the editing file

Creatine metabolism and collagen diseases

Color Index:

- Original content
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- Only in girls' slides
- Only in boys' slides

Biochemistry team 438

Objectives:

Slide No.4
1. Study the importance of creatine in muscle as a storage form of energy

Slide No.3
2. Understand the biosynthesis of creatine

Slide No.5
3. Study the process of creatine degradation and formation of creatinine as an end product

Slide No.6
4. Understand the clinical importance of creatinine as a sensitive indicator of kidney function

Slide No.8
5. study the structure , function , types , and biosynthesis of collagen.

Slide No.15
6. understand different diseases associated with collagen

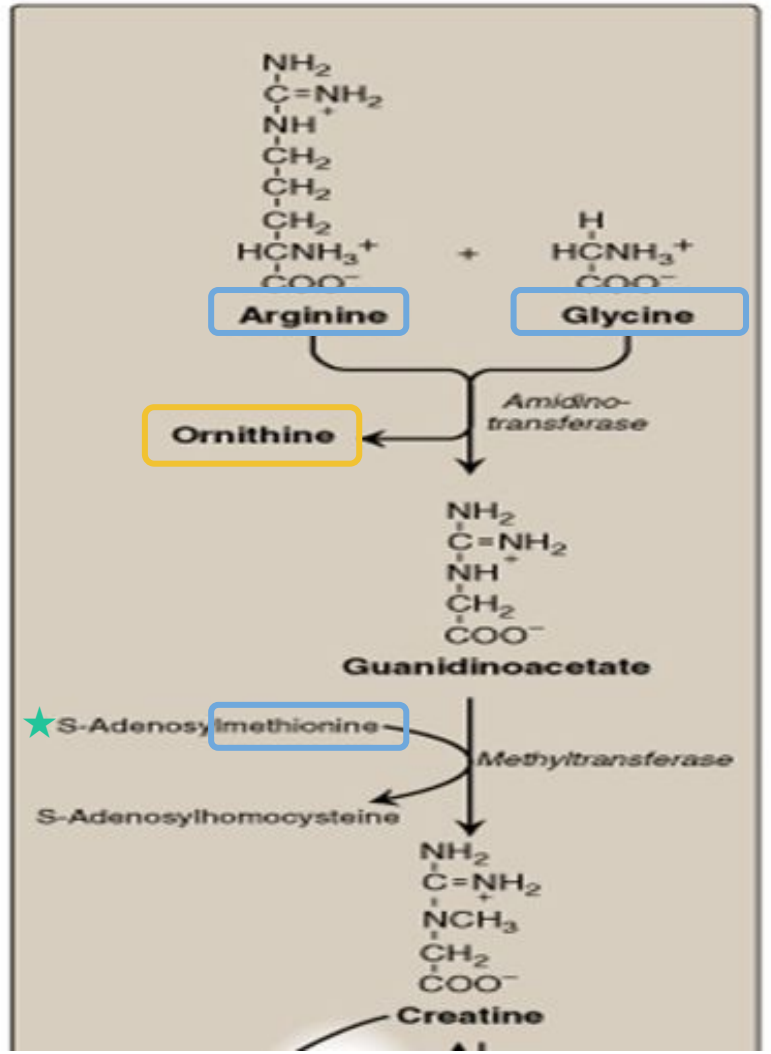
*This slide is important

Creatine biosynthesis:

- **3 amino acids are required:**
  1-glycine 2-arginine 3-methionine (as s-Adenosylmethionine)

- **1 amino acid is produced :**
  ornithine

- **Sites of biosynthesis**
  - Step 1: Kidney
    guanidinoacetate is produced
    through plasma
  - Step 2: Liver
    creatine is produced

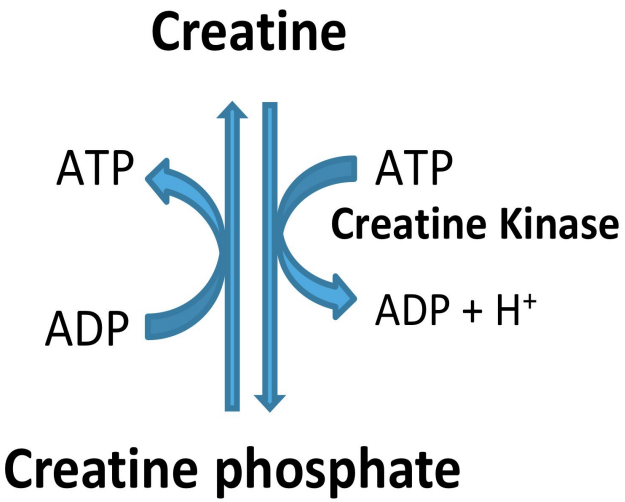


هنا بكل اختصار يتحدون الحمضين جلايسين و الارجينين
بوجود انزيم يسمى Amidinotransferase
ويعطيني ناتجين :
١- Ornithine : يتم الاستخلاص منه بواسطة kidney
٢- Guanidinoacetate : يروح للكبد ، وهو اللي نبيه عشان يعطيني الكيراتين ولكن بشرط وهو إضافة مجموعة ميثايل بواسطة انزيم Methyltransferase ليعطي الكيراتين.

