Creatine Metabolism and Collagen Diseases

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Objectives

1. To study the importance of creatine in muscle as a storage form of energy
2. To understand the biosynthesis of creatine
3. To study the process of creatine degradation and formation of creatinine as an end product
4. To understand the clinical importance of creatinine as a sensitive indicator of kidney function
5. To study the structure, function, types, and biosynthesis of collagen
6. To understand different diseases associated with collagen

Creatine Metabolism

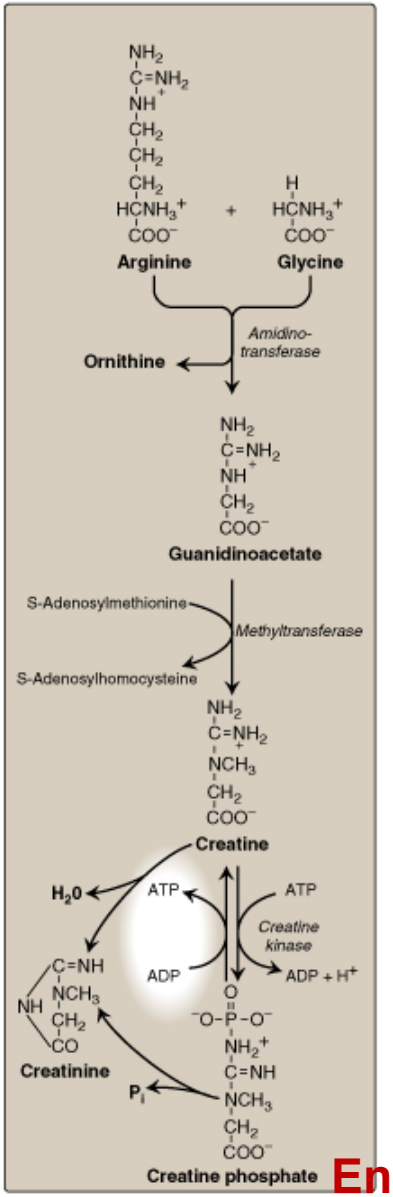


Figure 21.16
Synthesis of creatine.

End product

Energy Source

Creatine Biosynthesis

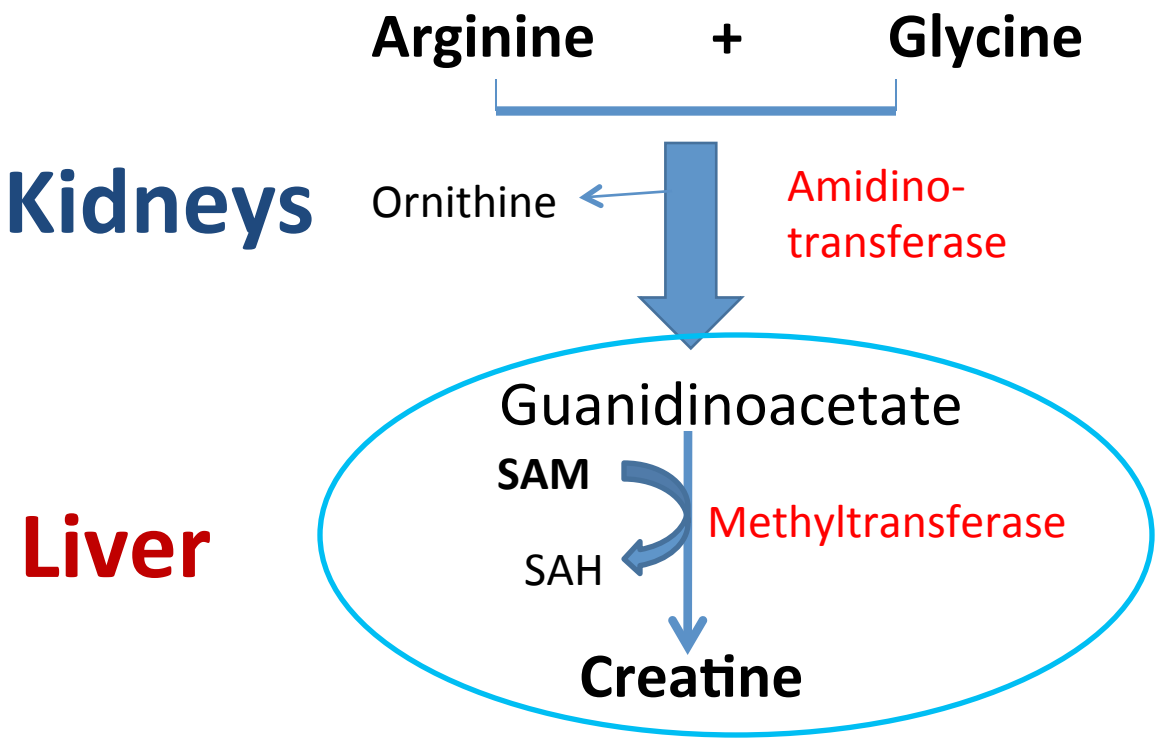
Three amino acids are required:

