VITAMINS B6 & B12

Color Index:

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- Only in girls' slides
- Only in boys' slides

Editing File

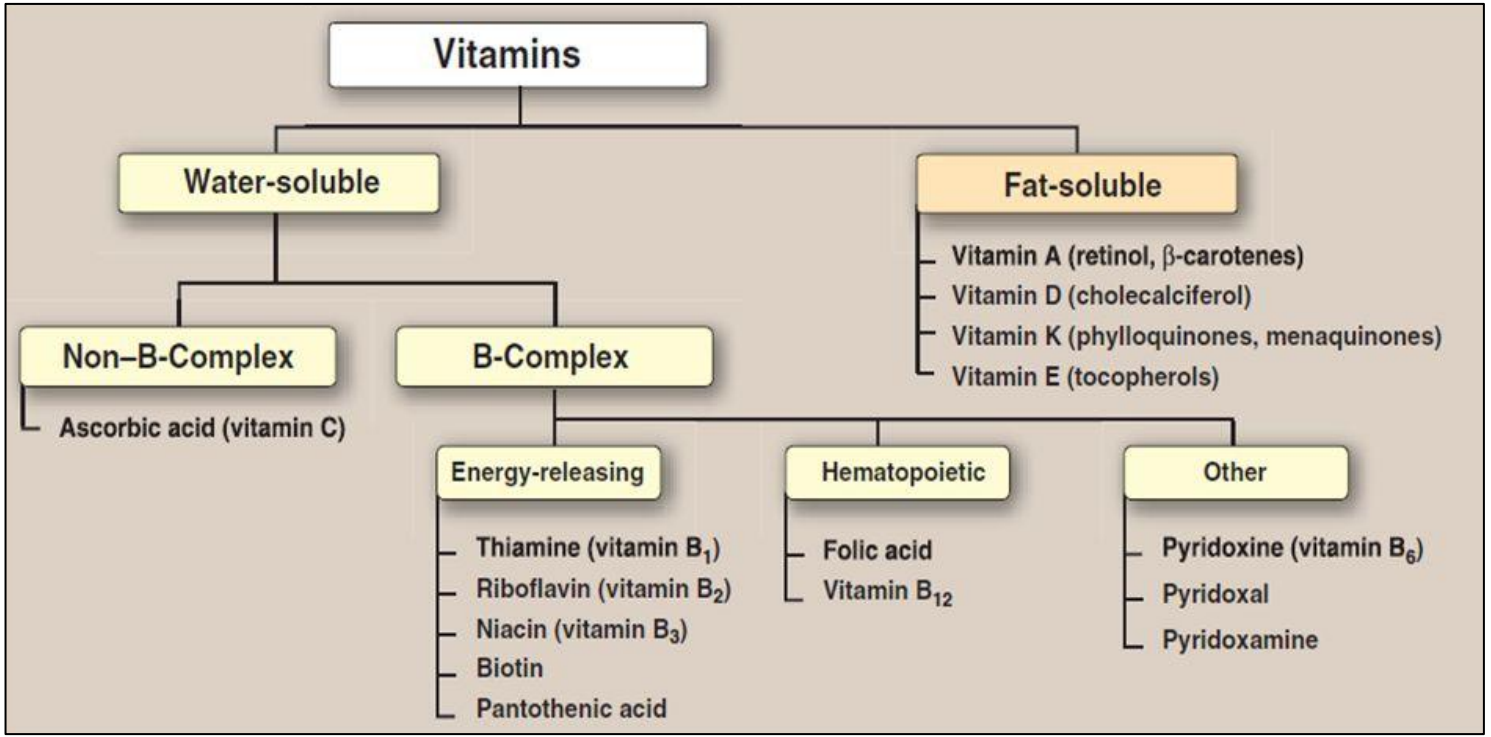
Objectives:

- Understand the types and functions of vitamins B_6 and B_{12}.
- Recognize the role of these vitamins in maintaining the myelin sheath of nerves and their function.
- Discuss the consequences of vitamin B_6 and B_{12} deficiency that can lead to nerve degeneration and irreversible neurological damage.

Overview:

- Types and functions of vitamins B_6 and B_{12}.
- Disorders due to vitamins B_6 and B_{12} deficiency.
- Vitamin B_{12} deficiency and folate trap.
- Demyelination, neuropathy and neuropsychiatric symptoms of Vitamin B_{12} deficiency.