★ S-Adenosylmethionine (SAM) = ATP + methionine
- provides methyl group
- it's found mainly in the liver (that's why creatine is synthesized in the liver)

Distribution of body creatine :

It is formed in the liver, then Transported from liver to other tissues
98% present in skeletal and heart muscles
In skeletal muscle it is converted to high-energy source creatine phosphate (phosphocreatine)



Creatine phosphate:

- A high-energy phosphate compound
- Acts as a storage form of energy in the muscle
- 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 these cases creatine phosphate gives you the energy immediately (as the stored ATP is only enough for the first 3 sec creatine phosphate is used in the first 10-15 sec "
- 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.

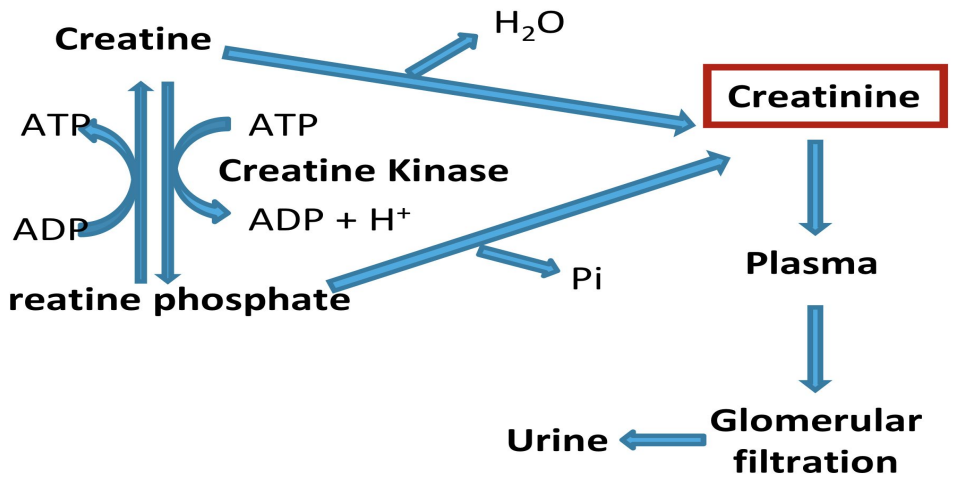
★ Why does the body make creatine phosphate?

Because muscle fibers can't store a lot of ATP
So it stores creatine phosphate for the body's need of quick energy source

by then creatine phosphate group to ADP to form 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) "not specific as it might indicate other diseases e.gm muscle diseases"
- Serum creatinine increases with the impairment of kidney function



Notes:

★ Creatinine:in hydride form of creatine it's very soluble
So the more muscle mass, the more creatinine will be observed in the urine

★ This system does not involve the respiratory chain

★ Spontaneously: it doesn't require enzyme or energy

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

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 from the Foundation block .

Notes:

★ the level of creatinine depends on muscle mass, gender, and age

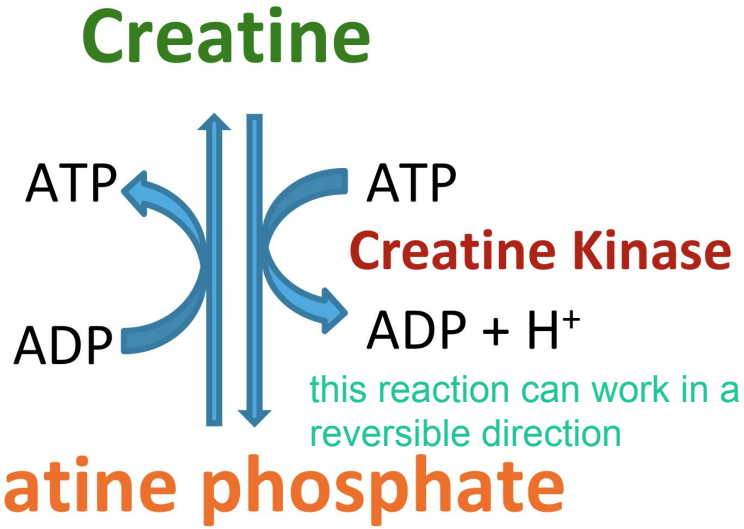
Creatine kinase (CK):

- CK is responsible for generation of energy in contractile muscular tissues

- CK levels change in cardiac and skeletal muscle disorders

★ (can be used as a biomarker)