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

Site of biosynthesis:

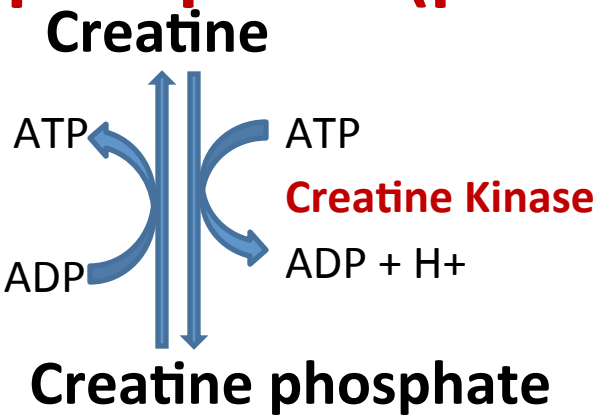
- **Step 1: Kidneys**
- **Step 2: Liver**

Creatine Biosynthesis



Distribution of body creatine

- From liver, transported to other tissues
- 98% are present in skeletal and heart muscles
- In Muscle, gets converted to the high energy source creatine phosphate (phosphocreatine)



Creatine Phosphate

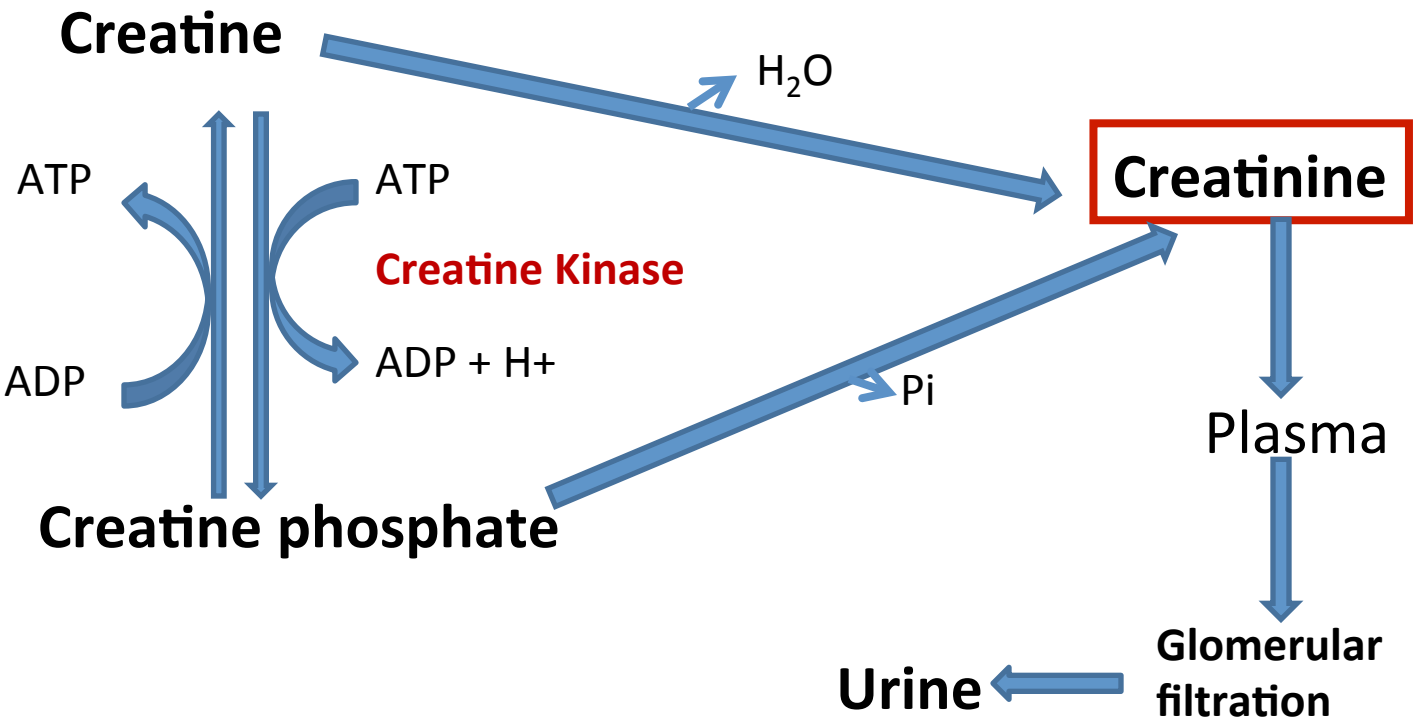
- Is a high-energy phosphate compound
- Acts as a storage form of energy in the muscle
- Provides a small but, ready source of energy during first few seconds of intense muscular contraction

