
- Intestinal bacteria.
- It is available as bound to protein.
- High level of vitamin C and presence of Iron have been shown to catalyze the oxidation of B_{12} to forms that are poorly utilized.

Absorption of B_{12}

- It is absorbed via active transport mechanism involving specific binding protein called intrinsic factor (IF).
- It is also absorbed by simple diffusion.
- Intrinsic factor is a glycoprotein secreted by the gastric parietal cells in response to histamine, gastrin, pentagastrin and the presence of food.
- Loss of these cells may be unable to absorbed dietary B_{12}.
- IF-B_{12} complex protects the vitamin from catabolism by intestinal bacteria.


Salivary Glands
Haptocorrin (HC)
B12
HC
Parietal Cells
HCl
IF
Intrinsic Factor (IF)
Pancreas
Pancreatic Proteases (PP)
PP
Large Intestine
Liver
Transcobalamin (TC)
Terminal Ileum

- The predominant form of B_{12} in the cell is 5-adenosylcobalamin.
- All forms of the vitamin is converted in the tissues to 5-adenosylcobalamin and methylcobalamin.

Metabolic functions of B_{12}

- Vitamin B_{12} functions in metabolism in two coenzyme forms; adenosylcobalamin and methylcobalamin through three enzymes.
- These enzymes play key roles in the metabolism of propionate, amino acids and single carbon.

Enzyme	Metabolic functions
1- Adenosylcobalamin	
Methylmalonyl-CoA mutase	Conversion of methylmalonyl-CoA to succinyl-CoA in the degradation of propionate
L-α-Leucine mutase	Conversion of L-α-Leucine to aminoisocapronate as the first step in the synthesis/degradation of the amino acid
2- Methylcobalamin	
Methionine synthetase	Methylation of homocysteine to produce methionine, serving as the methyl group carrier between the donor 5-methyl-FH_4 and the acceptor homocysteine

Recommended Daily Allowance (RDA)

- 2.4 ug/day for men and women 14 years of age and older.
- 2.6 ug/day for pregnant women.

Vitamin B_{12} deficiency

- It is caused by

1- Vegetarian diets.

2- Lack of IF.

3- Pancreatic insufficiency.

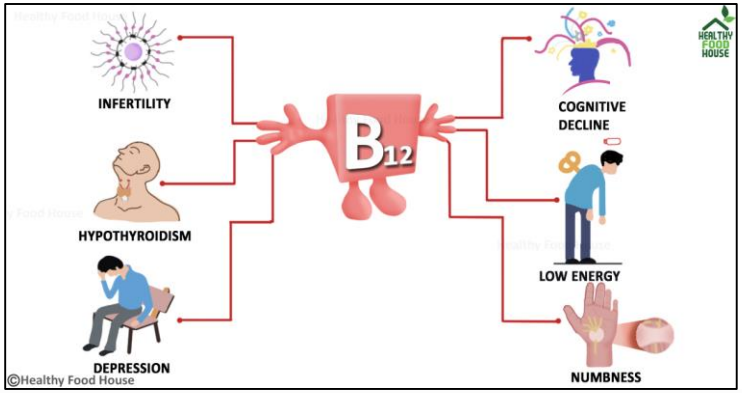
4- Parasitism (tapeworm infection).