★ troponin is a better biomarker for cardiac assessment



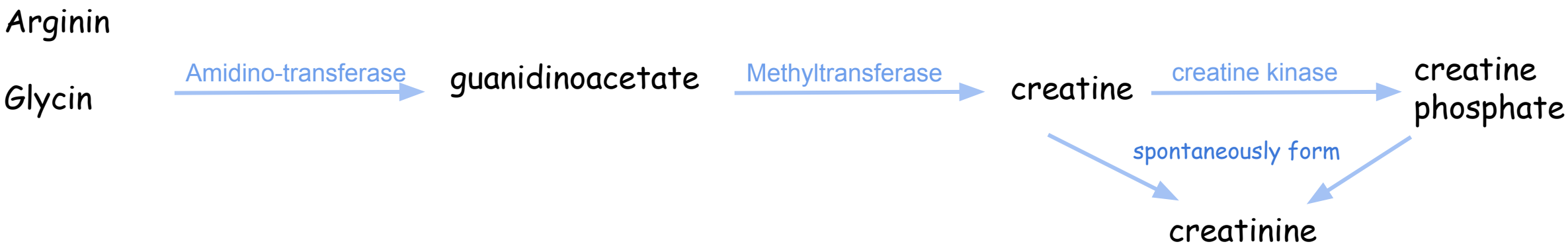
CK is found in the muscle —(muscle damage)→ CK goes out in plasma (it can be tested)

Notes:

★ 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, because. checking creatine levels is more difficult

summary of creatine metabolism



Collagen

Overview of collagen:

- Most abundant protein in the human body. (20-30% of total body proteins)
- a highly stable molecule with a half-life as long as several years.
- long and rigid structure (sometimes with a bit of flexibility)
- A fibrous protein that serves structural functions as part of:

connective tissues, bone, teeth, cartilage, tendons, skin, blood vessels.

2 examples of protein secondary structures

a-helix → disruption → collagen helix

3 a-chains wound around one another in a rope-like triple helix

alpha-chain (~1,000 amino acids long)

held together by hydrogen bonds

rich in proline and glycine amino acids

- The glycine residues are part of a repeating sequence of:

-Gly-X-Y-

X = Frequently proline

Y = Often hydroxyproline (OH+ prolinen)

"it can be also hydroxylysine (OH+lysin)"

$(-Gly-Pro-Hyp)_{333}$ → No. of repetition

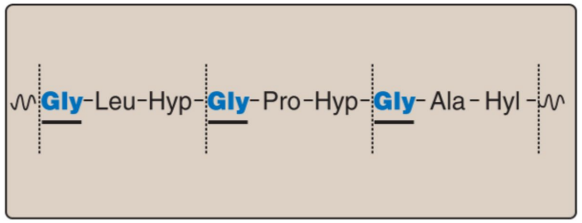


Figure 4.5
Amino acid sequence of a portion of the α1 chain of collagen. [Note: Hyp is hydroxyproline and Hyl is hydroxylysine.]

is collagen helix "the disrupted form" of a-helix ?

recall that collagen is Rich in proline :

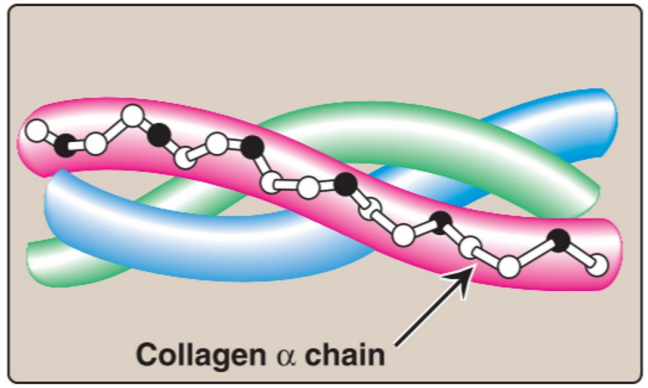


Figure 4.1
Triple-stranded helix of collagen.

★ **Proline prevents collagen chains to form a-helix because:**

- Proline has no backbone amino group (it is a ring structure with secondary amino group)
- Therefore hydrogen bonding **within the helix** is not possible

" in alpha helix, which is different from collagen helix", hydrogen bonding is possible within the helix"

with the aid of non-standard amino acids like hydroxyproline collagen helix can be stabilized by hydrogen bonds between the chain

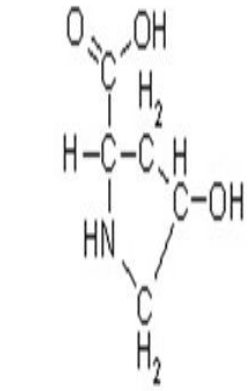
➔ from lippincott's:

★ Proline structure contains a secondary amino group which forms a ring around itself, therefore it causes 'kinks' in the alpha helix, these kinks act like narrow lanes to allow for the triple helix to wind around one another.