The amount of creatine phosphate in the body is proportional to the muscle mass

Creatine Degradation

1. Creatine and creatine phosphate spontaneously form creatinine as an end product
2. Creatinine is excreted in the urine
3. Serum creatinine is a sensitive indicator of kidney disease (Kidney function test)
4. Serum creatinine increases with the impairment of kidney function

Creatine Degradation

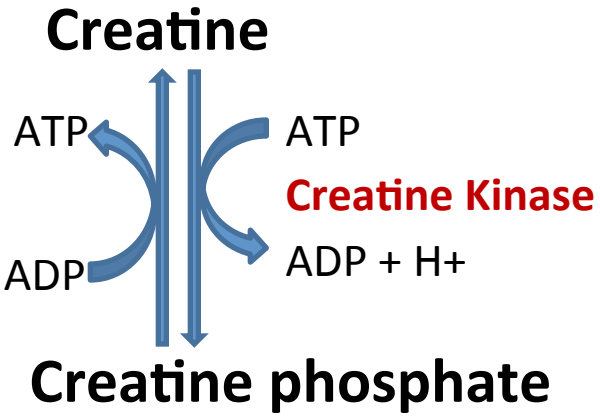


Urinary Creatinine

- A typical male excretes about 15mmol of creatinine per day
- A decrease in muscle mass due to muscular dystrophy or paralysis leads to decreased level of creatinine in urine
- The amount of creatinine in urine is used as an indicator for the proper collection of 24 hours urine sample

Creatine Kinase (CK)

- CK is responsible for the generation of energy in contractile muscular tissues
- CK levels are changed in disorders of cardiac and skeletal muscle



Collagen Diseases

Collagen: Overview

- Most abundant protein in the human body
- Collagens are highly stable molecules, having half-lives as long as several years
- A fibrous protein that serves structural functions
- Is a part of connective tissues: bone, teeth, cartilage, tendon, skin, blood vessels
- Has a long rigid structure

Collagen structure: The α-chain

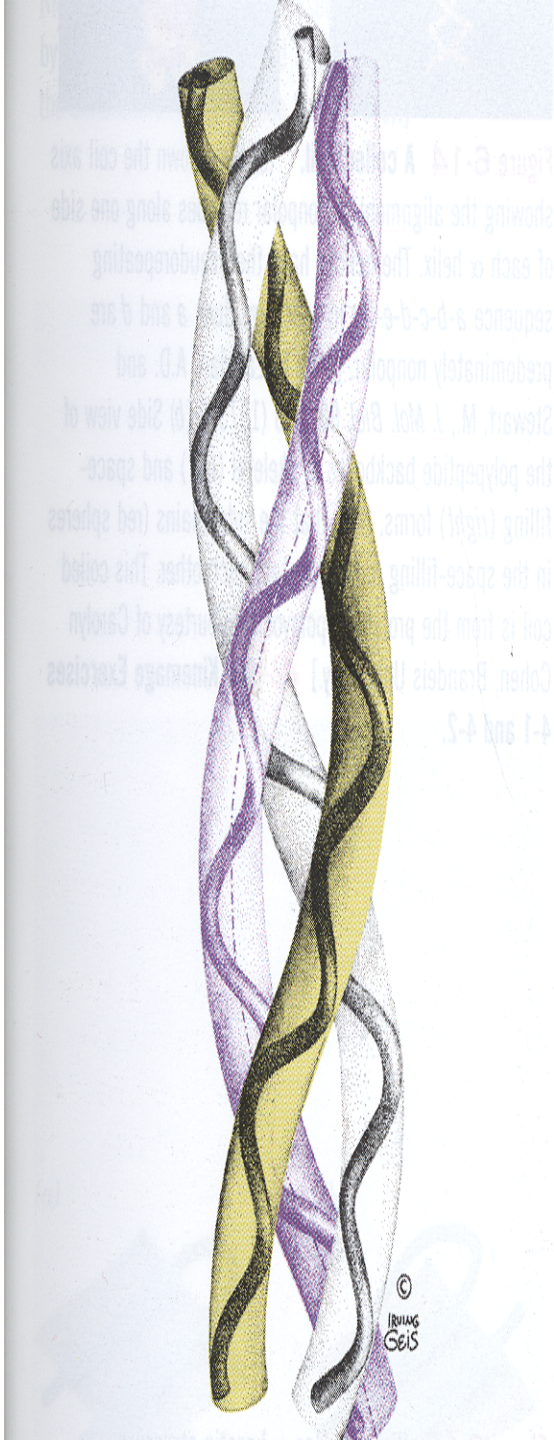
- Collagen α-chain (~1,000 amino acids long), is rich in proline and glycine
- The glycine residues are part of a repeating sequence, –Gly–X–Y–, where X is frequently proline and Y is often hydroxyproline $(–Gly–Pro–Hyp)_{333}$