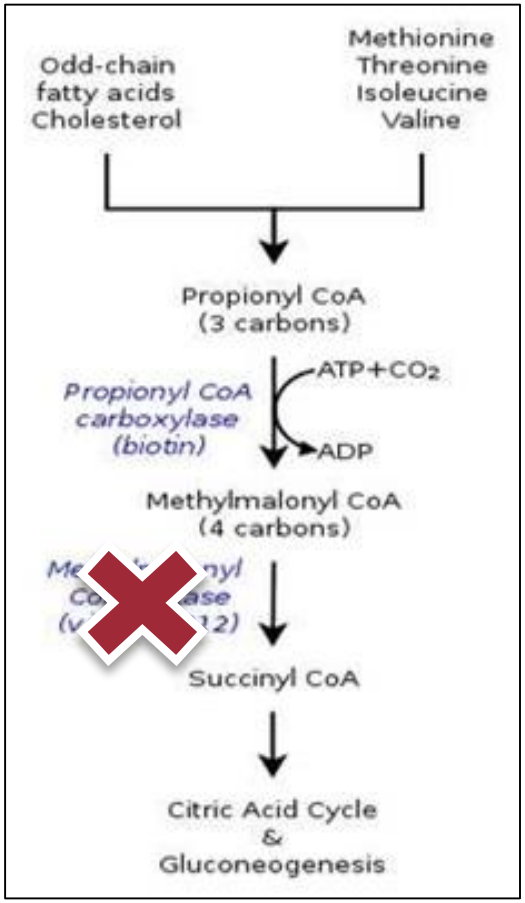
5- Xenobiotic agents such as biguanides, alcohol and smoking.

- Vitamin B_{12} deficiency is characterized by anemia and peripheral neuropathy.
- In case of lack of IF, this anemia is called pernicious anemia.
- Peripheral neuropathy is characterized by numbness of the hands and feet, memory loss and dementia.
- Methylmalonic aciduria (high level of methylmalonic acid in urine) is useful indicator for the vitamin B_{12} deficiency and differentiate it from folate deficiency.