- Glycine is a small amino acid, with an H atom only as a side group, therefore it will fit in the tight places in the structure and allow bends to take place which will make the triple helix more wound on itself.

Non-standard Amino Acids in Collagen

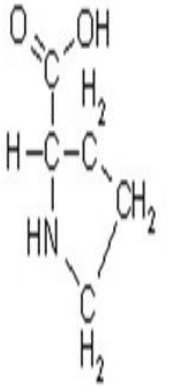
Non-standard Amino Acids are amino acids that are not encoded within the genome but can be made within the cell after the amino acid's synthesis, when needed, they are made from the modification of non-essential amino acids.

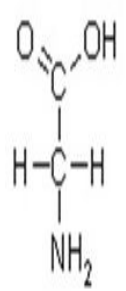


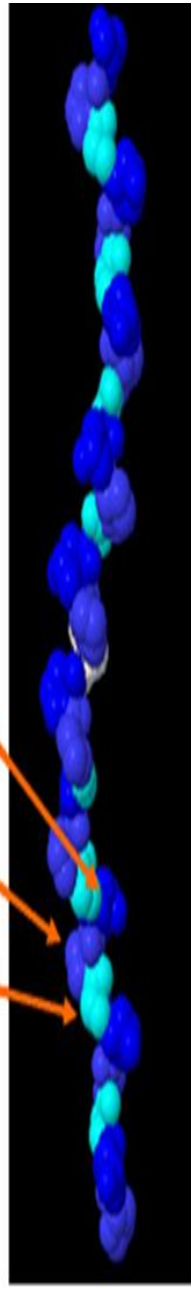
- **During post-translational modifications hydroxylase enzymes play an important role:**

Proline —(prolyl hydroxylase)→ Hydroxyproline

lysine —(lysyl hydroxylase)→ Hydroxylysine







- **The enzyme requires Vitamin C** (also called ascorbic acid) **for its function**

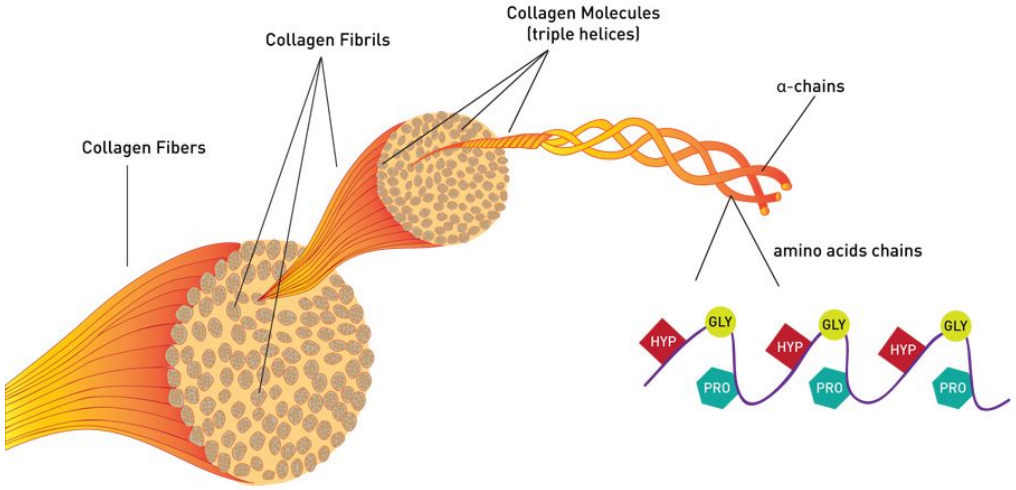
(Vitamin C is an essential cofactor that is required for the synthesis of Collagen, deficiency in Vitamin C leads to having inactivated enzymes that are required for the synthesis of Collagen. Which is why we have many diseases like osteoporosis in the bones and scurvy in the teeth that may arise due to Vitamin C irregularities).

