جامعة الملك سعود
King Saud University

Biochemistry team 436

Creatine Metabolism and Collagen Diseases

- Color Index:
  - Doctor's notes
  - Important.
  - Extra Information.
  - **Doctors slides.**

436 Biochemistry team

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Objectives:

By the end of the lecture. Students should be familiar with :

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

Creatine phosphate

- A high-energy phosphate compound
- Acts as a storage form of energy in the muscle (main storage form for intense and immediate muscle contraction)
- Provides small but, ready source of energy during first few seconds of intense muscular contraction * it is stored in the muscle, and when intense muscle contraction is needed, such as running as fast as you can, lifting weights. In this cases creatine phosphate gives you the energy immediately (as the stored ATP is only enough for 3 seconds).
- The amount of creatine phosphate in the body is proportional to the muscle mass * directly proportional, when the mass increases it needs more energy, so it will be stored in higher amounts.

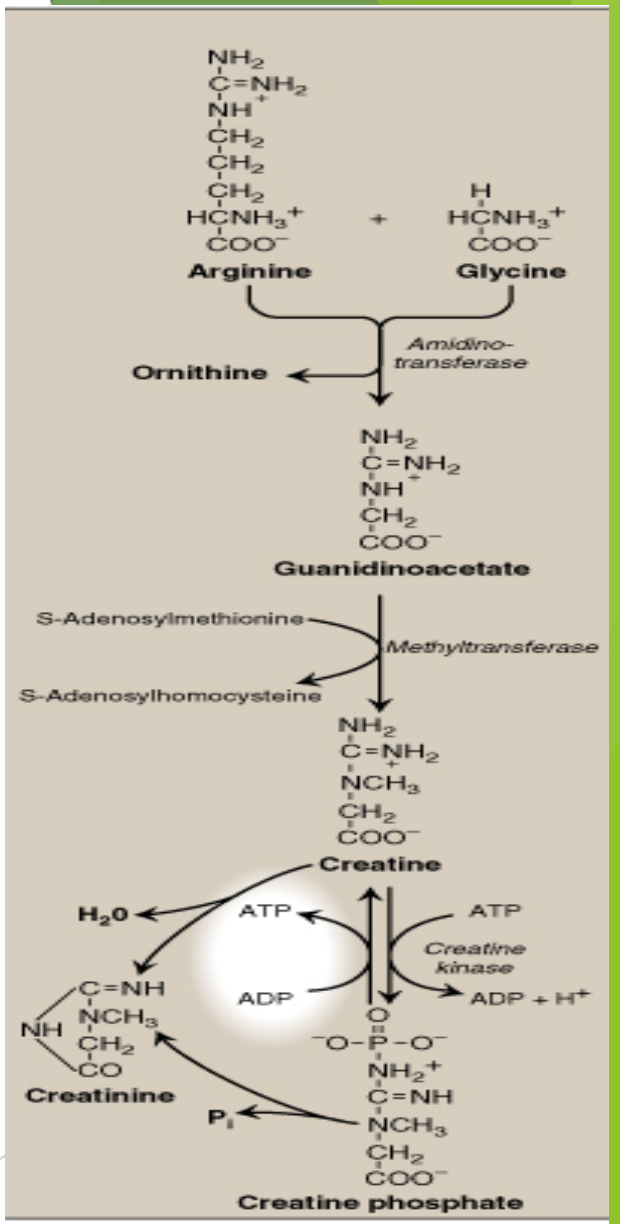


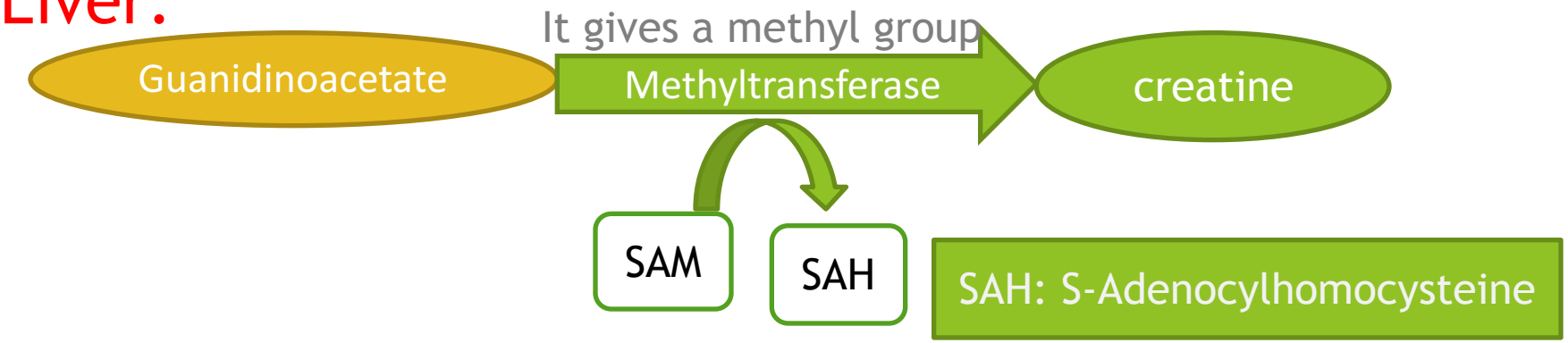
Figure 21.16
Synthesis of creatine.