  (Y can be also hydroxylysine).
- Collage consists of three α-chains wound around one another in rope like triple helix

  Compare between the 2 examples of secondary structure of proteins: the collagen helix & the α-helix
- The three polypeptide chains are held together by hydrogen bonds

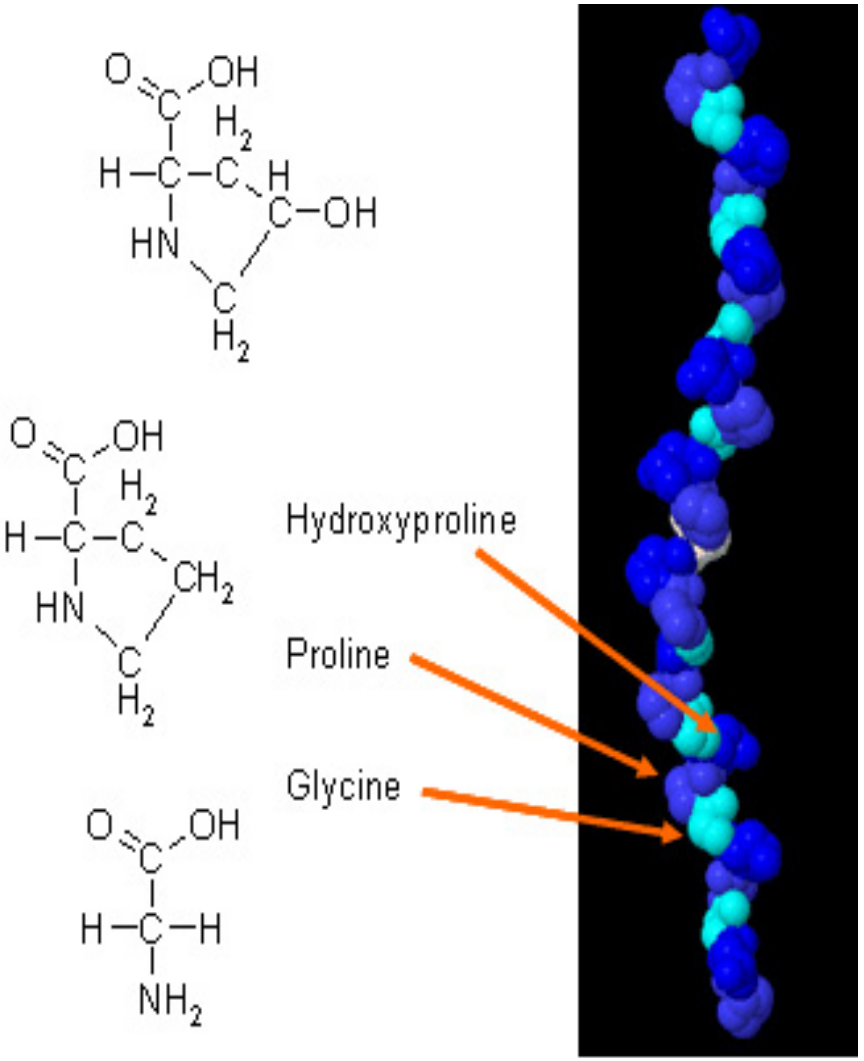
Structure of Collagen

- Rich in proline and glycine amino acids
- Proline prevents collagen chains to form α-helix because:
  - It does not have back bone amino group (it is a ring structure with secondary amino group)
  - Therefore hydrogen bonding within the helix is not possible