Types of Collagen

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

Examples:

Type I: $(a1)_2\ a_2$
Type II: $(a1)_3$



*important

TYPE	TISSUE DISTRIBUTION
	Fibril-forming
I	Skin, bone, tendon, blood vessels, cornea
II	Cartilage, intervertebral disk, vitreous body
III	Blood vessels, skin, muscle
	Network-forming
IV	Basement membrane
VIII	Corneal and vascular endothelium
	Fibril-associated*
IX	Cartilage
XII	Tendon, ligaments, some other tissues

Notes:

the different types and organization of collagen are dictated by the structural role collagen plays in a particular organ. In some tissues, collagen may be dispersed as a gel that gives support to the structure, as in the extracellular matrix or the vitreous humor of the eye, Collagen of bone occurs as fibers arranged at an angle to each other so as to resist mechanical shear from any direction

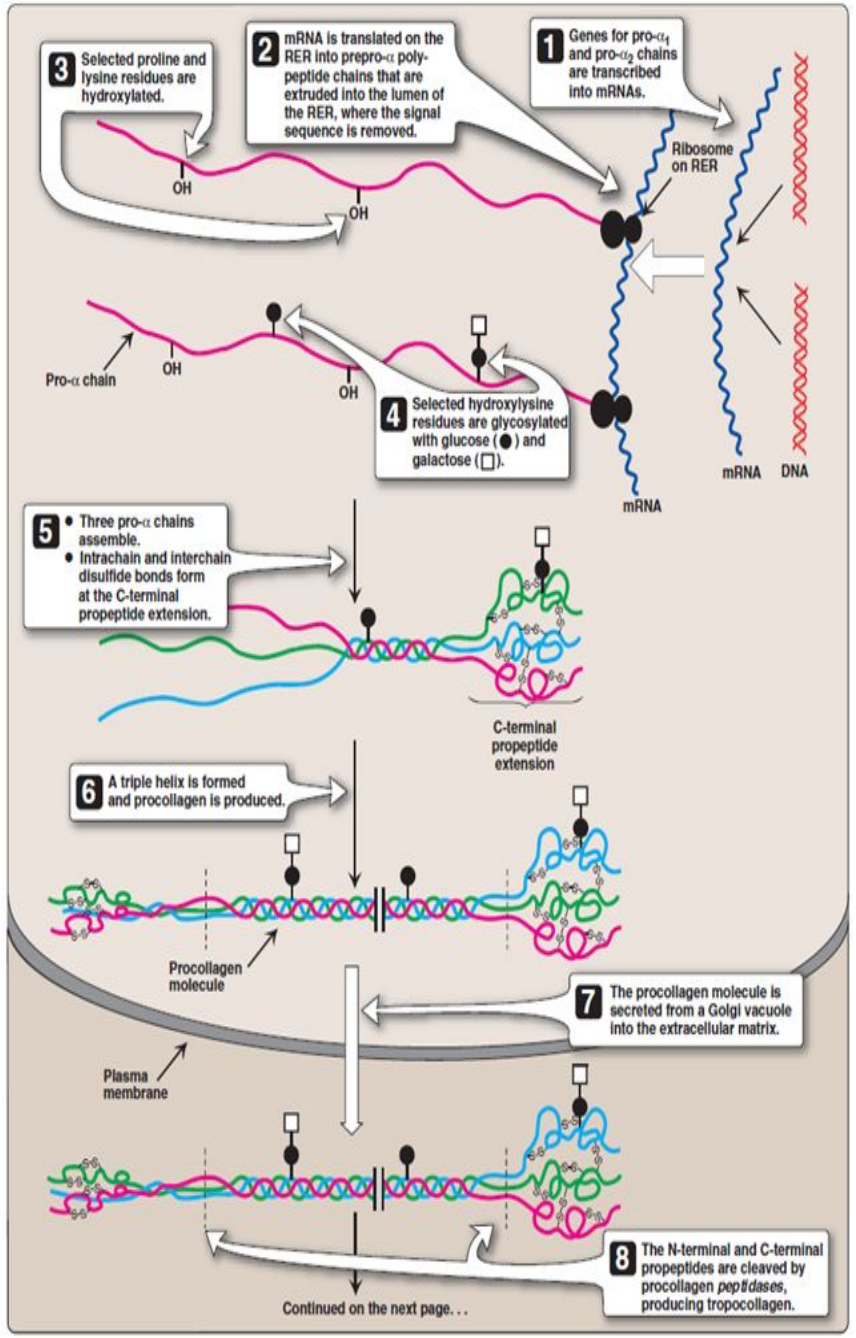
Biosynthesis of Collagen

★ overview:

- Synthesized in fibroblasts, osteoblasts, chondroblasts
- Pre-pro → Pro → Mature collagen
- Polypeptide precursors are enzymatically modified to form triple helix

★ steps:

1. Genes for pro chains are transcribed into the mRNA
2. transformation of Pre-pro → Pro in RER
3. Hydroxylation of proline and lysine residues by the hydroxylase enzyme
4. Glycosylation of some hydroxylysine (only) residues with glucose or galactose
5. Three pro-a chains assemble, intrachain and interchain disulfide bonds form at the C-terminal propeptide extension.
6. A triple helix is formed and procollagen is produced.
7. Secreted from Golgi vacuoles into the extracellular matrix as procollagen
8. Cleaved by N- and C- procollagen peptidases to release triple helical tropocollagen molecules