Creatine biosynthesis

Sites of biosynthesis:

Kidney:

Liver:



1 amino acid is **produced**:
ornithine
3 amino acids are required:
glycine arginine Methionine as (S-AdenosylMethionine) (SAM)

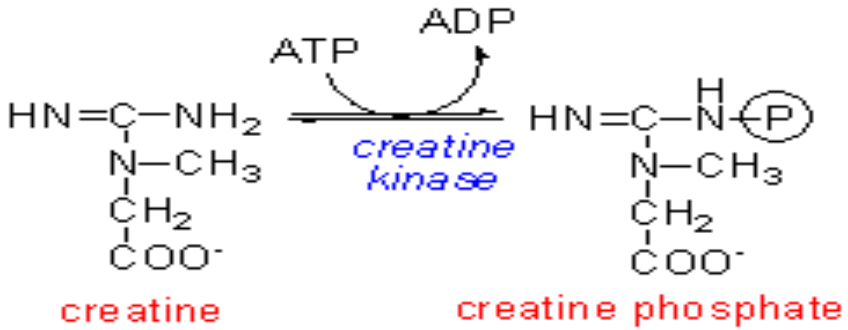
Ornithine is a non proteinogenic amino acids that is used to remove ammonia during urea cycle.
(The 20 amino acids we have studied in the foundation block are called “proteinogenic amino acids”)

Where creatin is synthesized ? liver

Note: creatine is not the same as creatinine.

Distribution of body creatine

- Transported from liver to other tissues
- 98% present in skeletal and heart muscles
- In skeletal muscles it is converted to high-energy source creatine phosphate (phosphocreatine)
- Most of the creatine comes from the diet.



Creatine and creatine phosphate are non-enzymatic (they don't require any enzyme)

Creatine degradation

N.B.
This system does NOT involve the respiratory chain

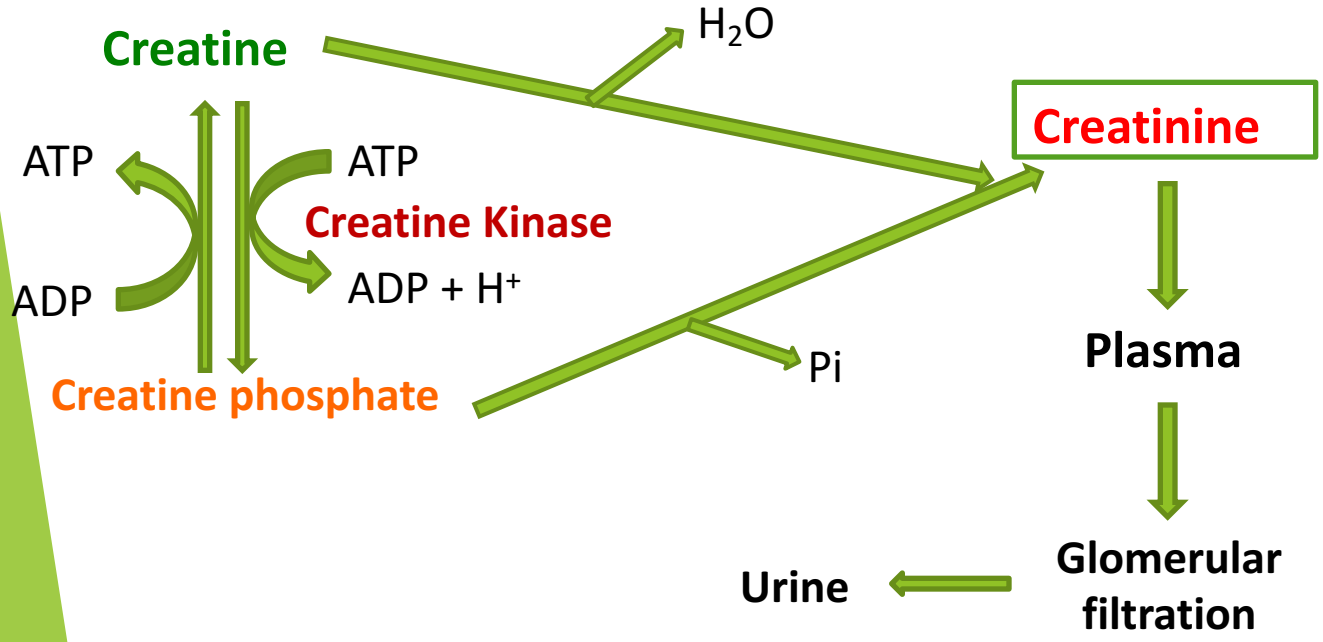
Creatine and creatine phosphate are spontaneously degraded into their end product which is creatinine and it is excreted in the urine .