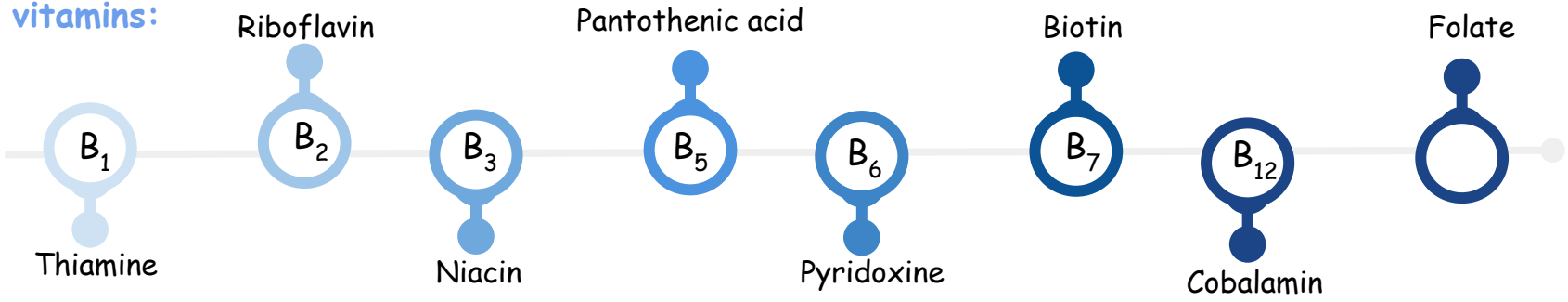
Classification of Vitamins



★ Fat soluble vit (AKED اكيد) stored in adipose tissue and liver
★ Water soluble usually NOT stored in the body except vit B_{12} which is stored in the liver

Water-Soluble Vitamins

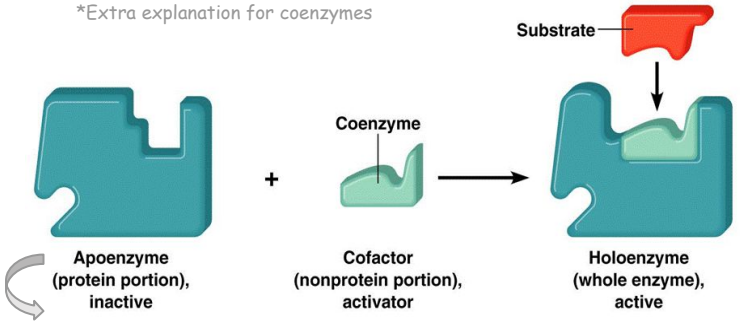
★ **B vitamins:**



★ **vitamins B complex**

1. Present in small quantities in different types of food
2. Important for growth and good health
3. Help in various biochemical processes in cell
4. Function as coenzymes
5. Not significantly stored in the body except vit B_{12} (in the liver)
6. Must be supplied regularly in the diet
7. Excess excreted

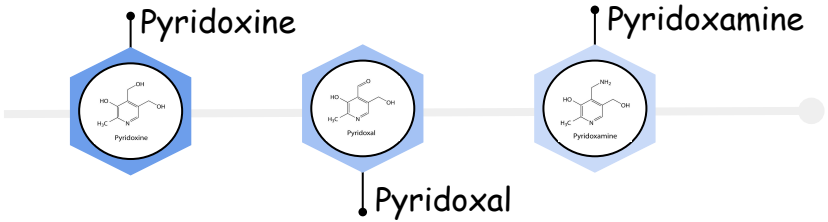
*Extra explanation for coenzymes



Non functional enzyme that needs to bound to non - protein coenzyme or cofactor

Vitamin B_6

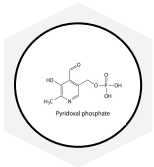
★ Three forms:



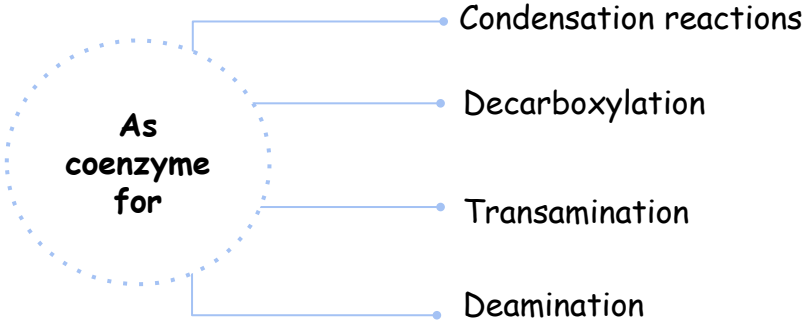
* Pyridoxine is a plant source while pyridoxal and Pyridoxamine are animal sources

Active form

All 3 are converted to pyridoxal phosphate (PLP)



★ Function:



Dr explains | **Pyridoxal phosphate:**

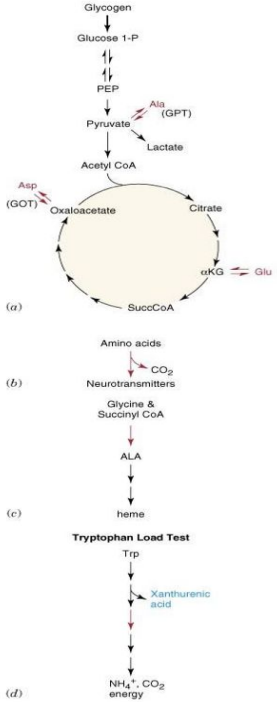
Some metabolic roles played by pyridoxal phosphate "vit B6" in metabolism:

A) **During krebs cycle you need PLP for:**
- Conversion of alanine to pyruvate and vice versa.
- Conversion of alpha ketoglutarate to glutamate and vice versa.
- Conversion of aspartic acid to oxaloacetate and vice versa.
(All of these reactions are transamination)

B) **Amino acids are decarboxylated with the help of PLP to synthesize neurotransmitters.**

C) **Glycine and succinyl CoA are conjoined together with the help of PLP to ultimately make heme.**

D) **Tryptophan load test:**
- While degrading tryptophan "an amino acid" the body makes Xanthurenic acid in one of the steps.
- To degrade Xanthurenic acid, the body requires vit B6.
- So in case of vit B6 deficiency, there will be accumulation of XAnthurenic acid.
- So using this information, if we want to test for vit B6 deficiency, we give the patient a big load of tryptophan, then measure the Xanthurenic acid they produce,accumulation of it points to vit B6 deficiency.



Don't memorize the structure
Knowing which molecule give rise to which and where is the decarboxylation that is IMPORTANT.

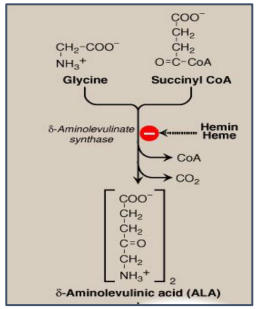
Vitamin B_6

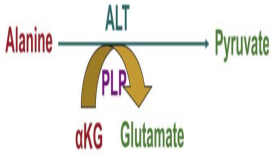
Reactions require Vitamin B_6

1) Condensation Reaction

Formation of **ALA** by **ALA synthase**, The regulatory step in hemoglobin synthesis

- **Glycine and succinyl CoA** condense in the presence of the enzyme **delta aminolevulinate synthase** (ALA synthase) to form **delta aminolevulinic acid** (ALA).
- This step is important in the **synthesis of heme.**
- Deficiency of B6 will lead to inhibition of heme synthesis → Hemoglobin deficiency → Anemia.
- This anemia is called **Sideroblastic anemia.**





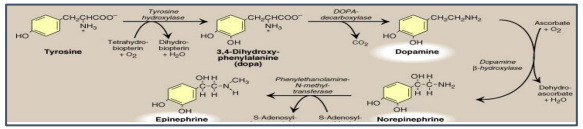
3) Transamination Reaction

- **Alanin** transfer its amino group to alpha ketoglutarate which then turns alpha ketoglutarate into **glutamate, and alanine to pyruvate.**
- Pyruvate then is converted to **acetyl CoA** and it enters TCA cycle.
- This reaction is **catalyzed** by **ALT** "alanine transaminase" which needs PLP.