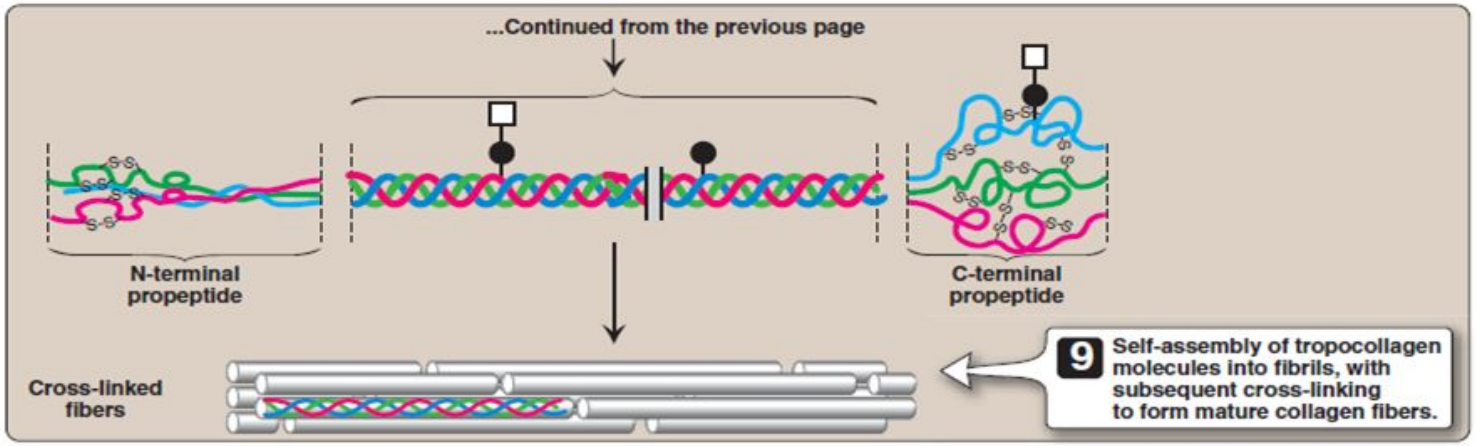
Notes:

★ **signal sequences:** sequences of amino acids that communicate with protein transport system within the cell to deliver the amino acid to its desired destination, and usually is removed after performing its function

★ Glycosylation: addition of sugar

★ peptidases: enzyme that breaks the peptide bond

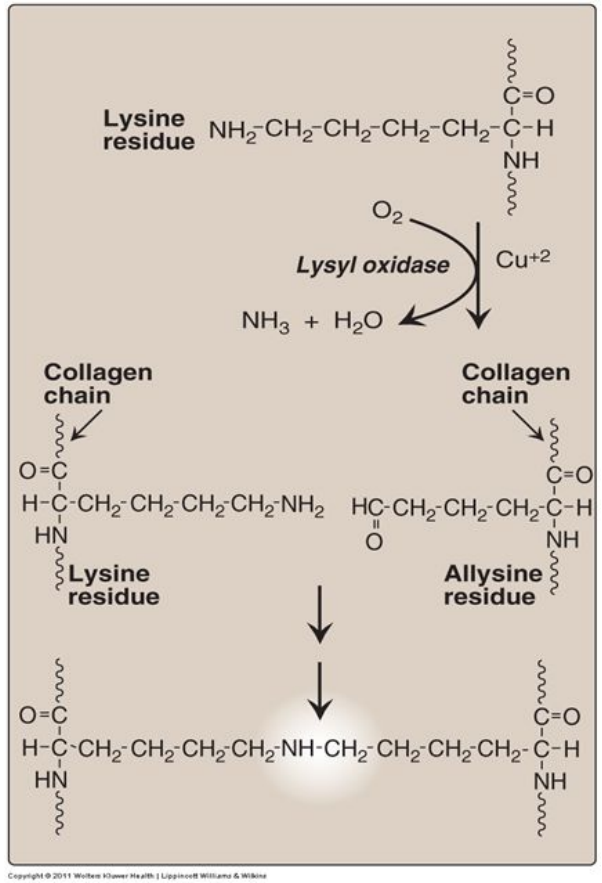
Final Step and Cross-Linking



step 9:

A. Tropocollagen molecules spontaneously associate to form collagen fibrils.

B. Lysyl oxidase oxidatively deaminates some of the lysine and hydroxylysine residues in collagen
   - The 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.



