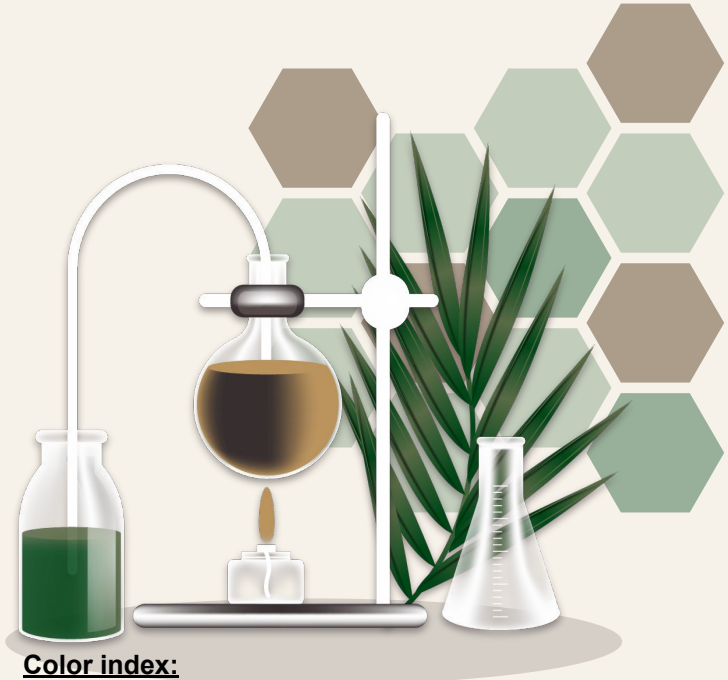
BIOCHEMISTRY

Creatinine Metabolism and Collagen Diseases



Color index:
-Main text -Girls' slides -Boys' slides
-Important - Dr's notes -Extra

Editing File

Objectives

By the end of this lecture, the first year students will be able able to:

- Study the importance of creatine in muscle as a storage form of energy
- Understand the biosynthesis of creatine
- Study the process of creatine degradation and formation of creatinine as an end product
- Understand the clinical importance of creatinine as a sensitive indicator of kidney function
- Study the structure, function, types, and biosynthesis of collagen
- Understand different diseases associated with collagen

Creatine Metabolism & Biosynthesis

Three amino acids are required for creatine biosynthesis:

- Glycine
- Arginine
- Methionine (as S-adenosylmethionine)

Sites of creatine biosynthesis:

- Kidney (first step)
- Liver (second step)

amino acids and enzymes are very important for MCQ or SAQ. For SAQ, you might be given this picture with blanks and you have to name enzymes or amino acids.

Enzymes required for creatine biosynthesis:

- Amidinotransferase (in kidney)
- Methyltransferase (in liver)