So the more muscle mass, the more creatinine will be observed in the urine

Spontaneously: it doesn't require enzyme or energy

Serum creatinine is a sensitive indicator of kidney disease (kidney function test).

Creatinine: inhydryde form of creatine and its very slouble



Serum creatinine increases with the impairment of kidney function.

Its level depends on the muscle mass also.

Urinary creatinine

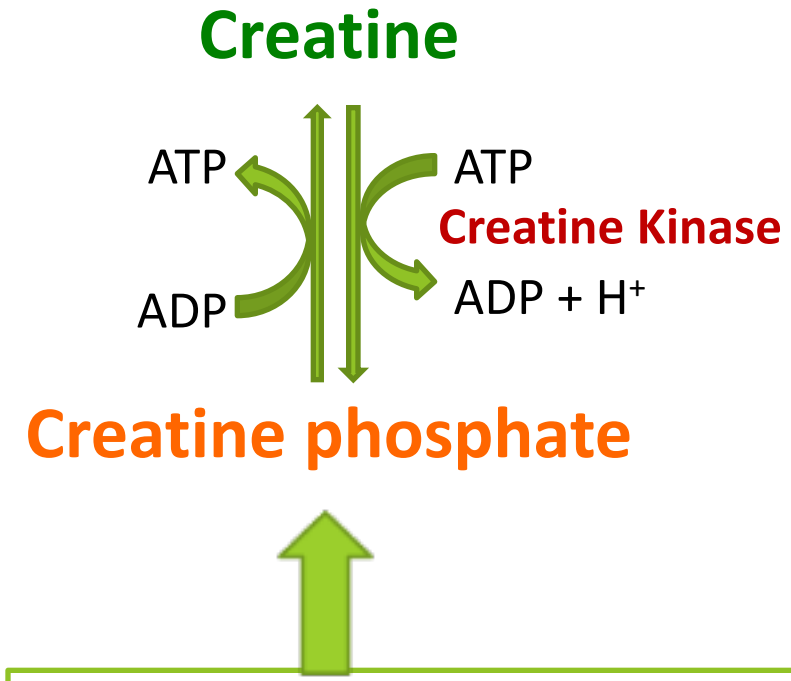
- A typical male excretes about 15 mmol creatinine/day
- Decrease in muscle mass (Atrophy) (in muscular dystrophy, paralysis) leads to decreased level of urinary creatinine
- The amount of creatinine in urine is used as an indicator for the proper collection of 24 hours urine sample
- ** Note : its level depends on muscle mass, gender, and age.
- Cystatin C is also a biomarker for assessing GFR and kidney function, it is better than creatinine because it doesn't depend in muscle mass, age, or gender. – recall it from the Foundation block ☺ -

Creatine kinase (CK)

- CK is responsible for generation of energy in contractile muscular tissues as it is the enzyme that used to regenerate ATP from creatine phosphate

- CK levels change in cardiac and skeletal muscle disorders because it is mostly found in these tissues (can be used as a biomarker) – troponin is better than it for cardiac assessment -

*Creatine Kinase isozyme (CK):
CK in brain (CKBB)
CK in skeletal muscle (CKMM)
CK in cardiac (CKMB)



Creatine kinase and creatinine levels are usually checked in testing, beacause checking creatine levels is more difficult.

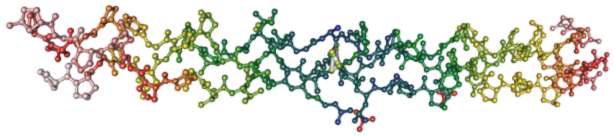
Explanation:
CK can be used in two reactions (reversible reactions)
1- generating creatine phosphate, by taking one phosphate group from ATP and convert it to ADP (during rest).

2- generating ATP from creatine phosphate, by taking the phosphate from it(C ~ P) and adds it to ADP (during intense and immediate muscle contraction).

Collagen

It's the most abundant protein in the body.

HUMAN COLLAGEN MOLECULE



Highly stable molecules, having half-lives as long as several years.

part of connective tissues:
bone, teeth, cartilage, tendon, skin, blood vessels.