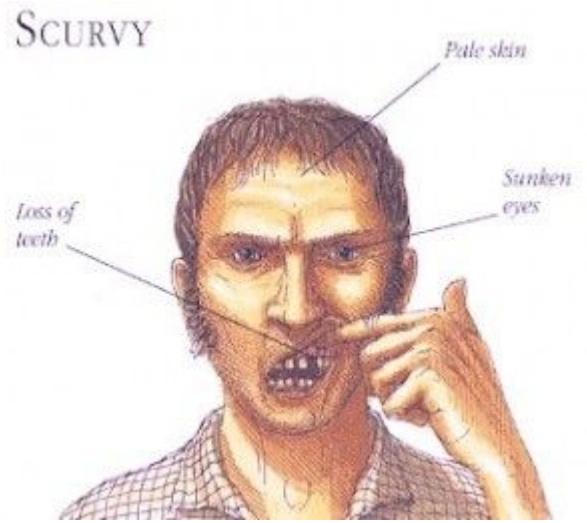
lysin —L-oxidase→ allysine

hydroxylysine —L-oxidase→ Hydroxyallysine

summary of collagen synthesis enzymes

substrate:	a. proline b. lysine	procollagen	a. lysine b. hydroxylysine
enzyme:	Hydroxylase	N- and C- procollagen peptidases	Lysyl oxidase
enzyme's function:	addition of OH	cleavage of N and C terminals	1. oxidation 2. deamination
product:	a. Hydroxyproline, b. hydroxylysine	tropocollagen	a. allysine b. Hydroxyallysine

Collagen Diseases



★ Acquired disease:

- Scurvy due to vitamin C deficiency

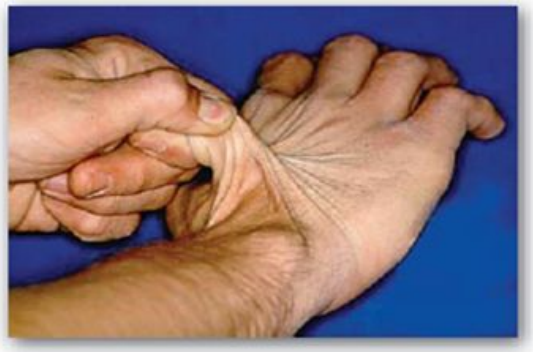
(you can read more about it in the pathology lectures, the picture is courtesy of 434's pathology team)

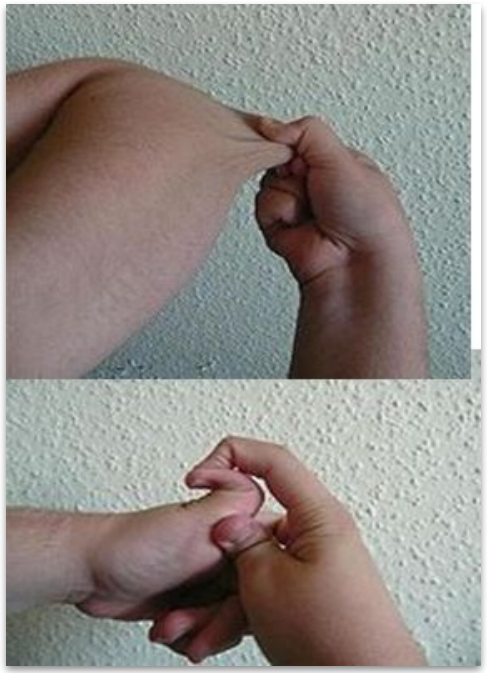
★ Genetically inherited diseases:

A. Ehlers-Danlos syndromes (EDS)
B. Osteogenesis imperfecta (OI)

A. Ehlers-Danlos syndrome

- 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



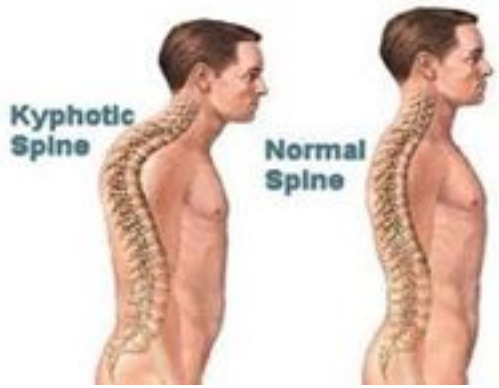


B. Osteogenesis imperfecta (brittle bone disease) الجسم الزجاجي :

- Bones 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.