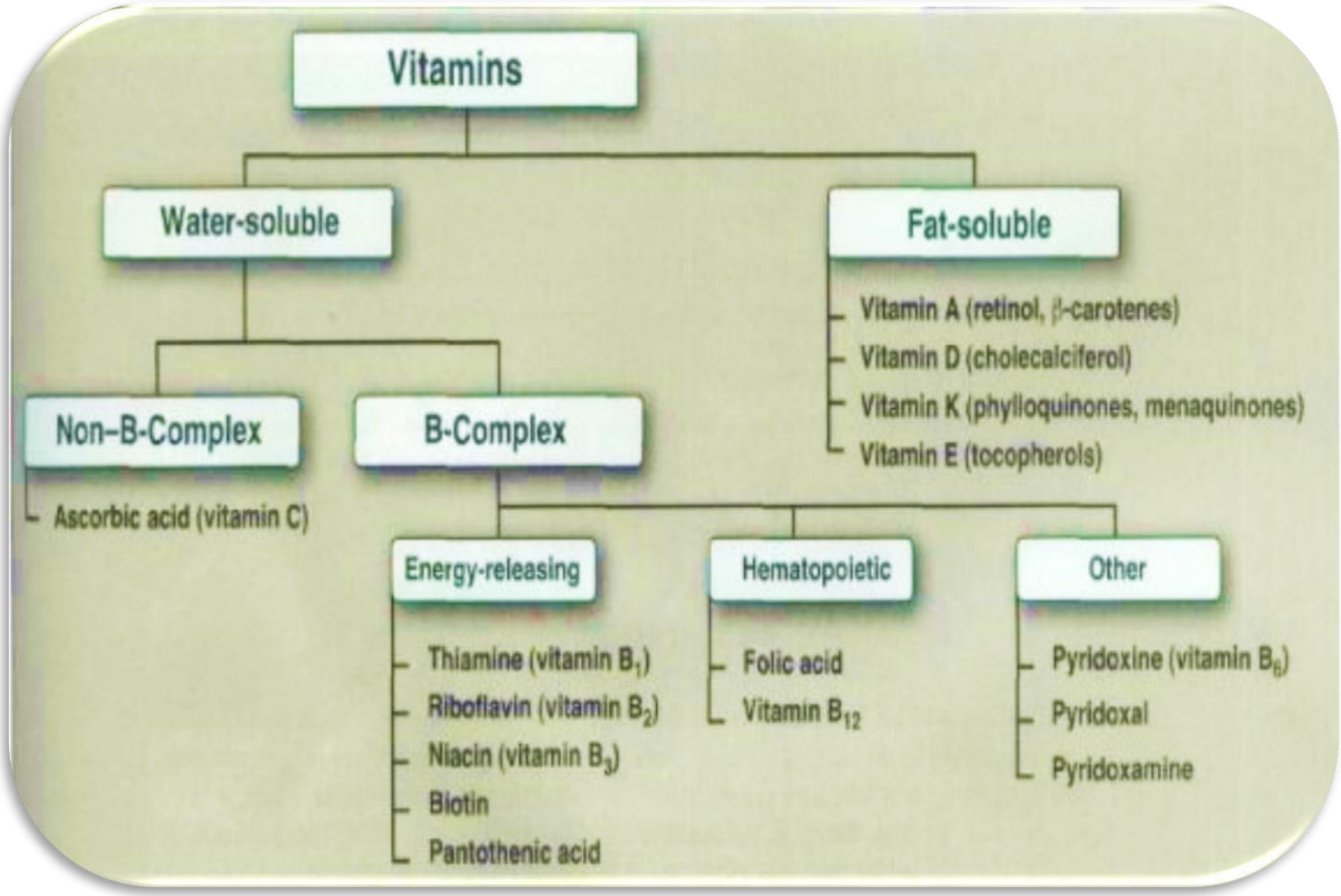
Vitamin B_{12} toxicity

- It has no appreciable toxicity and considered a safe vitamin.

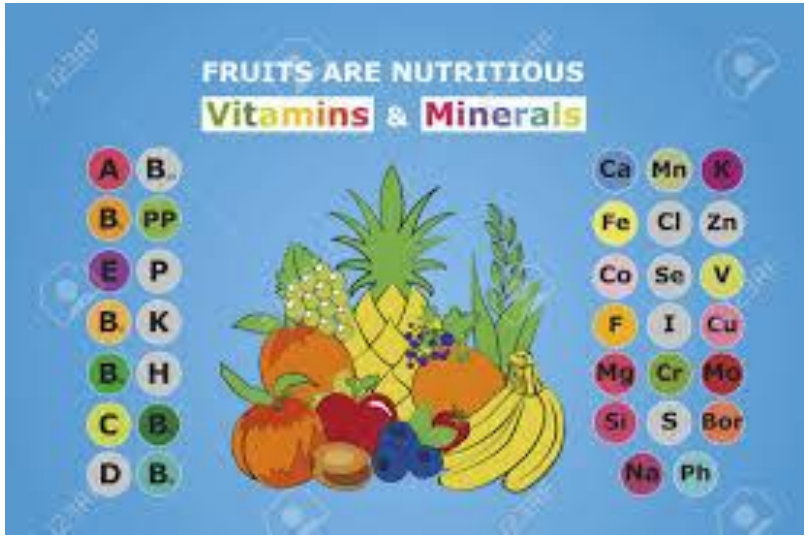



Odd-chain
fatty acids
Cholesterol
Methionine
Threonine
Isoleucine
Valine
Propionyl CoA
(3 carbons)
Propionyl CoA
carboxylase
(biotin)
ATP+CO2
ADP
Methylmalonyl CoA
(4 carbons)
Succinyl CoA
Citric Acid Cycle
&
Gluconeogenesis


SUMMARY


Vitamins
Water-soluble
Fat-soluble
Vitamin A (retinol, β-carotenes)
Vitamin D (cholecalciferol)
Vitamin K (phylloquinones, menaquinones)
Vitamin E (tocopherols)
Non–B-Complex
B-Complex
Ascorbic acid (vitamin C)
Energy-releasing
Hematopoietic
Other
Thiamine (vitamin B_1)
Riboflavin (vitamin B_2)
Niacin (vitamin B_3)
Biotin
Pantothenic acid
Folic acid
Vitamin B_{12}
Pyridoxine (vitamin B_6)
Pyridoxal
Pyridoxamine

Minerals & Trace elements



- Minerals and Trace elements are inorganic nutrients that are needed for human health.

- What is the difference between them?