Non-standard amino acids in collagen

- Proline and lysine is converted to hydroxyproline and hydroxylysine by hydroxylase enzymes during post-translational modification
- The enzyme requires vitamin C for its function



Types of collagen molecules

- Type and organization of collagen depends on its function
- Variations in the amino acid sequence of α-chains result in different properties e.g.
  - type I- $(\alpha 1)_2\ \alpha 2$
  - Type II- $(\alpha 1)_3$

TYPE	TISSUE DISTRIBUTION
	Fibril-forming
I	Skin, bone, tendon, blood vessels, cornea
II	Cartilage, intervertebral disk, vitreous body
III	Blood vessels, fetal skin
	Network-forming
IV	Basement membrane
VII	Beneath stratified squamous epithelia
	Fibril-associated
IX	Cartilage
XII	Tendon, ligaments, some other tissues

Biosynthesis of Collagen

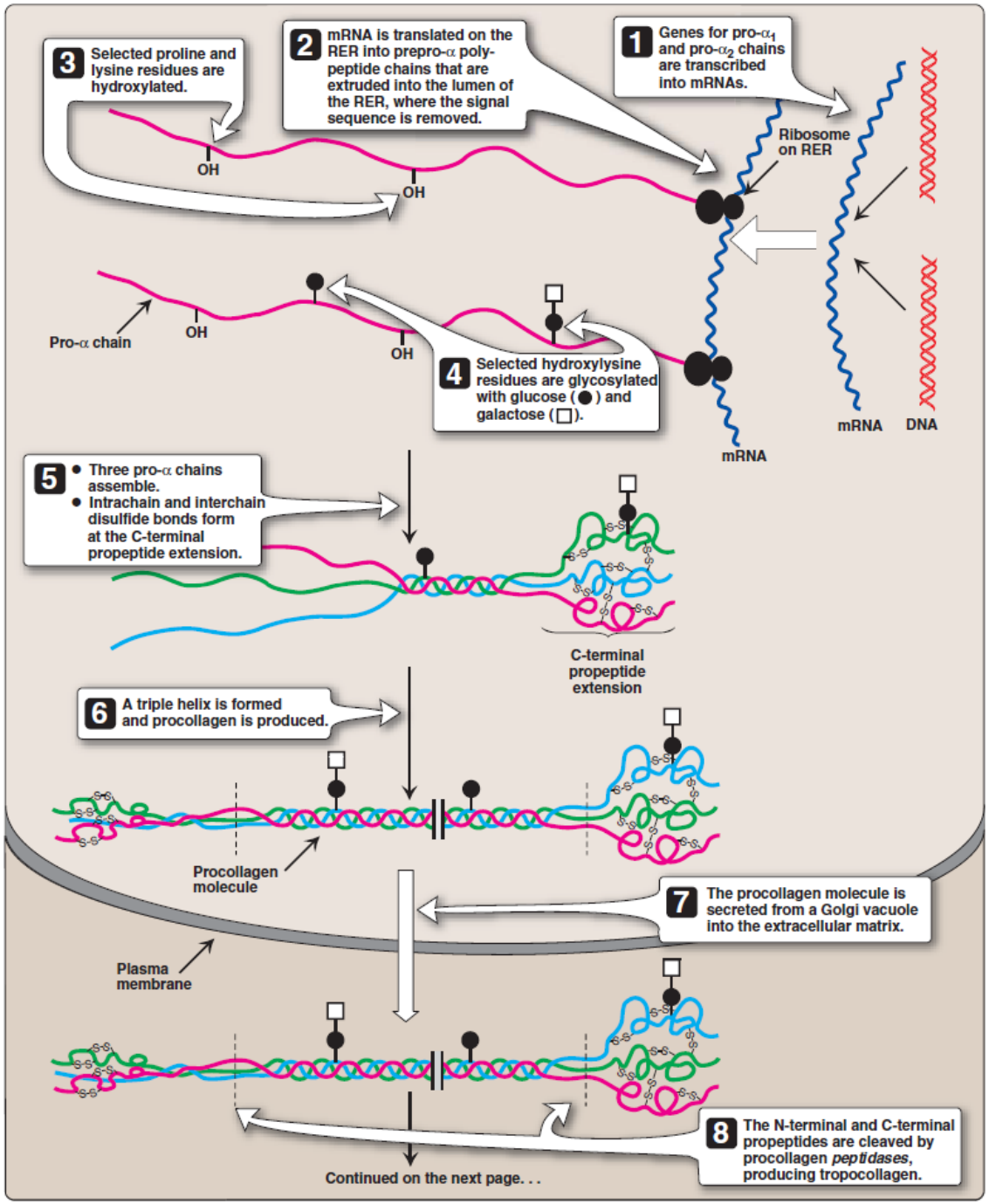
- Synthesized in fibroblasts, osteoblasts and chondroblasts (pre-pro- then pro- and finally mature -collagen)
- Polypeptide precursors are enzymatically modified and form triple helix which is secreted into the extracellular matrix as procollagen
- Procollagen molecules are cleaved by N- and C-procollagen peptidases releasing triple helical tropocollagen molecules
- Tropocollagen molecules spontaneously associate to form collagen fibrils