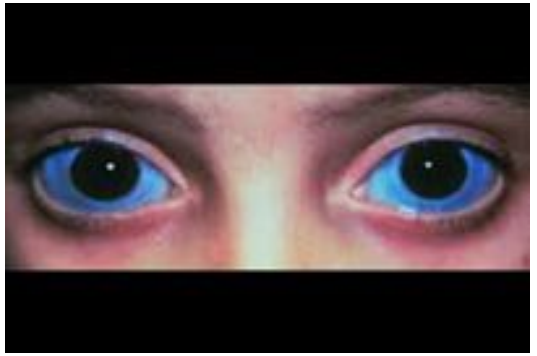


❑ Type II (most severe)

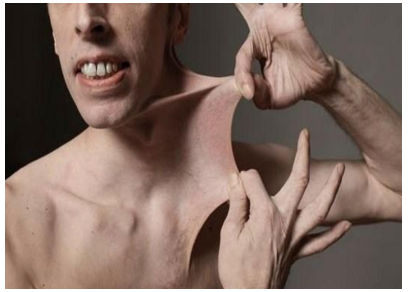
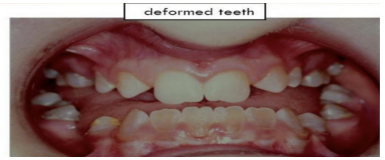
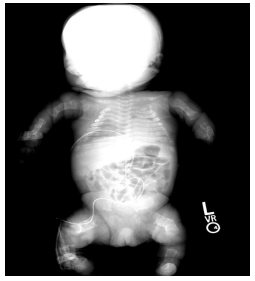
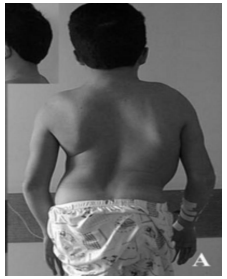
lethal in the perinatal period (fractures *in utero*)

❑ Type III (severe form)

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



summary of collagen diseases

Acquired disease:	Scurvy	vitamin C deficiency	
Genetically inherited diseases:	EDS	• deficiency of lysyl hydroxylase • N-procollagen peptidase • Mutations in the amino acid sequences of collagen I, III and V	hyperextensibility of joints and skin 
Genetically inherited diseases:	OI • Type I (most common) • Type II (most severe) • Type III (severe form)	Type 1 > characterized by mild bone fragility, hearing loss and blue sclerae. Type 2 > lethal in the perinatal period (fractures *in utero*) Type 3> Fractures at birth, short stature, spinal curvature Leading to a humped back (kyphotic) appearance and blue sclerae.	  

MCQs

Q1: the site of creatine synthesis is ……			
A) kidney	B) liver	C) heart	D) muscle
Q2: which of the following is used as an indicator of kidney disease ?			
A) creatine	B) creatine phosphate	C) serum creatinine	D) creatine kinase
Q3: which of the following collagen types are related to Ehlers-Danlos syndrome?			
A) collagen type I	B) collagen type III	C) collagen type V	D) all of the above

Answer key:

1) B
2) C
3) D

MCQs

Q1: Which of the following is an acquired collagen diseases resulting from Vitamin C deficiency:			
A) Scurvy	B) Osteopetrosis	C) Osteomyelitis	D) Rheumatoid Arthirits
Q2: Which of the following is responsible for oxidative deamination of lysine and hydroxylysine:			
A) Lysyl oxidase	B) Protein Kinase	C) Phosphofructokinase	D) None of the previous
Q3: Synthesis of collagen occurs in:			
A) Fibroblasts	B) Chondroblasts	C) Osteoblasts	D) All of them
Q4: Vitamin C is a necessary cofactor for which of the following enzymes?			
A) Hydroxylase	B) Lysyl oxidase	C) Glutathione peroxidase	D) None of the previous
Q5: Where Guanidinoacetate synthesized			
A) Liver	B) Kidney	C) Muscle	D) Blood
Q6: Creatine is a sensitive indicator of kidney disease			
A) True	B) False		
Q7: Decrease in muscle mass leads to :			
A) Increased level of urinary creatine	B) Decreased level of urinary creatine	C) Increased level of urinary creatinine	D) Decreased level of urinary creatinine
Q8: which one of the amino acids below prevents collagen chains to form α - helix ?			
A) Glycine	B) Lysine	C) Proline	D) Tyrosine

Answer key:

1) A. .
2) A.
3) D.
4) A.
5) B.
6) B.
7) D.
8) C.

SAQs

Q1: Mention two diseases associated with collagen abnormality:

Osteogenesis imperfecta, Ehlers-Danlos syndrome

Q2: What is the function of Lysyl oxidase?

oxidatively deaminates some of the lysine and hydroxylysine residues in collagen

Q3:mention three forms of the tissue distribution in collagen type I

skin , bone , tendon , blood vessels , cornea.

Q4: CK is responsible for what ?

generation of energy in contractile muscular tissue.

❖ Team leaders:

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- Taif Alotaibi
- Noura almazrou
- Elaf Almusahel
- Noura Alturki
- Nouf Alhumaidhi
- Abeer Alkhodair
- Alwateeen albalawi
- Shahd Alsalamh

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- ➔ **Alkaseem Binobaid**
- Saad Dammas
- Omar alghamdi
- Mohannad alqarni
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★ ان الله لا يعطي أصعب المعارك، إلا لأقوى جنوده.

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