Macrominerals

- The daily requirement of macrominerals **exceeds 100 mg**
- Calcium
- Phosphorus
- Potassium
- Sulfur
- Chloride
- Magnesium

Microminerals

- The daily requirement of microminerals (trace elements) is **less than 100 mg**
- Iron
- Zinc
- Copper
- Manganese
- Iodine
- Selenium

- **A mineral** is said a macronutrient.
- **A trace element** is a micronutrient.
- Nutrients that can be in the category of minerals are: Calcium, Phosphorus, Sodium, Chloride, Potassium, maganisum and Sulfur.
- Nutrients that can be in the category of trace elements are: iron, Zinc, Copper, manganese, Chromium, Selenium, Vanadium, Iodine, Cobalt, Boron, Fluoride and Molybdenum.
- Water is also considered under the category of minerals.

Calcium

- It is the most abundant mineral in the body.
- Calcium, together with phosphorous and magnesium, is a primary ingredient of bones, teeth and the skeletal framework.
- Bones and teeth contain 99% of the body's supply of calcium.
- The remaining 1% plays the critical roles of calcium in the body.
- Calcium is needed for normal blood clotting, heart function, muscle contraction, nerve function and storage and release of hormones.

- Bone is a dynamic tissue that undergoes constant breakdown and rebuilding.
- Bone formation is greater than breakdown in growing children and is balanced in healthy adults.
- Breakdown exceeds rebuilding in women after menopause and in all older adults.

Sources of calcium

- It can be obtained from foods or dietary supplements.
- Foods calcium is better absorbed than calcium taken as supplements.

- Most of the calcium in our diet comes from milk and milk products.
- Cheese and yogurt are good calcium sources because most of their calcium is calcium caseinate.
- Many calcium supplements are difficult for people to take because they do not taste good and may be hard to swallow.
- Children absorbs higher percentage of calcium than adults.
- Vitamin D is necessary for intestinal absorption.
- Vitamin D-fortified milk is a very well absorbed form of calcium.

- Vitamin C and lactose in milk enhance the absorption of calcium.
- Meals high in fat and proteins decrease absorption.
- Excess phosphorous consumption (as in carbonated sodas) can decrease calcium absorption.
- The average daily calcium intake is 2–2.5 g/day.
- Blood calcium level is tightly controlled by complex hormone system involving vitamin D, PTH and calcitonin.
- Normal range is 8.5 – 10.8 mg/dl.

- At hypocalcemia case, PTH is secreted, which causes:

A- Phosphate diuresis from kidney.

B- Stimulation of 25-OH-1-hydoxylase and leads to formation of 1,25-$(OH)_2$-D_3.

C- Both 1,25-$(OH)_2$-D_3 and PTH act in bone to promote the mobilization of calcium and phosphate.

- Under hypercalcemia, Calcitonin (CT) is secreted from thyroid gland and causes:

A- Suppression of bone mobilization.

B- Increases the renal excretion of both calcium and phosphate.

C- 25-OH-1-hydroxylase feedback inhibited by 1,25-$(OH)_2$-D_3.

Extracellular calcium exists in three forms:

1. Complexed to bicarbonate, citrates, and phosphates (6%)
2. Protein bound, mostly to albumin (40%)
3. Ionized or free fraction (54%)

- Calcium enters cells through one of the three types of calcium channels that have been identified:

T (transient or fast), N (neuronal), and L (long lasting or slow). Subsets of these channels may exist.

- Calcium channel blockers are likely to affect the L channels.

- Calcium is bound primarily to serum albumin (80%) and globulins (20%).
- Protein-bound calcium is in equilibrium with ionized calcium, which is affected by the serum anion concentration and blood pH.
- This equilibrium is important since ionized calcium is the physiologically active moiety.

