Metals and Coenzymes in Clinical Biochemistry

Metals and vitamins play a crucial role in maintaining normal metabolic functions, **as shown in Table 1 below**.

Their absence or deficiency can lead to enzymatic dysfunction and various metabolic disorders.

1- Metals Acting as Enzyme Cofactors

1. Zinc (Zn^{2+})

Zn^{2+} (Zinc): A structural metal ion essential for the stability of enzymes such as carbonic anhydrase, which regulates acid–base balance.

- **Associated Enzyme:** Carbonic anhydrase, Alcohol dehydrogenase
- **Reaction:** $CO_2 + H_2O \rightleftharpoons H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$
- **Function:** Maintains acid–base balance and supports enzyme catalytic activity.
- **Deficiency:** Impaired growth delayed wound healing, and dermatitis.
- نقص: ضعف النمو، وتأخر التئام الجروح، والتهاب الجلد

2. Copper (Cu^{2+})

Cu^{2+} (Copper): Functions as a redox cofactor in cytochrome c oxidase within the respiratory chain.

- **Associated Enzyme:** Cytochrome c oxidase, Superoxide dismutase
- **Reaction:** $O_2 + 4H^+ + 4e^- \rightarrow 2H_2O$
- **Function:** Participates in oxidative phosphorylation and antioxidant defense.
- **Deficiency:** Anemia, depigmentation, neurological dysfunctions.
- نقص: فقر الدم، **نقص أو زوال الصبغة** من الجلد أو الشعر أو العينين.، الاختلالات العصبية.

3. Iron (Fe^{2+} / Fe^{3+})

Fe^{2+}/Fe^{3+} (Iron): Present in the heme structure of enzymes such as catalase and cytochromes, playing a key role in oxidation–reduction reactions.

- **Associated Enzyme:** Catalase, Cytochromes, Peroxidase
- **Reaction:** $2H_2O_2 \rightarrow 2H_2O + O_2$
- **Function:** Electron transfer in mitochondrial respiration and redox reactions.
- **Deficiency:** Microcytic anemia, fatigue, decreased immunity.
- نقص: فقر الدم الكريات الصغيرة، والتعب، وانخفاض المناعة

4. Magnesium (Mg^{2+})

Mg^{2+} (Magnesium): Stabilizes phosphate groups in ATP and acts together with kinases.

- **Associated Enzyme:** Kinases, ATPase, DNA polymerase
- **Reaction:** ATP + substrate → ADP + phosphorylated product
- **Function:** Stabilizes ATP and acts as a cofactor in phosphorylation reactions.
- **Deficiency:** Muscle weakness, arrhythmia, hypocalcemia.
- نقص: ضعف العضلات، عدم انتظام ضربات القلب، نقص كالسيوم الدم

5. Manganese (Mn^{2+})

Mn^{2+} (Manganese): Serves as a cofactor in Mn-superoxide dismutase (Mn-SOD), an antioxidant enzyme.

- **Associated Enzyme:** Manganese superoxide dismutase (Mn-SOD)
- **Reaction:** $2O_2^- + 2H^+ \rightarrow H_2O_2 + O_2$
- **Function:** Protects mitochondria from oxidative damage.
- **Deficiency:** Skeletal deformities, impaired glucose tolerance.
- نقص: تشوهات الهيكل العظمي، وضعف تحمل الكلوكوز

6. Selenium (Se)

Se (Selenium): Incorporated as selenocysteine in glutathione peroxidase, which removes toxic peroxides.

- **Associated Enzyme:** Glutathione peroxidase
- **Reaction:** $2GSH + H_2O_2 \rightarrow GSSG + 2H_2O$
- **Function:** Neutralizes hydrogen peroxide and lipid peroxides.
- **Deficiency:** Cardiomyopathy (Keshan disease), muscle weakness.
- نقصه: اعتلال عضلة القلب (مرض كيشان (وهو اعتلال عضلة قلب ناتج عن **نقص عنصر السيليني**))، ضعف العضلات.