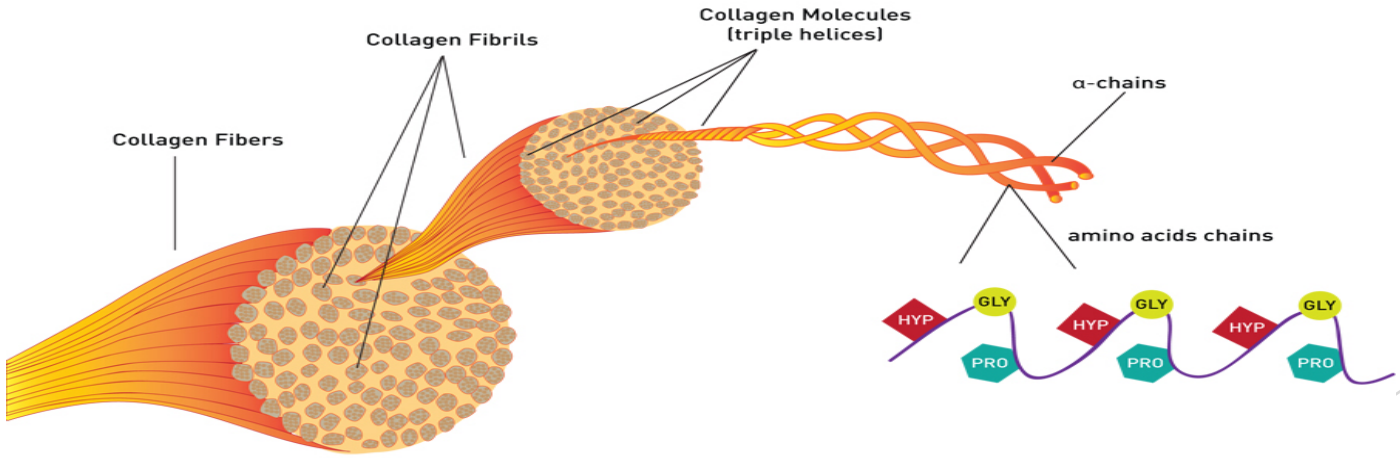
Fibrous protein
(Row like structure)
that serves structural functions.

Has a long rigid structure.

Collagen structure

- It's a **1000** amino acids long.
- Rich in **proline** & **glycine**.
- The glycine residues are part of a repeating sequence, (-Gly-X-Y-)333, where X is frequently proline and Y is often hydroxyproline, or hydroxylysine.

- Collage consists of **three α-chains** wound around one another in rope like triple helix.
- The three polypeptide chains are held together by **hydrogen bonds. (interchain hydrogen bonds).**



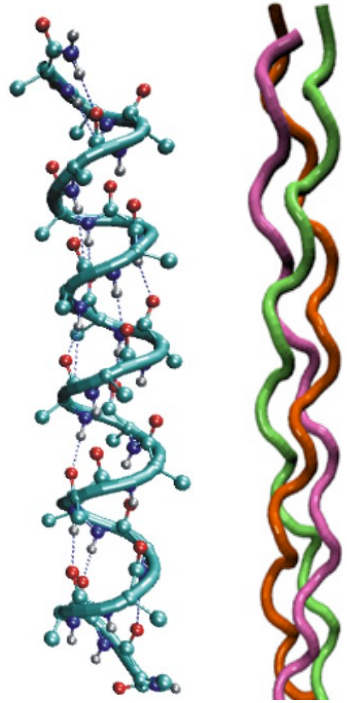
Collagen structure

Proline prevents collagen chains to form α-helix because:

1- It does not have back bone amino group
(it is a ring structure with secondary
amino group).

2-Therefore hydrogen bonding within the helix is not possible

α-helix



Collagen helix

Note: The secondary structure α-helix is different from collagen helix:
hydrogen bond between the chains (interchain)
not
within chains (intrachain).

Non-Standard Amino Acids in Collagen

Proline is converted to Hydroxyproline

Lysine is converted to Hydroxylysine

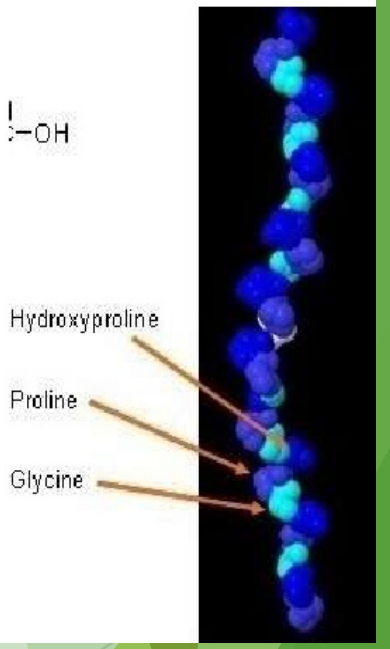
By *hydroxylase
**(during post-transitional modifications)