End product

Energy source

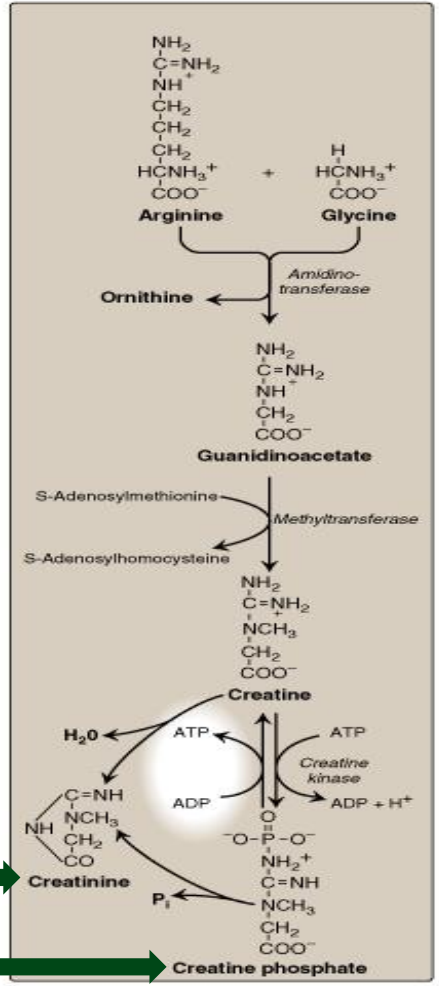
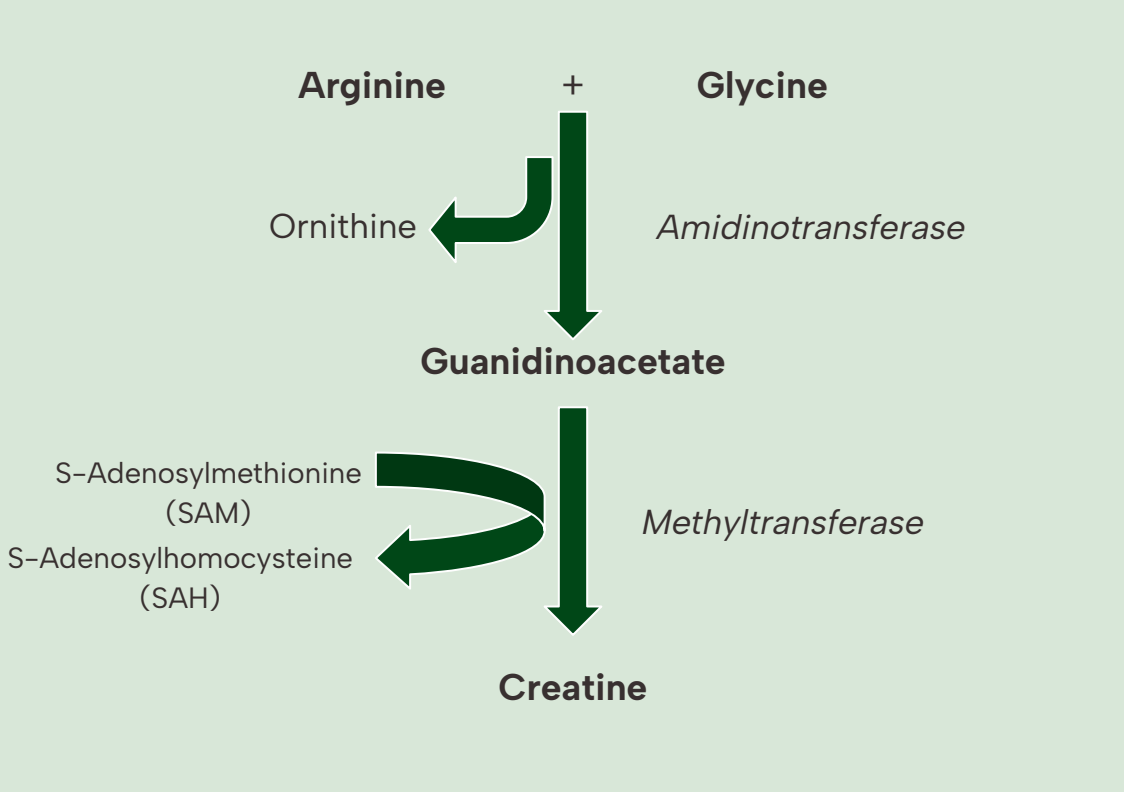


Figure 21.16
Synthesis of creatine.