7. Molybdenum (Mo)

Mo (Molybdenum): Exists in the form of a molybdopterin complex in xanthine oxidase, which participates in purine metabolism.

- **Associated Enzyme:** Xanthine oxidase, Sulfite oxidase
- **Reaction:** Hypoxanthine → Xanthine → Uric acid
- **Function:** Catalyzes oxidation of purines and sulfur metabolism.
- **Deficiency:** Rare but may cause neurological abnormalities.
- النقص: نادر؛ قد يسبب تشوهات عصبية.

2- Vitamins Acting as Coenzymes

1. Vitamin B_1 (Thiamine)

Vitamin B_1 (Thiamine): In the form of thiamine pyrophosphate (TPP), it functions in pyruvate dehydrogenase during oxidative decarboxylation reactions.

- **Coenzyme Form:** Thiamine pyrophosphate (TPP)
- **Enzyme:** Pyruvate dehydrogenase, α-Ketoglutarate dehydrogenase
- **Reaction:** $Pyruvate + CoA + NAD^+ \rightarrow Acetyl\text{-}CoA + CO_2 + NADH$
- **Deficiency:** *Beriberi, Wernicke–Korsakoff syndrome*
- نقص: مرض البري بري، متلازمة فيرنيكه كورساكوف(**وو** هي اضطراب عصبي ناتج عن **نقص فيتامين B_1 الثيامين** (يسبب **ارتباكًا، اضطراب التوازن، وفقدان الذاكرة**).

2. Vitamin B_2 (Riboflavin)

Vitamin B_2 (Riboflavin): A component of FAD and FMN in enzymes such as succinate dehydrogenase, responsible for electron transfer.

- **Coenzyme Form:** FAD, FMN
- **Enzyme:** Succinate dehydrogenase
- **Reaction:** Succinate + FAD → Fumarate + $FADH_2$
- **Deficiency:** *Cheilosis, glossitis, dermatitis*
- نقص:التهاب الشفة الزاوي، التهاب اللسان، التهاب الجلد

3. Vitamin B_3 (Niacin)

Vitamin B_3 (Niacin): Forms NAD^+ and $NADP^+$, which participate in oxidation and reduction reactions.

- **Coenzyme Form:** NAD^+, $NADP^+$
- **Enzyme:** Lactate dehydrogenase
- **Reaction:** Lactate + NAD^+ → Pyruvate + NADH + H^+
- **Deficiency:** *Pellagra (dermatitis, diarrhea, dementia)*
- نقص: البلاجرا (التهاب الجلد، الإسهال، الخرف)

4. Vitamin B_5 (Pantothenic Acid)

Vitamin B_5 (Pantothenic acid): A component of coenzyme A (CoA), required for the formation of acyl-CoA in fatty acid activation.

- **Coenzyme Form:** Coenzyme A (CoA)
- **Enzyme:** Acyl-CoA synthetase
- **Reaction:** Fatty acid + ATP + CoA → Acyl-CoA + AMP + PP_i
- **Deficiency:** *Fatigue, hypoglycemia, impaired fatty acid metabolism.*
- النقص: التعب، نقص السكر في الدم، ضعف استقلاب الأحماض الدهنية.

5. Vitamin B_6 (Pyridoxine)

Vitamin B_6 (Pyridoxine): In the form of pyridoxal phosphate (PLP), acts in transaminases for amino acid metabolism.

- **Coenzyme Form:** Pyridoxal phosphate (PLP)
- **Enzyme:** Transaminases (ALT, AST)
- **Reaction:** Amino acid + α-Ketoglutarate ⇌ Keto acid + Glutamate
- **Deficiency:** *Microcytic anemia, seizures, depression*
- نقصه: فقر الدم الكريات الصغيرة، نوبات، اكتئاب

6. Vitamin B_7 (Biotin)

Vitamin B_7 (Biotin): Acts as a coenzyme for carboxylases, binding carbon dioxide (CO_2).