The enzyme requires Vitamin C for its function

--(--GLY---X---Y--GLY---X---Y--)--

X= PROLINE

Y= Hydroxy Proline
Hydroxy Lysine



*By Adding a hydroxyl group (OH)
** After translation the protein is form, then it's modified

Why is Hydroxyproline important?
To stabilize the triple- helical structure

Non-Standard Amino Acids in Collagen:
If vitamin C is decreased, the amount of the enzyme (hydroxylase) will be deficient and as a result (proline & lysine) won't be hydroxylated and the resulting collagen will be defected (doesn't have proper strength)

Types of Collagen

- Types of collagen depend on function and location.
- Variations in the amino acid sequence of α-chains result in different properties.

Examples:

Type I: $(\alpha\text{-}1)_2$ $(\alpha\text{-}2)_1$ (Two α-1-chain + α–2- chain)

Type II: $(\alpha\text{-}1)_3$ (Three α-1-chain)

Collagen can be categorized into 3 groups, based on their location and functions :

Fibril-forming (Type 1, 2 and 3)	They are high strength and very tough
Network-forming (Type 4 and 7)	Form networks (Mesh)
Fibril-associated (Type 9 and 12)	They bind to the surface of collagen fibrils for linking them together, and to link them with the other components

You have to memorize it

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

Fibril associated collagen is the most abundant

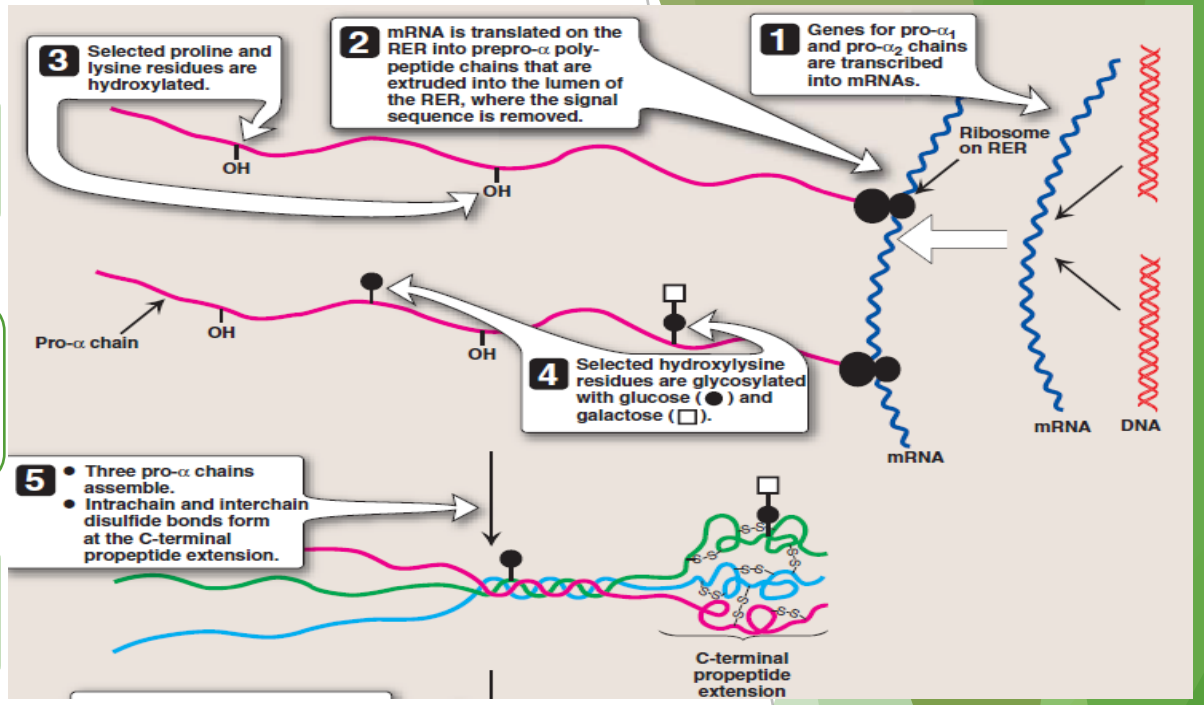
Biosynthesis of Collagen

This process explained in details on the next three slides

- Collagen is Synthesized in: fibroblasts, osteoblasts and chondroblasts
  Pre-pro ⟶ Pro ⟶ Mature collagen
- Polypeptide precursors (pre-pro) are enzymatically modified to form triple helix which is Secreted from Golgi vacuoles into the extracellular matrix as procollagen
- procollagen cleaved by N- and C- procollagen peptidases to release triple helical tropocollagen molecules
- Glycosylation of some hydroxylysine residues with glucose or galactose
- Tropocollagen molecules spontaneously associate to form collagen fibrils