Biosynthesis of Collagen … CONT'D

- Glycosylation of some hydroxylysine residues with glucose or galactose
- Tropocollagen molecules spontaneously associate to form collagen fibrils

Cross-linking of Collagen fibrils

- Lysyl oxidase oxidatively deaminates some of the lysine and hydroxylysine residues in collagen
- The produced reactive aldehydes- allysine and hydroxyallysine condense with lysine or hydroxylysine residues in neighbouring collagen molecules to form covalent cross-links
- This produces mature collagen fibres


1 Genes for pro-α1 and pro-α2 chains are transcribed into mRNAs.
2 mRNA is translated on the RER into prepro-α polypeptide chains that are extruded into the lumen of the RER, where the signal sequence is removed.
3 Selected proline and lysine residues are hydroxylated.
Ribosome on RER
OH
OH
Pro-α chain
OH
OH
4 Selected hydroxylysine residues are glycosylated with glucose (●) and galactose (□).
mRNA
mRNA
DNA
5 • Three pro-α chains assemble.
• Intrachain and interchain disulfide bonds form at the C-terminal propeptide extension.
C-terminal propeptide extension
6 A triple helix is formed and procollagen is produced.
Procollagen molecule
7 The procollagen molecule is secreted from a Golgi vacuole into the extracellular matrix.
Plasma membrane
8 The N-terminal and C-terminal propeptides are cleaved by procollagen peptidases, producing tropocollagen.
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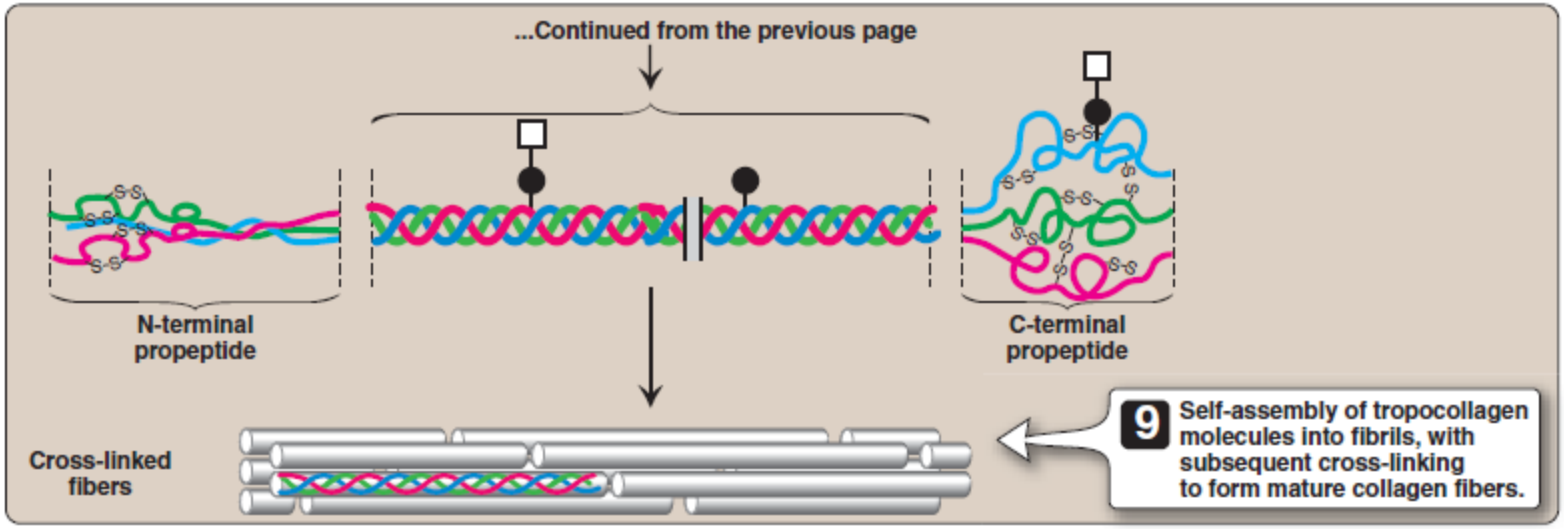
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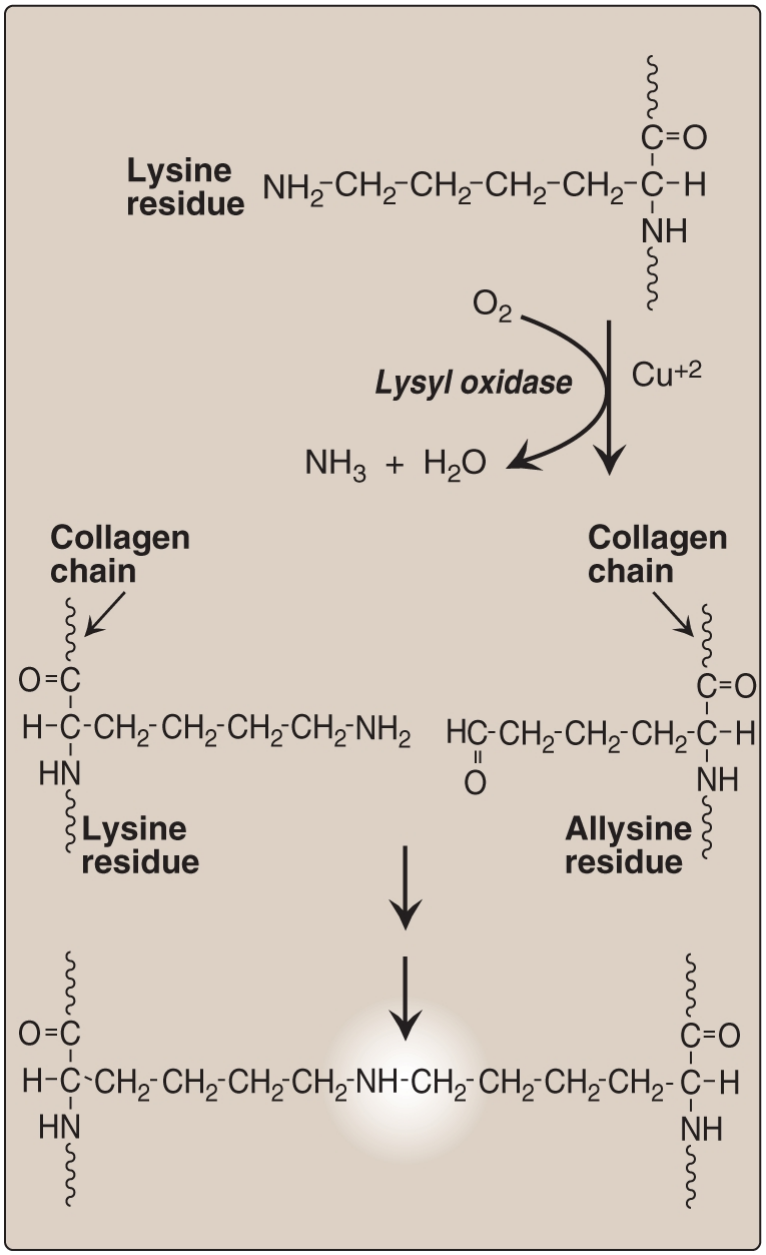
N-terminal propeptide
C-terminal propeptide
Cross-linked fibers
9
Self-assembly of tropocollagen molecules into fibrils, with subsequent cross-linking to form mature collagen fibers.