- **Coenzyme Form:** Biocytin
- **Enzyme:** Carboxylases (Pyruvate carboxylase)
- **Reaction:** Pyruvate + CO_2 + ATP → Oxaloacetate + ADP + Pi
- **Deficiency:** *Dermatitis, alopecia, neurological symptoms*
- نقصه: التهاب الجلد، الثعلبة، الأعراض العصبية

7. Vitamin B_9 (Folic Acid)

Vitamin B_9 (Folic acid): In the form of tetrahydrofolate (THF), participates in one-carbon transfer reactions catalyzed by thymidylate synthase.

- **Coenzyme Form:** Tetrahydrofolate (THF)
- **Enzyme:** Thymidylate synthase, Serine hydroxymethyltransferase
- **Reaction:** Serine + THF → Glycine + Methylene-THF
- **Deficiency:** *Megaloblastic anemia, neural tube defects.*
- نقصه: فقر الدم الضخم الأرومات (فقر الدم يتميّز بوجود **خلايا دم حمراء غير ناضجة وكبيرة الحجم)** ، عيوب الأنبوب العصبي.

8. Vitamin B_{12} (Cobalamin)

Vitamin B_{12} (Cobalamin): In the form of methyl cobalamin, it acts with methionine synthase to transfer methyl groups.

- **Coenzyme Form:** Methyl cobalamin, Adenosyl cobalamin
- **Enzyme:** Methionine synthase, Methyl malonyl-CoA mutase
- **Reaction:** Homocysteine → Methionine
- **Deficiency:** *Pernicious anemia, neuropathy*
- نقصه: فقر الدم الخبيث، والاعتلال العصبي

9. Vitamin C (Ascorbic Acid)

Vitamin C (Ascorbic acid): Functions as ascorbate in prolyl hydroxylase for collagen synthesis.

- **Coenzyme Form:** Ascorbate
- **Enzyme:** Prolyl hydroxylase
- **Reaction:** Proline → Hydroxyproline (collagen synthesis)
- **Deficiency:** *Scurvy (bleeding gums, poor wound healing)*
- نقص: الاسقربوط (نزيف اللثة، ضعف التئام الجروح)

10. Vitamin K (Phylloquinone / Menaquinone)

Vitamin K: In its hydroquinone form, it serves as a cofactor for γ-carboxylase, responsible for the activation of blood clotting factors.

- **Coenzyme Form:** Vitamin K hydroquinone
- **Enzyme:** γ-Glutamyl carboxylase
- **Reaction:** Glutamate → γ-Carboxyglutamate (clotting factors II, VII, IX, X)
- **Deficiency:** *Bleeding tendency, prolonged PT.*
- النقص: ميل للنزيف، PT طويل الأمد.

As shown in Table 1, several important enzyme cofactors, including essential metals and vitamin-derived coenzymes, are listed along with their representative enzymes and the types of reactions in which they participate.

Table 1: Metals and vitamins as cofactors and coenzymes with their enzymatic functions