Biosynthesis of Collagen

1. • Pro-α chains are transcribed into mRNA
2. • This mRNA translated on the RER into prepro-α-polypeptide chains that are extruded (forced out) into RER lumen, where the signal sequence is removed
3. • Selected proline and lysine are hydroxylated in the presence of vitamin C
4. • Glycosylation of selected hydroxylysine residues with glucose or glucosyl-galactose
5. • 3 pro-α chains assemble and interchain & intrachain disulfide bonds are formed at the C-terminal propeptide extension.



3-Proline → hydroxyproline & lysine → hydroxylysine
3-Deficiency in vitamin C causes Scurvy disease
4-Glycosylation: the attachment of sugar moieties to proteins

**3 & 4 are post-translational modification steps Which are very important for the proper function of collagen

Biosynthesis of Collagen

6

- Formation of triple helix
- Procollagen molecule is produced

7

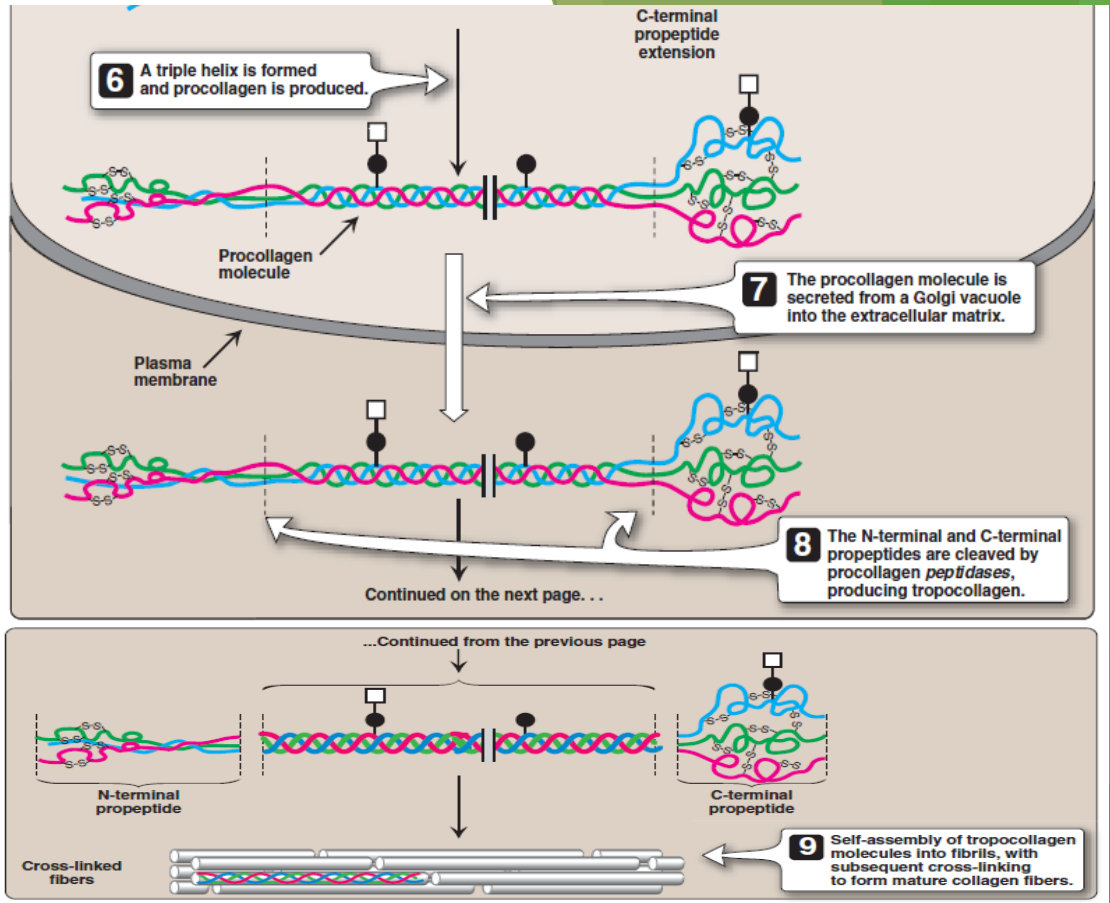
- The procollagen molecule is secreted through the Golgi apparatus to ECM in Golgi vacuole.