Creatine Biosynthesis

Kidney

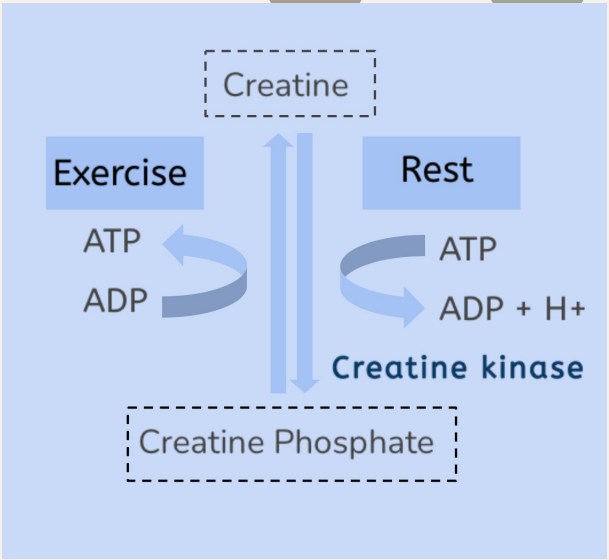
Liver



441: Arginine exists intensively in the kidneys: that's why the first reaction takes place in the kidney. Whereas GAA exists intensively in the liver: that's why the second reaction takes place in the liver.

Distribution of body creatine

- Transported from the liver to other tissues
- 98% present in skeletal and cardiac muscles
- In skeletal muscles, it's converted to high energy creatine phosphate (phosphocreatine)



Creatine phosphate

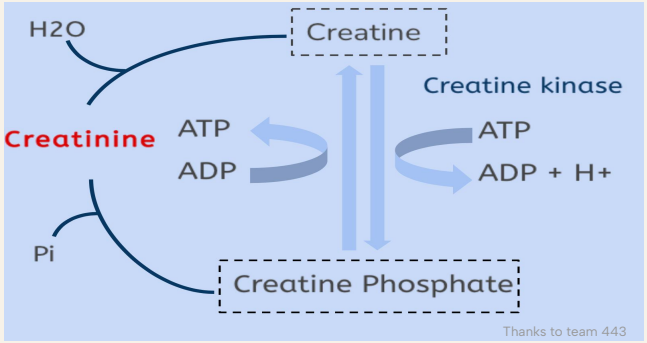
- A high-energy phosphate compound
- Acts as a storage form of energy in muscles
- Proves **small but ready** source of energy during first few seconds of intense muscular contraction
- The amount of creatine phosphate in the body is proportional to the mass

443 notes:It is stored in the muscle and when sudden intense muscle contraction is needed, creatine phosphate gives the energy immediately
Why does the body make creatine phosphate? Because muscle fibers can't store s lot of ATP so it stores creatine phosphate for the body's need of quick energy source bc the creatine phosphate group is given to ADP to make ATP

Creatine degradation

- Creatine and creatine phosphate **spontaneously** form creatinine as an end product.
- Creatinine is excreted in the urine.
- Serum creatinine is a sensitive indicator of kidney disease (kidney function test).
- Serum creatinine increase with impairment of kidney function.

Urine ← Glomerular filtration ← Plasma ←



Urinary creatinine

- A typical male excretes about 15 mmol creatinine/day
- Decrease in muscle mass (in muscular dystrophy or paralysis) leads to decrease level of urinary creatinine
- The amount of creatinine in urine is used as an indicator for the proper collection of **24 hour** urine sample
- The level of creatinine depends on muscle mass, gender, and age

Creatine Kinase (CK) (This enzyme is important)

- CK is responsible for the generation of energy in contractile muscle tissues
- CK level change in cardiac and skeletal muscle disorders

Overview of collagen

Most abundant protein in the human body

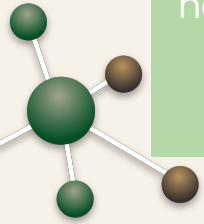
Highly stable molecule with a half-life as long as several years

Classified as fibrous protein that serves **structural function**

Part of structural function: CT, Bone, teeth, skin, cartilage, blood vessels, and tendons

Long rigid structure

There are 2 main classes of protein tertiary structure:
-Fibrous proteins: generally composed of long & narrow strands & have a structural role (they are something)
e.g. collagen
-Globular proteins: generally have more compact shape & have functional roles (they do something)
e.g. enzymes