Calcium dietary supplement products

Supplement	Elemental calcium by weight	Comment
Calcium carbonate	40%	Most commonly used, Least expensive Less well absorbed in persons with decreased stomach acid
Calcium citrate	21%	Better absorbed, especially by those with decreased stomach acid, More expensive May protect against kidney stones
Calcium phosphate	38%	Absorption similar to calcium carbonate
Calcium gluconate	9%	Used intravenously for severe hypocalcemia Very expensive
Calcium glubionate	6.5%	Available as syrup for children
Calcium lactate	13%	Well absorbed, but low content elemental calcium

Calcium deficiency

- The most common causes of hypocalcemia are disorders of vitamin D metabolism or impaired PTH.
- Diminished calcium intake, especially in patients receiving long term total parental nutrition solutions.
- Drugs like loop diuretics, glucocorticoids and calcitonin, among others.
- Secondary hyperparathyroidism from chronic kidney disease.

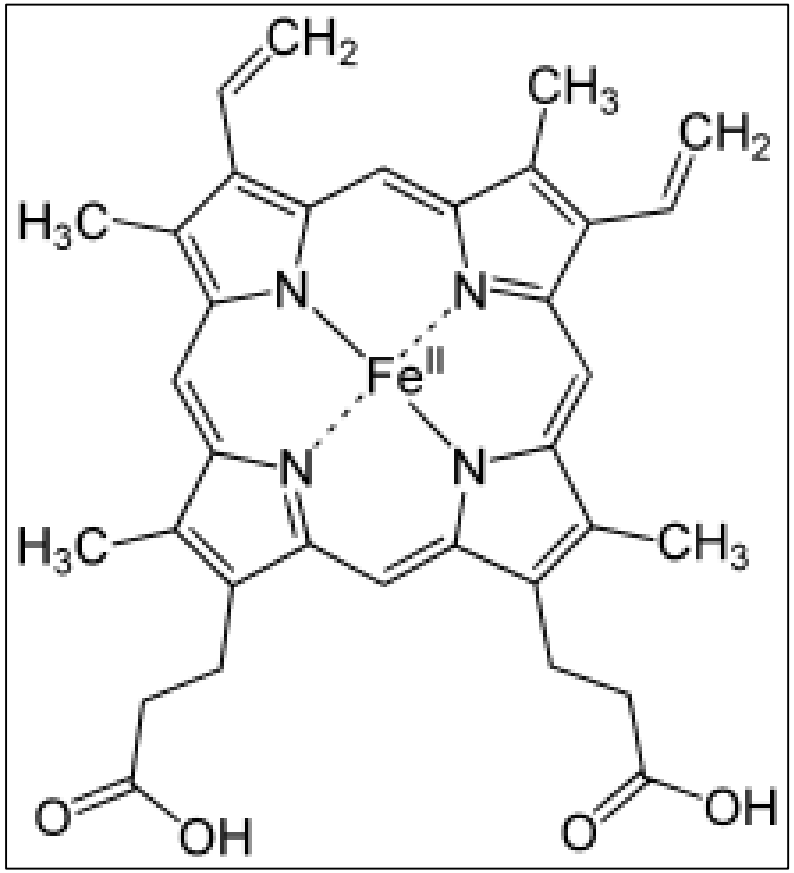
- The early signs of hypocalcemia are finger numbness, tingling and burning of extremities.
- Osteomalacia (in adults) and rickets (in children) can result from deficiency in dietary calcium or vitamin D, diminished synthesis of vitamin D_3 from insufficient sunlight exposure, or resistance of the intestinal wall to the action of vitamin D.
- It may leads to secondary hyperparathyroidism and tetany in severe hypocalcemia.

Calcium toxicity

- The most common causes are malignancy and primary hyperparathyroidism.
- Drugs like thiazide diuretics, milk-alkali syndrome (now a days is rare).
- Hyperthyroidism, calcium supplements, excessive vitamin D, A and thyroid hormone.
- Hypercalciumic patients show signs of nausea, vomiting, abdominal pain, dyspepsia and anorexia.
- It may results in calcium-phosphate and calcium-oxalate stones.

Iron

- is one of the most abundant metals on Earth.
- It is essential to most life forms and to normal human physiology.
- Iron is found in human in association with many proteins such as hemoglobin and myoglobin.
- Almost two-thirds of iron in the body is found in hemoglobin.
- Hemoglobin is the protein in RBC'S that carries oxygen to tissues.
- Small amount of iron is present in myoglobin, a protein that helps supply oxygen to muscle.