2) Decarboxylation Reaction

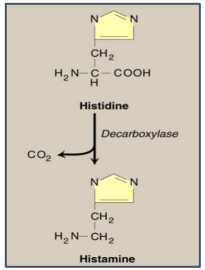
Formation of **Catecholamines**: Dopamine, norepinephrine and epinephrine

- **Tyrosine** is decarboxylated to **Dopamine** which is requires vit B_6.
- **dopamine gets converted to epinephrine and norepinephrine.**
- deficiency of vit B6 leads to deficiency of the 3 catecholamines.



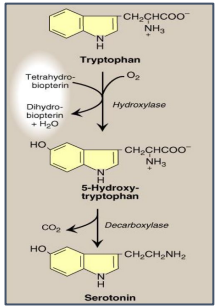
Formation of **histamine**

Decarboxylation of **histidine** to **histamine** requires vit B_6



Formation of **Serotonin**

Decarboxylation of **tryptophan** to **serotonin** requires vit B_6



Disorders of Vitamin B_6 Deficiency

Dietary deficiency is rare, but it is observed in:

- Newborn infants fed on formulas low in B_6
- Women on oral contraceptives[1]
- Alcoholics[1]

Isoniazid treatment for tuberculosis can lead to vit B_6 deficiency by forming inactive derivative with PLP

Deficiency leads to poor activity of PLP-dependent enzymes causing:

- Deficient amino acid metabolism
- Deficient lipid metabolism
- Deficient neurotransmitter synthesis:
  - ➔ Serotonin,epinephrine,norepinephrine and gamma-aminobutyric acid (GABA)

PLP is involved in the synthesis of sphingolipids
➔ Its deficiency leads to demyelination of nerves and consequent peripheral neuritis

Mild[2] deficiency Leads to	Severe deficiency leads to
➢ Irritability ➢ Nervousness ➢ Depression	➢ Peripheral neuropathy ➢ Convulsions

1. In these two cases, there is impairment of vit B_6 **absorption**
2. Mainly reverse if you give supplements

Vitamin B_{12}

Forms of Vitamin B_{12} (Cobalamin)

- **Cyanocobalamin**[1]
- **Hydroxycobalamin**[1]
- **Adenosylcobalamin** (major storage form in the liver)
- **Methylcobalamin**[2] (mostly found in blood circulation)

Coenzyme Forms of Vitamin B_{12} (Cobalamin)

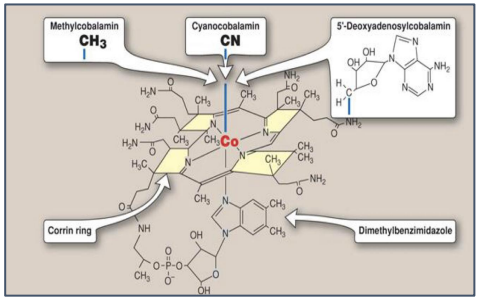
1. **Adenosylcobalamin**
2. **Methylcobalamin**

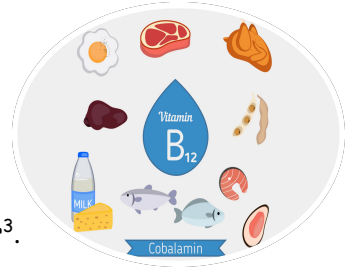
Coenzymes for metabolic reactions

Body can convert other cobalamins into active coenzymes.

Dr's notes| **Structure of cobalamin:**
- corrin ring with a cobalt in the center.
- the cobalt has a valency of 6 "can make 6 bonds".
- 4 of these bonds are with the pyrrole nitrogen of the corrin ring, one bond with dimethylbenzimidazole (DMZ) and the last bond is either with:

A) **methyl** group to make methylcobalamin
B) **cyanide** to make cyanocobalamin
C) **deoxyadenosine** to make 5-deoxyadenosylcobalamin





01 Mainly found in animal liver[3].

02 Bound to protein as
- **Methylcobalamin**[4] or
- **5'-deoxyadenosylcobalamin**[4]

03 Essential for normal nervous system function and red blood cell maturation.

04 Not synthesized in the body and must be supplied in the diet.

05 Binds to **intrinsic factor** (is a protein[5] secreted by cells in the stomach) and absorbed by the ileum.

1. Commercially synthesized form
2. Bound to vit. B binding protein or to trans-cobalamin

3. It is mainly synthesized by the bacteria present in guts.
4. These two forms are stored in the liver.
5. (Glycoprotein) required for the proper absorption of the vitamin B_{12}, so deficiency of intrinsic factor will lead to deficiency of vitamin B_{12}.