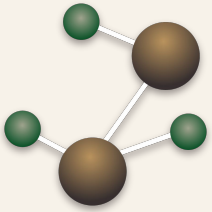


Collagen structure

- Collagen helix and α-helix are examples of **protein secondary structure** (collagen helix is not a type of α- helix)
- Collagen consists of three α-chains wound around one another in a rope-like triple helix & are held together by hydrogen bonds
- Collagen α-chain (~1000 amino acids long) is rich in **glycine** and **proline**
- The glycine residues are part of a repeating sequence
- -Gly-X-Y- (this can come in MCQ, like "what does X mean?")
- X = frequently proline
- Y = often hydroxyproline (can also be hydroxylysine)
- (-Gly-Pro-Hyp-) then 333 more of each so = 1000
- Proline prevents collagen chains to form α-helix (will form collagen helix instead) because: (this could come in SAQ)
- Proline has no backbone amino group (it is a ring structure with seconds amino group) therefore hydrogen bonding within the helix is not possible

NON-STANDARD AMINO ACIDS IN COLLAGEN

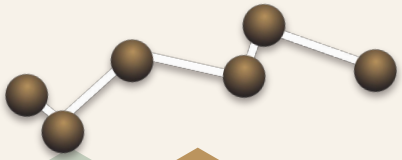
hydroxylase is very important



During post-translational modifications:
Proline and lysine are converted to hydroxyproline and hydroxylysine by Hydroxylase enzymes.

Hydroxylase requires Vitamin C (cofactor) for its function.

so deficiency in Vit. C leads to having inactivated enzymes therefore no functional Collagen. Such as many diseases osteoporosis in the bones and scurvy in the teeth.



TYPES OF COLLAGEN

Types of collagen depend on their function. Variations in the amino acid sequence of a-chains result in different properties.

Examples:

1. Type I: $(\alpha 1)_2\ \alpha_2$
2. Type II: $(\alpha)_3$

Fibril forming
Type I: Skin, bone, tendon,blood vessels and cornea
Type II: Cartilage, intervertebral disk and vitreous body
Type III: Blood vessels, skin and muscle.

Network forming	Fibril associated
Type IV: Basement membrane	Type IX: Cartilage
Type VIII: Corneal and vascular endothelium	Type XII: Tendon, ligaments, some other tissues

BIOSYNTHESIS OF COLLAGEN

I

Synthesized in fibroblasts, osteoblasts and chondroblasts.
Pre-Pro -> Pro -> Mature collagen

II

Polypeptide precursors are enzymatically modified to form triple helix.

III

Hydroxylation of proline and lysine residues.
(By **hydroxylase**)

IV

Glycosylation of some hydroxylysine residues with glucose or galactose.

V

Secreted from Golgi vacuoles into the extracellular matrix as procollagen.

VI

Cleaved by N- and C-procollagen peptidases (Dr said this enzyme is important) to release triple helical tropocollagen molecules.

BIOSYNTHESIS OF COLLAGEN (CONT'D)