8

- The N- & C-terminal propeptides of the procollagen molecule are cleaved by procollagen peptidases, producing tropocollagen

9

- Tropocollagen molecules spontaneously associate to form collagen fibrils, then they cross-link to form mature collagen . (explained in next slide)



9- only cleaved tropocollagen molecules is used to form mature collagen fibers by assembly of tropocollagen into fibrils with subsequent cross linking.

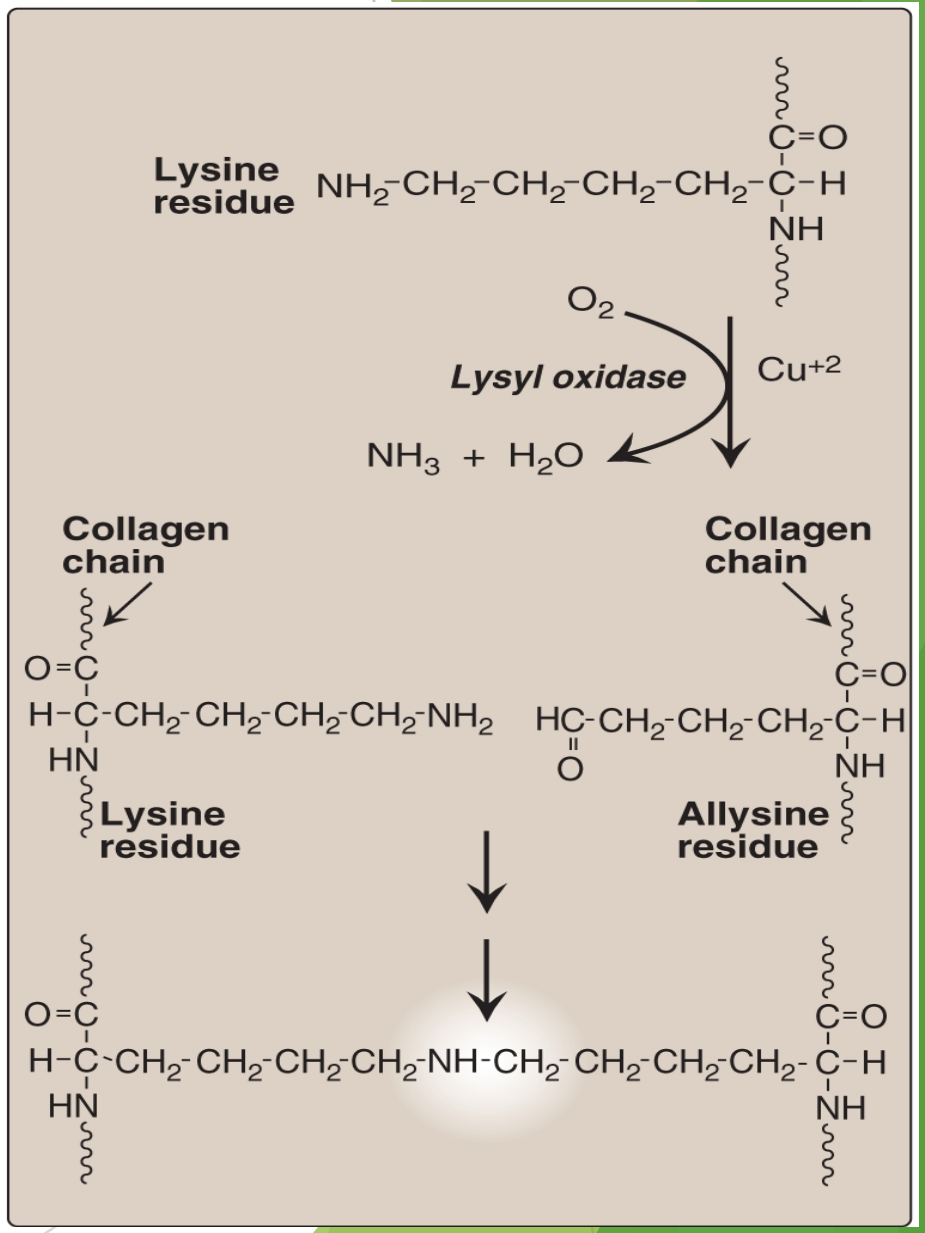
N.B. Step 8 & 9 occur in the matrix.

Crosslinking of Collagen Fibrils

1- Lysyl oxidase oxidatively deaminates some of the lysine and hydroxylysine residues in collagen.
(By removing the amino group from lysine and hydroxylysine residues)

2- The reactive aldehydes – allysine and hydroxyallysine condense with lysine or hydroxylysine residues in neighboring collagen molecules to form covalent cross-links
(**Deaminated** collagen chain binds with **non-deaminated** collagen chain)

3- This produces mature collagen fibres



Collagen diseases

- Acquired
  - Scurvy due to Vitamin C deficiency
- Genetically inherited
  - Ehlers-danlos Syndrome (EDS)
  - Osteogenesis Imperfecta (OI)

Acquired Scurvy due to Vitamin C deficiency

(also called sailors disease) :

This disease is due malnutrition and it mainly affects (gums and teeth).