Vitamin B_{12} (Storage)

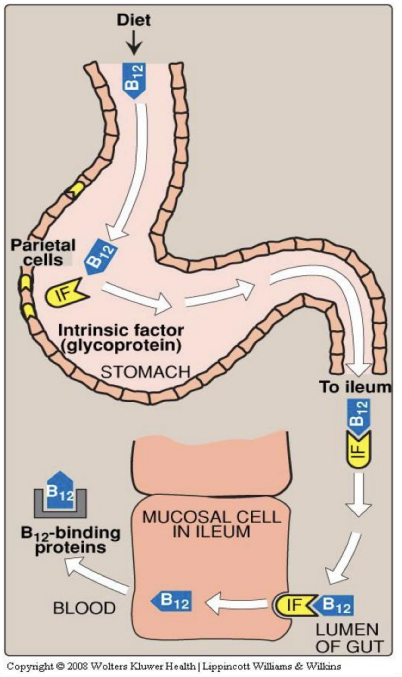
1. • **Liver** stores vitamin B_{12} (4-5 mg).

2. • Other B vitamins are not stored in the body.

3. • Vitamin B_{12} deficiency:
   is observed in patients with IF (intrinsic factor) deficiency due to autoimmunity[1] or by partial or total gastrectomy.
   - Clinical deficiency symptoms develop in several years.

Dr's notes| storage of Vitamin B12:

1. While eating, our salivary glands secrete a protein called **R protein**.
2. When the food reaches the stomach, the **acidity** of the stomach allows the R protein to bind to vitamin B_{12}.
3. In the intestine, the **pancreatic enzymes** act on the R protein and remove it from vitamin B_{12}.
4. Now that the vitamin B_{12} is free, it binds to the **intrinsic factor**, which is released from the parietal cells of the stomach.
5. Now vitamin B_{12} is ready for absorption.
6. Vitamin B_{12} and intrinsic factor complex bind to their special receptors present on the intestinal epithelial cells and it is taken inside the enterocytes.
7. From there the vitamin is thrown into the general circulation, bound to **trans-cobalamin** "B_{12} binding protein".
8. After that it goes to the liver to be stored.



1. They have antibodies against the parietal cells of the stomach, so synthesis of IF stops.

Vitamin B_{12} (Functions)

Two reactions that require B_{12}

A

Conversion of:
homocysteine to **methionine**

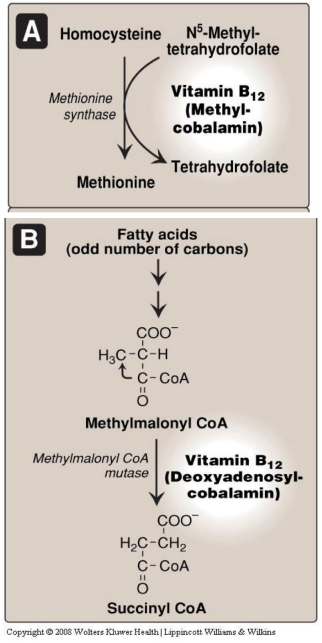
- **Methionine synthase** requires B_{12} in converting homocysteine to methionine.

Dr's notes|

- **Homocysteine** receives a methyl group and gets converted to **methionine**. now where does this methyl group come from?
- from a molecule called **N^5-methyltetrahydrofolate:** when N^5-methyltetrahydrofolate gives its methyl to homocysteine it gets converted to **tetrahydrofolate**, the biologically active form of folic acid.

- In case of deficiency of vitamin B_{12}:

1. **tetrahydrofolate will not be synthesized,** which will lead to: folic acid deficiency and the synthesis of purine and thiamine stops, which in turn stops DNA synthesis. this greatly affects Red blood cell synthesis, and the patient gets megaloblastic anemia.
2. **Accumulation of N^5-methyltetrahydrofolate** Which is also called folate trap, because folate is trapped in that form and is not converted to tetrahydrofolate the active form, so the body can't use it. "explained next slide"



B

Conversion of:
propionyl-CoA to **succinyl-CoA**

- The enzyme in this pathway, **methylmalonyl-CoA mutase**, requires B_{12}.