1. Tropocollagen molecules spontaneously associate to form collagen, fibrils

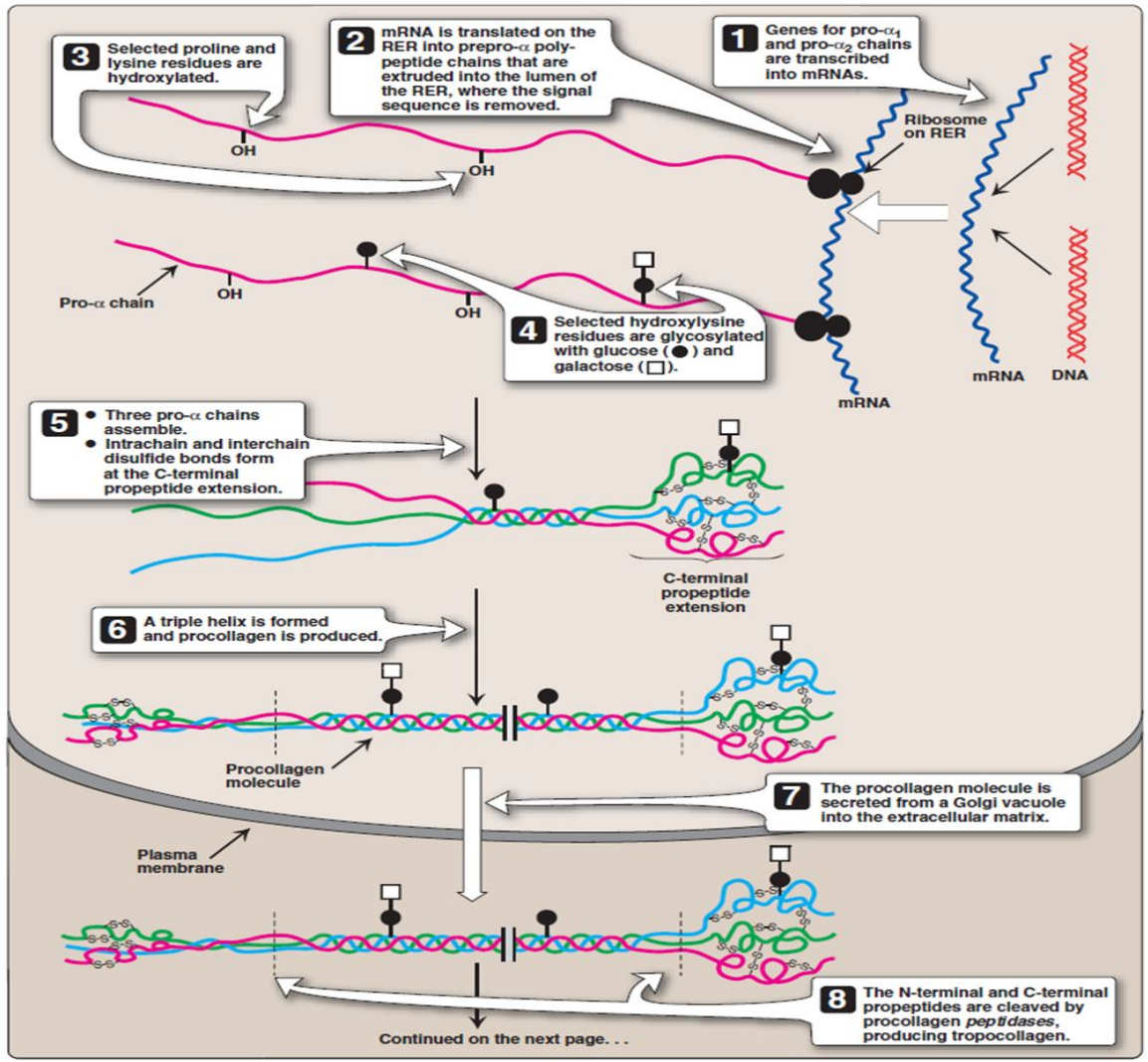
2. Lysyl oxidase (focuse on this enzyme) oxidatively deaminates some of the lysine & hydroxylysine residues in collagen.