Metal--Vitamin	Cofactor/ Coenzyme	Representative Enzyme	Function
Zn^{2+}	Structural metal ion	Carbonic anhydrase	Acid-base balance
Cu^{2+}	Redox cofactor	Cytochrome c oxidase	Electron transport
Fe^{2+}/Fe^{3+}	Heme iron	Catalase, Cytochromes	Oxidation-reduction
Mg^{2+}	Metal ion stabilizer	Kinases	ATP binding
Mn^{2+}	Cofactor	Mn-SOD	Antioxidant defense
Se	Selenocysteine	Glutathione peroxidase	Detoxifies peroxides
Mo	Molybdopterin complex	Xanthine oxidase	Purine metabolism
vitamins			
Vitamin B_1 (Thiamine)	Thiamine pyrophosphate (TPP)	Pyruvate dehydrogenase; aldehyde transfer	Oxidative decarboxylation
Vitamin B_2 (Riboflavin)	Flavin mononucleotide (FMN); Flavin adenine dinucleotide (FAD)	Succinate dehydrogenase	Electron transfer; oxidation–reduction
Vitamin B_3 (Niacin)	NAD^+; $NADP^+$	Dehydrogenases	Redox reactions
Vitamin B_5 (Pantothenic acid)	Coenzyme A (CoA)	Acyl-CoA synthetase	Acyl group activation and fatty acid metabolism
Vitamin B_6 (Pyridoxine)	Pyridoxal phosphate (PLP)	Transaminases	Amino acid metabolism and transamination
Vitamin B_7 (Biotin)	Biotin	Carboxylases	CO_2 activation and fixation (carboxylation reactions)
Lipoic acid	Lipoamide	Oxidative decarboxylation enzymes	Acyl group activation; redox reactions
Vitamin B_9 (Folic acid)	Tetrahydrofolate (THF)	Thymidylate synthase	One-carbon transfer in nucleotide synthesis
Vitamin B_{12} (Cobalamin)	Adenosylcobalamin; Methylcobalamin	Methionine synthase	Isomerization and methyl group transfer
Vitamin C (Ascorbic acid)	Ascorbate	Prolyl hydroxylase	Collagen synthesis
Vitamin K	Hydroquinone form	γ-Carboxylase	Blood coagulation (activation of clotting factors)

Regulation of Enzyme Activity:

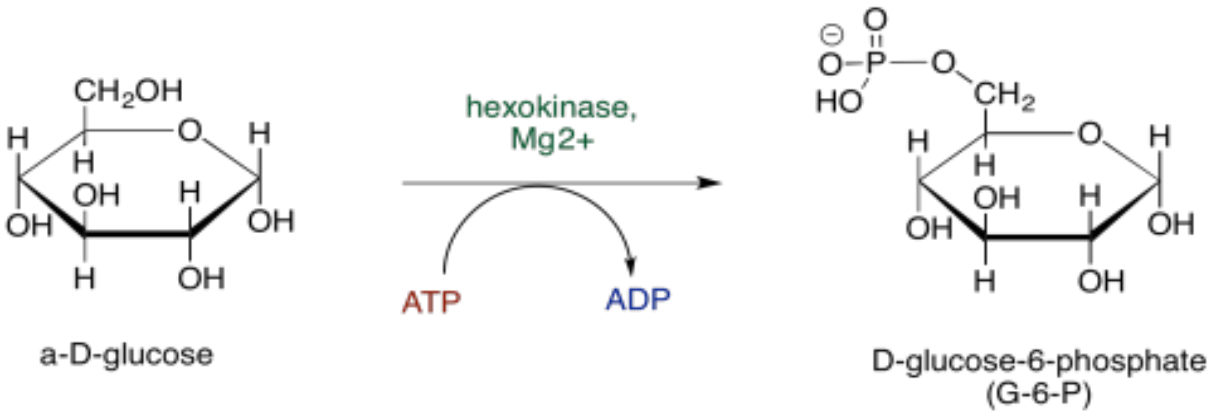
Regulation of enzyme activity is essential for metabolism

1- Substrate-Level Control

The substrates and products of each enzyme-catalyzed reaction interact directly with the enzyme to regulate it.

A kinetics study shows that increased substrate concentrations accelerate reactions until enzyme saturation.

As an example, consider the first step in glycolysis (see Chapter 13)—the phosphorylation of glucose to yield glucose-6-phosphate (G6P):



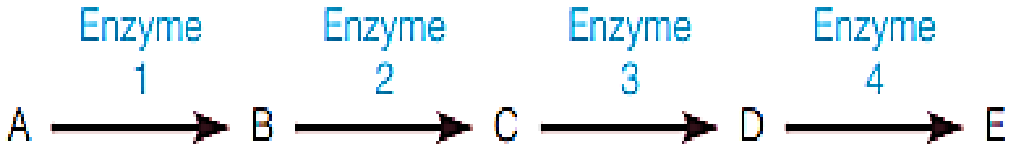
Hexokinase catalyzes this reaction and is inhibited by its product, glucose-6-phosphate (G6P). If any subsequent steps in glycolysis are blocked, G6P will accumulate and bind to hexokinase. This results in the inhibition of hexokinase and slows down further production of G6P from glucose.