Collagen diseases

- **Acquired disease:**

  Scurvy: due to vitamin C deficiency

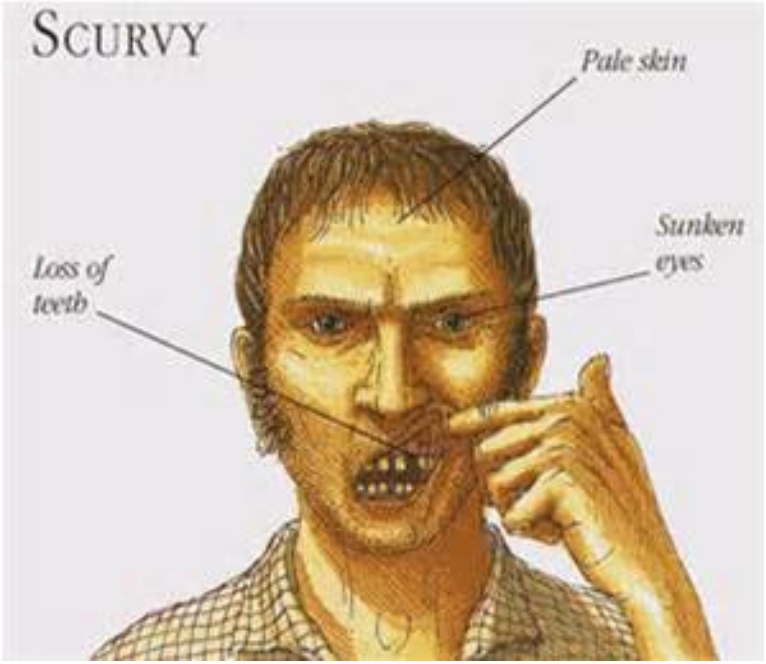
- **Genetic, inherited diseases:**

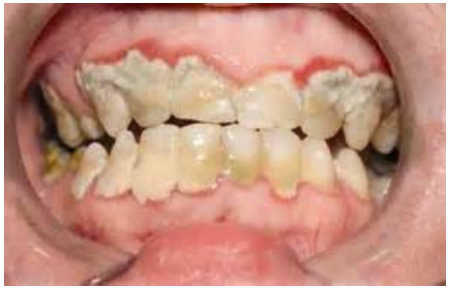
  Ehlers-Danlos syndromes (EDS)

  Osteogenesis imperfecta (OI)

Collagen diseases

- **Scurvy**: due to vitamin C deficiency





Collagen diseases

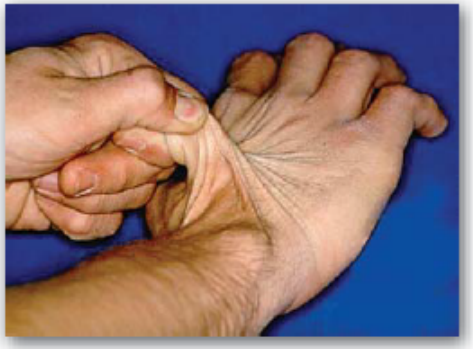
- **Ehlers-Danlos syndrome:**

  can be caused by

  – 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

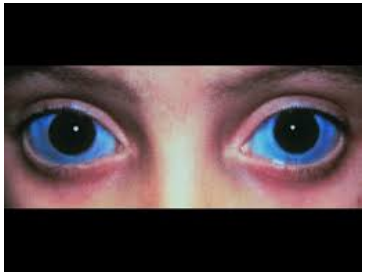


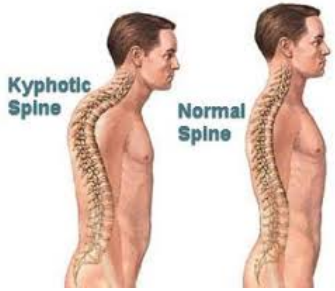
Collagen diseases

Osteogenesis imperfecta (brittle bone disease): Characterized by bones that fracture easily, with minor or no trauma.

Mutations replace glycine with amino acids having bulky side chains preventing the formation of triple helical conformation

- **Type I-** most common, characterized by mild bone fragility, hearing loss and blue sclerae
- **Type II-** most severe form and typically lethal in the perinatal period. Fractures are seen in utero.
- **Type III-** severe form, characterized by multiple fractures at birth, short stature, spinal curvature leading to a humped back (kyphotic) appearance and blue sclerae.





References

- Lippincott, pages 43-49 and 287-288
- Bishop 6th edition, page 223-227