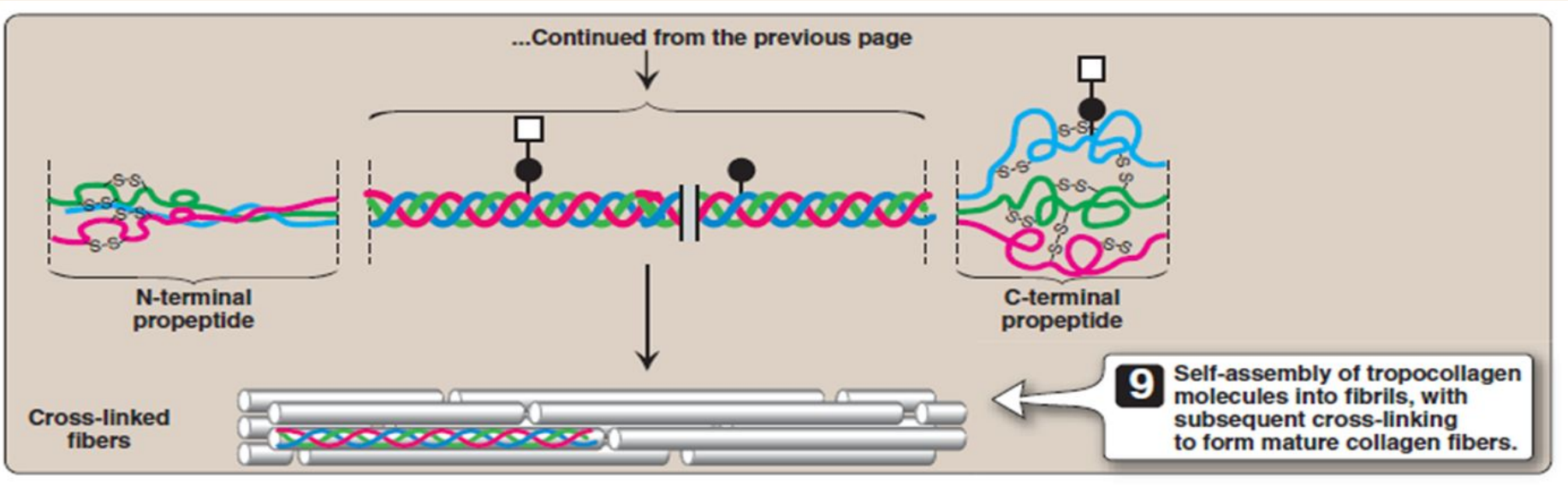
3. Reactive aldehydes (allysine & hydroxyalllysine) condense with lysine or hydroxylysine residues in neighbouring collagen molecules to form covalent cross-links.

4. This produces mature collagen fibrils.

The pictures on this slide and the next 2 are important for summary.

Don't Skip While Studying.