Dr's notes| **Steps:**

1. Usually when fatty acids are being metabolized or broken down, they are broken down into 2 carbon molecules "during β-oxidation".
2. If I have an odd number of carbons in a fatty acid, I will end up with a 3 carbon molecule called **propionyl-CoA**.
3. Propionyl-COA gets converted to **methylmalonyl COA**.
4. Methylmalonyl CoA is converted to **succinyl CoA** by the enzyme methylmalonyl CoA mutase, this enzyme requires vitamin B_{12} in the form of "deoxyadenosylcobalamin" for its activity.
5. Deficiency in this vitamin will lead to deficiency in succinyl CoA and accumulation of methylmalonyl-CoA in the membrane of neurons.

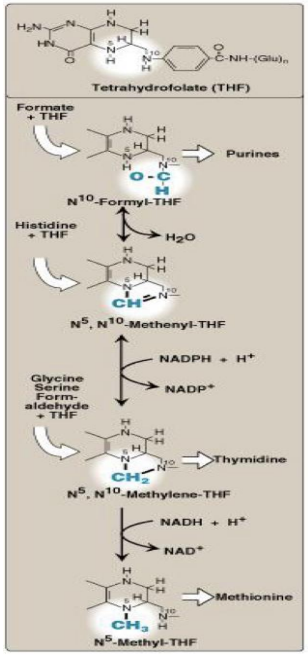
Vitamin B_{12} (Deficiency & Folate trap)

Folate Trap:

1. Homocysteine re-methylation reaction is the only pathway where **N^5-methyl TH4** can be returned back to tetrahydrofolate pool.
2. Hence folate is trapped as:
   - **N^5-methyltetrahydrofolate** (folate trap).
3. This leads to folate deficiency and deficiency of other TH4 derivatives: (**N^5 -N^{10}methylene TH4 & N^{10} formyl TH4**) required for purine and pyrimidine synthesis.

☆ **N^{10} formyl TH4** is required for purine synthesis
☆ **N^5 -N^{10}methylene TH4** is required for thymidine synthesis
☆ **N^5-methyl TH4** is required for methionine synthesis

Interconversion between TH4 carrier of "one-carbon units"



TH4: tetrahydrofolate
- Due to trapping of TH4 all of these reactions can't go on
- The functional form of folate is tetrahydrofolate.
- Folate is trapped because it can not be converted to the active form while it exists as inactive form

Disorders

Pernicious anemia:
- Megaloblastic anemia
- Vitamin B_{12} deficiency is mainly due to the deficiency of intrinsic factor.

Demyelination:
- Myelin sheath of nerves is chemically unstable and damaged. "because of accumulation of methylmalonyl-CoA"

Neuropathy:
- Peripheral nerve damage.

Vitamin B_{12} (Deficiency)

Causes of neuropathy:

1. Deficiency of vitamin B_{12} leads to accumulation of **methylmalonyl CoA**.
2. High levels of methylmalonyl CoA are used instead of **malonyl CoA** for fatty acid synthesis.
3. Myelin synthesized with these abnormal fatty acids is unstable and degraded causing neuropathy.

In a normal sphingomyelin contains two fatty acids and they are synthesized by malonyl CoA but because of the accumulation of methylmalonyl CoA the sphingomyelin will be made from methylmalonyl CoA making them unstable and degraded causing neuropathy.

Neurological and psychiatric Symptoms Of vit B12 deficiency

Neurological:

1. Paraesthesia (abnormal sensation) of hands and feet.
2. Reduced perception of vibration and position.
3. Absence of reflexes.
4. Unsteady gait and balance (ataxia).