In many cases, the reaction product binds the enzyme's active site and acts as a competitive inhibitor. Hexokinase is an interesting example because the product (G6P) can act as a competitive inhibitor (by binding to the enzyme's active site) and an uncompetitive inhibitor (by binding at another site on the enzyme).

2- *Feedback Control*

Feedback control is important in the efficient regulation of complex metabolic pathways.

The metabolic pathways resemble assembly lines. The simplest metabolic assembly line looks like this:

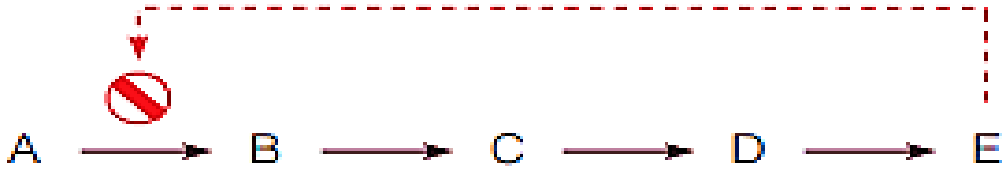


Where **A** represents the initial reactant or raw material (crud), **B**, **C**, and **D** represent intermediate products, and **E** represents the final product.

This pathway's end product **(E)** may be employed in another path, and **A** may be used in other processes. Consider that E's utilization slows. As previously pathway, E would accumulate, and A would be consumed. But this process is inefficient.

A more efficient process would solve this problem by closely monitoring E concentration and, when E accumulates, sending a signal to prevent its production. The cell can control the generation of the final product through activation (⬆) or inhibition (⊘) of a critical step in the pathway.

It would be most efficient to slow down the first step, converting A to B ($A \rightarrow B$). So, the "machine" should be regulated by the concentration of E.

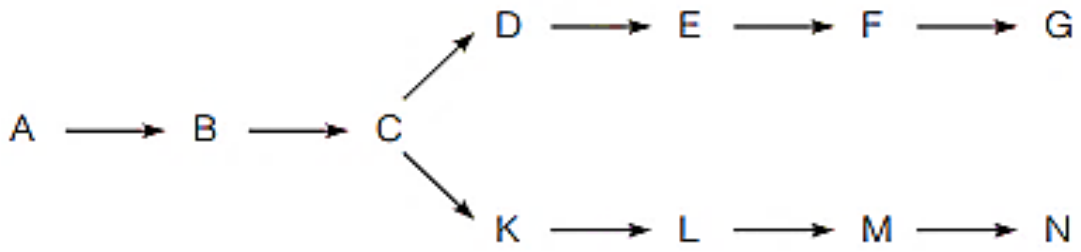


This type of feedback control is called feedback inhibition because an increase in the concentration of E leads to a decrease in its production rate.

Note that inhibiting the first step prevents unwanted utilization of A and accumulation of E.

3- *Substrate is fed into two pathways*

Other metabolic situations require more complicated patterns in which activation and inhibition may be useful. For example, consider a slightly more complex case in which ***A is fed into two pathways***, which leads to two products needed in roughly equivalent amounts. Then, a scheme like the following emerges:



To control the pathways so that **G and N** keep in balance, high concentrations of G might inhibit the C ⟶ D enzyme or activate C ⟶ K enzyme. Conversely, high concentrations of N might inhibit C ⟶ K enzyme or activate the C ⟶ D enzyme.

An example of this kind of control is found in the synthesis of the purine and pyrimidine monomers that go into making DNA, because approximately equal quantities of all four deoxyribonucleotides are required for DNA replication.