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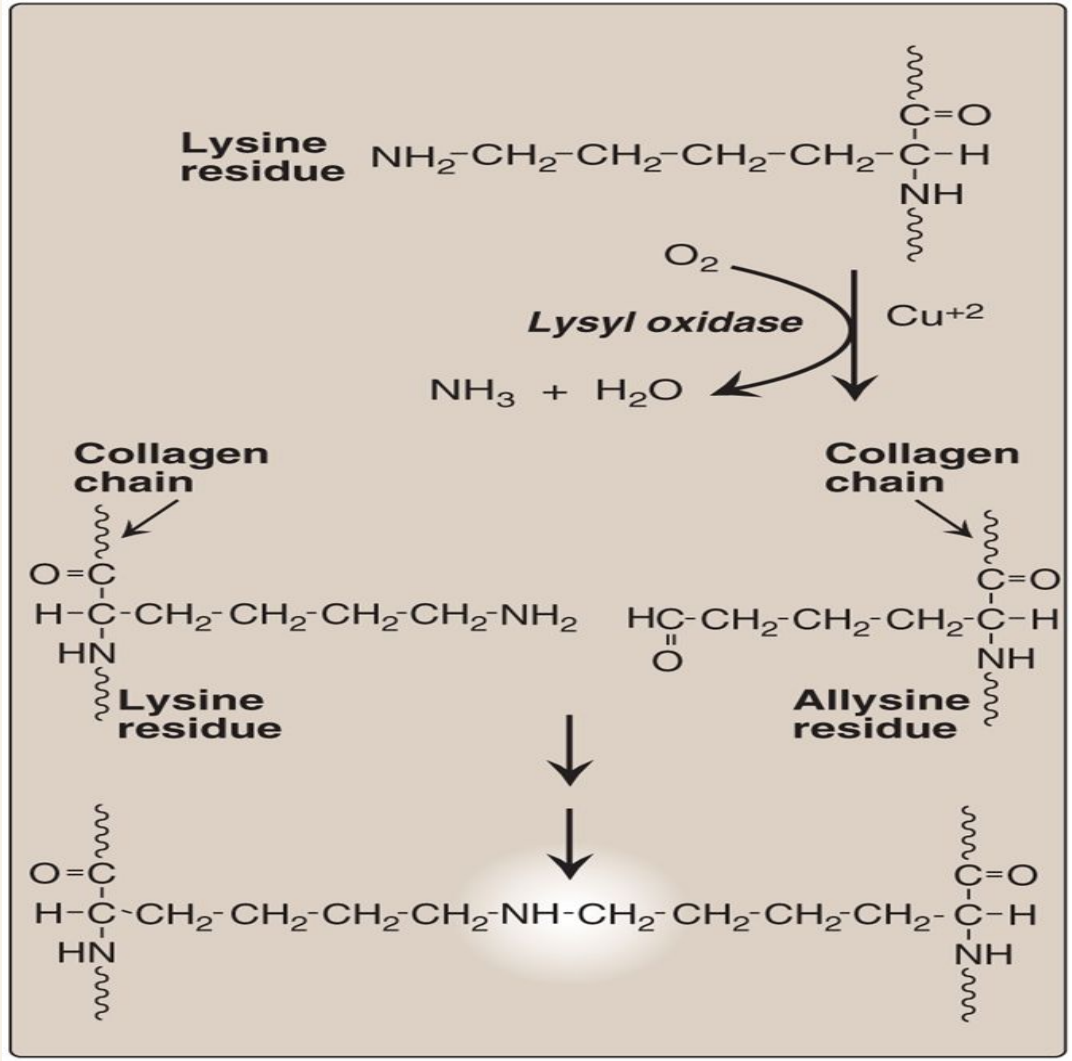
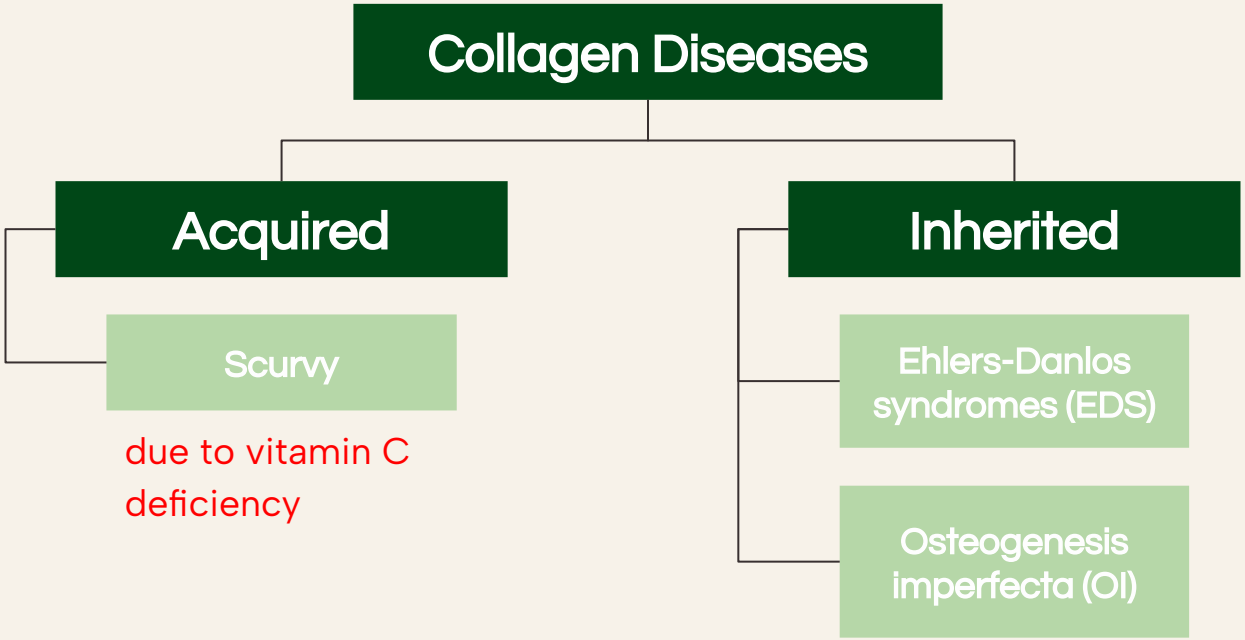
N-terminal propeptide
C-terminal propeptide
Cross-linked fibers
9
Self-assembly of tropocollagen molecules into fibrils, with subsequent cross-linking to form mature collagen fibers.