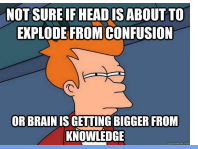
Psychiatric:

1. Confusion and memory loss.
2. Depression.
3. Unstable mood.

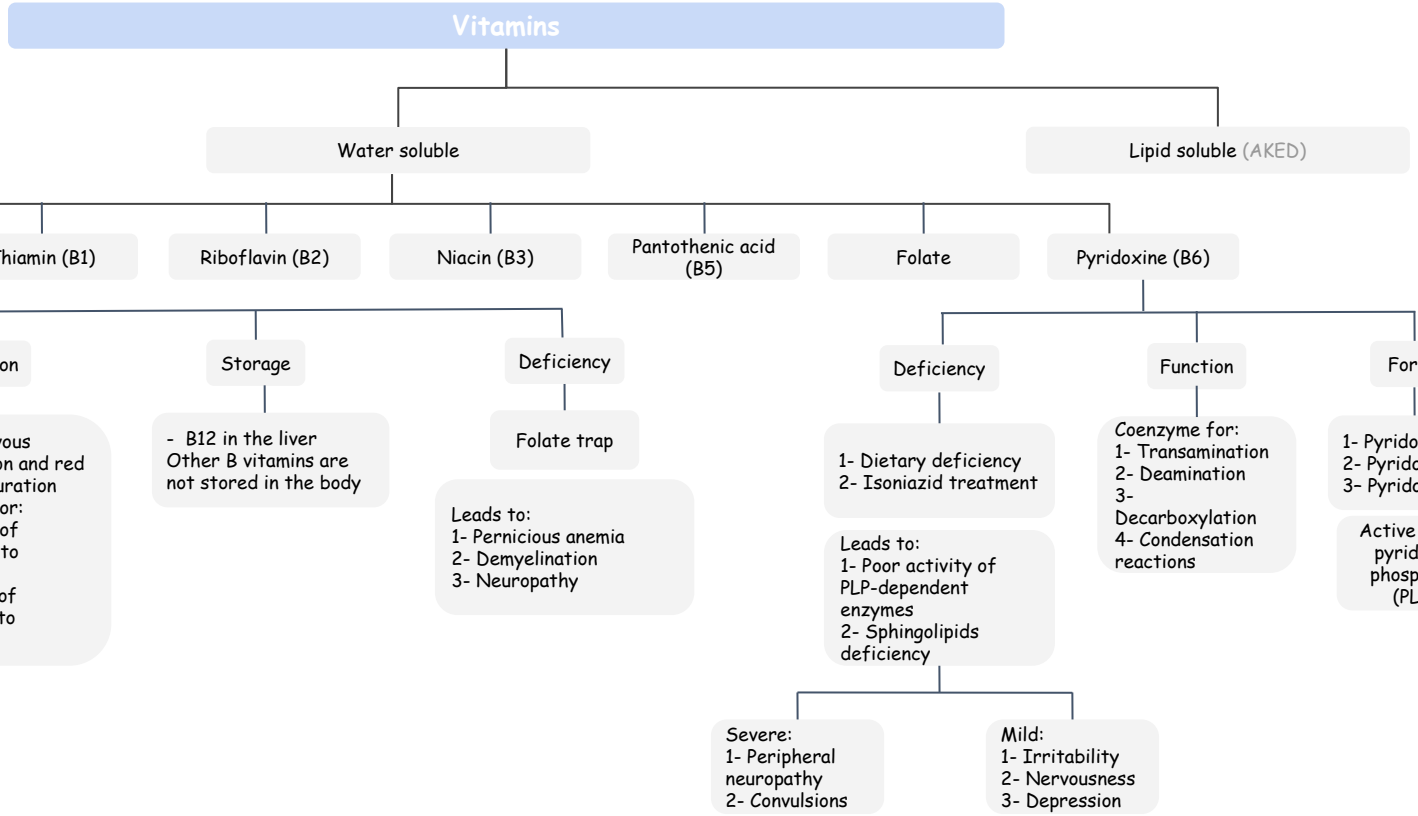
- Anemia is also the most common symptom of vitamin B_{12} deficiency, if you supply the patient with folic acid you treat the anemia.
- Patients who have done gastric bypass, and those with pancreatic insufficiency are at risk for vitamin B12 deficiency.

Take Home Messages

- Vitamins B_6 and B_{12} are essential in maintaining the nerve function and the central nervous system.
- Various neurological symptoms have been associated with their deficiency.