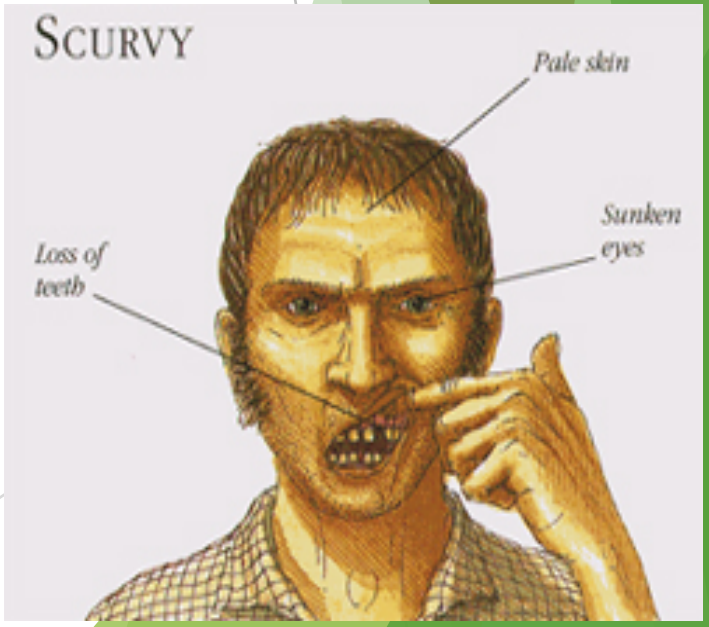
Symptoms :

Bleeding gums , the gums become spongy , painful and inflamed.

Detaching of the teeth from gums .

Skin problems

Enzyme affected : hydroxylase .

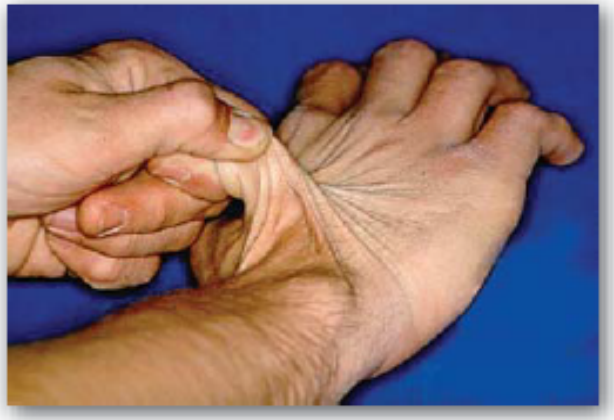


Ehlers-danlos syndrome due to :

deficiency of lysyl hydroxylase or N-procollagen peptidase

Mutations in the amino acid sequence of collagen 1 , 3 , 5 (The gene is present but mutated)

- Characterized by Hyper-extensibility (the skin can become stretched) of skin and joints.

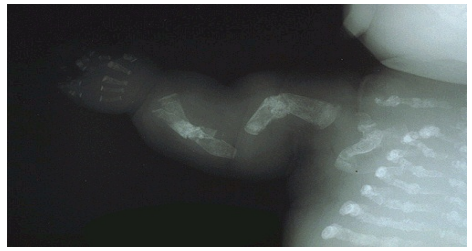


Osteogenesis imperfecta (brittle bone disease):

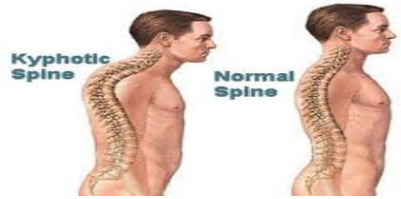
Characterized by bones that fracture easily, with minor or no trauma (normal weight of the body).
Mutations replace glycine with amino acids having bulky side chains preventing the formation of triple helical conformation.

Type I most common, characterized by mild bone fragility, hearing loss and blue sclerae.

Type II most severe, (in fetus) form and typically lethal in the perinatal period. Fractures are seen in utero.



Type III severe form, fractures at birth, short stature, spinal curvature leading to a humped back (kyphotic) appearance and blue sclerae.



MCQ's

https://www.onlineexambuilder.com/creatine-metabolism-and-collagen-diseases/exam-120719

Click HERE to have a better look at the Qs

Girls team members:

1- نورة الشبيب
2-مها الغامدي

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٢- محمد حكمي
٣- طلال الطخيم
٤- صالح التويجري
٥- عبد العزيز الصومالي
٦- فهد الزهراني
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