Overview of Collagen Diseases



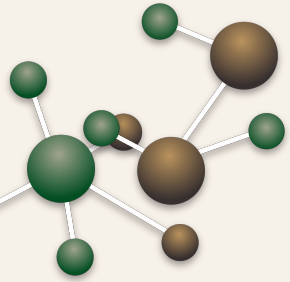
Collagen diseases

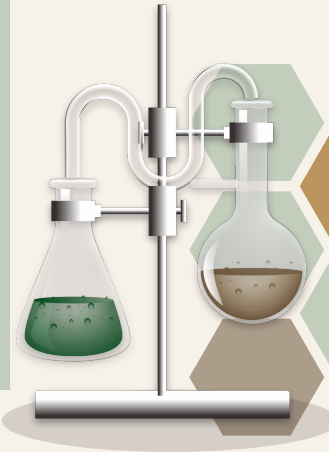
Ehlers-Danlos syndrome: (Inherited)

- Due to deficiency of lysyl hydroxylase or N-procollagen peptidase.
- Mutations in the amino acid sequences of collagen I, III and V.
- Characterized by hyperextensibility of joints and skin.

Osteogenesis imperfecta (brittle bone disease): (Inherited)

1. Bones fracture easily with minor or no trauma.
2. Mutations replace glycine with amino acids having bulky side chains preventing the formation of triple helical conformation.
3. Type I (most common) characterized by mild bone fragility, hearing loss and blue sclerae.





Collagen diseases (Cont'd)

Osteogenesis imperfecta

Type II (most severe)

- Lethal in the perinatal period (fractures in utero)

Type III (severe form)

- Fractures at birth, short stature, spinal curvature
- Leading to a humped back (kyphotic) appearance and blue sclerae

Examples and characteristics about diseases are important.

Multiple choice questions

1. Where in the body are creatine molecules synthesized?

   A) Kidney B) Liver C) Pancreas

2. Which of the following is the end product of creatine metabolism?

   A) Creatine phosphate B) Methionine C) Creatinine

3. What does hydroxylase require for its function?

   A) Vitamin A B) Vitamin C C) Vitamin D

4. What is the most severe type of osteogenesis imperfecta?

   A) Type I B) Type II C) Type III

5. What is the most common type of osteogenesis imperfecta?

   A) Type 1 B) Type 2 C) Type 3

MCQ Answers : 1:B / 2:C / 3:B / 4:B / 5:A

SAQs

Q1/ List two examples of collagen diseases?

Q2/ List the main enzymes required for synthesis of creatine

Answers of SAQs:
Q1/ Scurvy (acquired)
Osteogenesis imperfecta (genetically inherited)
Ehlers-danlos syndrome (genetically inherited)

Q2/ amidinotransferase and methyltransferase

Meet our Team

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