Summary


Vitamins
Water soluble
Lipid soluble (AKED)
Cobalamin (B12)
Thiamin (B1)
Riboflavin (B2)
Niacin (B3)
Pantothenic acid (B5)
Folate
Pyridoxine (B6)
Forms
1- Cyanocobalamin
2- Hydroxycobalamin
3- Adenosylcobalamin (Active form)
4- Methylcobalamin (Active form)
Function
1- Normal nervous system function and red blood cell maturation
2- Coenzyme for:
A- Conversion of propionyl-CoA to succinyl-CoA
B- Conversion of homocysteine to methionine
Storage
- B12 in the liver
Other B vitamins are not stored in the body
Deficiency
Folate trap
Leads to:
1- Pernicious anemia
2- Demyelination
3- Neuropathy
Deficiency
1- Dietary deficiency
2- Isoniazid treatment
Leads to:
1- Poor activity of PLP-dependent enzymes
2- Sphingolipids deficiency
Severe:
1- Peripheral neuropathy
2- Convulsions
Mild:
1- Irritability
2- Nervousness
3- Depression
Function
Coenzyme for:
1- Transamination
2- Deamination
3- Decarboxylation
4- Condensation reactions
Forms
1- Pyridoxine
2- Pyridoxal
3- Pyridoxamine
Active form: pyridoxal phosphate (PLP)

Quiz

MCQs :

Q1: Which of the following is a fat soluble vitamin?

a) Vit K **b)** Folic acid **c)** Vit B_{12} **d)** Vit C

Q2: The active form of vitamin B_6 is called:

a) Pyridoxine **b)** Pyridoxal **c)** Pyridoxal phosphate **d)** Pyridoxamine

Q3: Formation of histamine is a ..... reaction?

a) Condensation **b)** Deamination **c)** Decarboxylation **d)** Transamination

Q4: Mild deficiency of vit B_6 leads to which of the following?

a) Irritability **b)** Convulsions **c)** Depression **d)** Both A & C

Q5: Vitamin B_{12} bound to protein as:

a) Cyanocobalamin **b)** Methylcobalamin
c) 5'-deoxyadenosylcobalamin **d)** Bothe b&c

Q6: The major storage form of vitamin B_{12} in the liver:

a) Cyanocobalamin **b)** Hydroxocobalamin
c) Adenosylcobalamin **d)** Methylcobalamin

SAQs :

Q1: What are the reactions in which vitamin B_6 is a required coenzyme?

Q2: List some of the mild and severe manifestations of pyridoxine deficiency?

Q3: The two reactions that require vitamin B_{12}?

Q4: Mentions 2 neurological & psychiatric symptoms of vitamin B_{12} deficiency.

★ **MCQs Answer key:**

1) A 2) C 3)C 4) D 5) D 6) C

★ **SAQs Answer key:**

1) transamination, Deamination, Decarboxylation, condensation reaction
2)
- In mild cases:
1- irritability
2- nervousness and depression.
- In severe cases:
1- Peripheral neuropathy 2- convulsions
3) Conversion of:
  - **homocysteine** to **methionine** (*Methionine synthase*)
  - **propionyl-CoA** to **succinyl-CoA** (*methylmalonyl-CoA mutase*)
4)

- **Neurological symptoms:** Paraesthesia of hands and feet, Reduced perception of vibration & position, Absence of reflexes, Unsteady gait and balance (ataxia).
- **Psychiatric symptoms:** Confusion & memory loss, Depression, Unstable mood.

Team members

Girls Team:

- Ajeed Al-Rashoud
- Alwateen Albalawi
- Amira AlDakhilallah
- Arwa Al Emam
- Deema Almaziad
- Ghaliah Alnufaei
- Haifa Alwaily
- Leena Alnassar
- Lama Aldakhil
- Lamiss Alzahrani
- Nouf Alhumaidhi
- Noura Alturki
- Sarah Alkhalife
- Shahd Alsalamah
- Taif Alotaibi

Boys Team:

- Abdulrahman Bedaiwi
- Alkassem Binobaid
- Naif Alsolais
- Omar Alyabis
- Rayyan Almousa
- Sultan Alhammad
- Tariq Alanezi

Team Leaders

Lina Alosaimi

Mohannad Alqarni

★ Yesterday is not ours to recover, but tomorrow is ours to win or lose.

438 BIOCHEMISTRY TEAM

We hear you