Iron in heme

- Another small amount available in enzymes for biochemical reactions and storage.

Sources of iron

There are two types of iron.

A- Heme iron and nonheme iron.

B- Heme iron is derived from hemoglobin.

- Animal foods are the source of heme iron such as liver, meat, fish, poultry.
- Plant foods like lentils and beans provide us with nonheme iron.
- Nonheme iron is the form of iron added to iron-enriched and iron-fortified foods.

- Heme iron is absorbed better than nonheme iron.
- Many factors can influence the absorption of iron.

1- Storage levels of iron have the greatest influence on iron absorption.

2- Type of dietary iron consumed.

- Absorption of heme iron ranges from 15% to 35%, and is not significantly affected by diet.
- Nonheme iron absorption is poor and is significantly influenced by various food components
- Presence of meat and vitamin C will increase nonheme absorption and decreased by tea and antacids and tetracycline antibiotics.

Recommended Daily Allowance (RDA)

- 11 mg/day for infants (7-12 months).

(Breast milk provides 50% of iron needs)

- 11 mg/day for men age from 14-18 years.
- 15 mg/day for women age from 14-18 years.
- 8 mg/day for men from 19 and older.
- 18 mg/day for women from 19 to 50.

Functions of iron in the body

- iron is an essential component of proteins involved in oxygen transport.
- It is also essential for the regulation of cell growth and differentiation.
- It is important to the function of many enzymes involved in the body's energy generation system.
- Iron is stored in spleen, bone marrow and liver.

Iron deficiency

- The World Health Organization considers iron deficiency the number one nutritional disorder in the world.
- Around 80% of the world's population may be iron deficient, while 30% may have iron deficiency anemia.
- Iron deficiency develops gradually.
- Iron deficiency anemia is an advanced stage of iron depletion.
- It is characterized by small RBC’s and pale in color.

- It occurs when storage sites of iron are deficient and blood levels of iron cannot meet daily needs.
- Blood hemoglobin levels are below normal with iron deficiency anemia.
- Physicians often measure serum ferritin, the storage form of iron.
- A serum ferritin level less than or equal to 15 micrograms per liter confirms iron deficiency anemia in women, and suggests a possible need for iron supplementation.
- Iron deficiency anemia can be associated with low dietary intake of iron, inadequate absorption of iron, or excessive blood loss.

Individuals who may at a risk of developing iron deficiency anemia:

a. Women of childbearing age.

b. pregnant women.

c. preterm and low birth weight infants.

d. older infants, toddlers and teenage girls.

e. Women with heavy menstrual losses.

f. kidney failure patients, especially those being treated with dialysis.

g. vitamin A deficiency.

h. GIT problems.

Signs of iron deficiency anemia

1- Feeling tired and weak.

2- Heart palpitations on exertion.

3- Irritability.

4- Pale in appearance.

5- Inflammation of lips and tongue.

- Iron supplements may be recommended to the above mentioned groups of individuals.

- Supplemental iron is available in two forms: ferrous and ferric.
- Ferrous iron salts (ferrous fumarate, ferrous sulfate, and ferrous gluconate) are the best absorbed forms of iron supplements.
- iron supplement is usually taken in two or three equally spaced doses.
- Iron from enteric coated or delayed-release preparations may have fewer side effects, but is not as well absorbed and not usually recommended.

Individuals who should not take iron supplements:

1- People with normal level of iron (old men and postmenopausal women).

2- People with hemochromatosis.

3- Individuals with blood disorders that require frequent blood transfusions.

Iron toxicity

- There is considerable potential for iron toxicity because very little iron is excreted from the body.
- In children, death has occurred from ingesting 200 mg of iron.
- It is important to keep iron supplements tightly capped and away from children's reach.
- Doses of iron prescribed for iron deficiency anemia in adults are associated with constipation, nausea, vomiting, and diarrhea, especially when the supplements are taken on an empty stomach.