جامعة الملك سعود
King Saud University

بِسْم الله الرحمن الرحيم

MED437 KING SAUD UNIVERSITY

BIO TEAM

Creatine metabolism and collagen diseases

437 Biochemistry Team

Color index:
Doctors slides
Notes and explanations
Extra information
Highlights

Musculoskeletal block

Objectives:

#By the end of this lecture the First Year students will be 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 :

1 amino acid is produced:

ornithine

3 amino acids are required:

glycine arginine methionine

DOCTOR'S NOTE :

Process occur kidney-----→ blood --------liver

Creatine biosynthesis

Required 3 amino acids

1- Glycine
2- Arginine
3- Methionine (as s-Adenosylmethionine)

Sites of biosynthesis

Step 1: Kidneys
Step 2: Liver

steps of biosynthesis

Glycine + Arginine

Amidinotransferase

Ornithine

Creatine

SAH

SAM

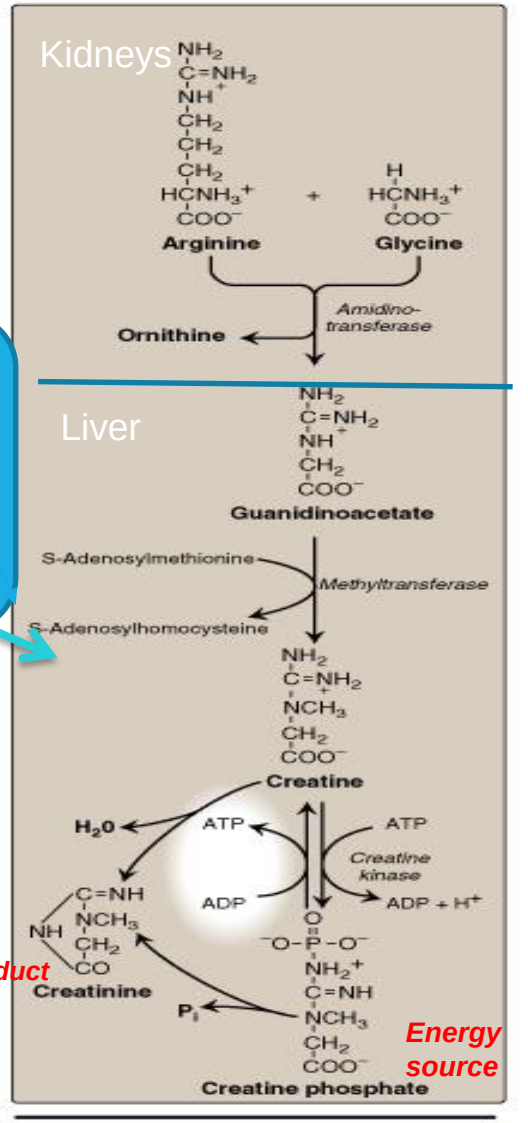
Methyltransferase

Guanidinoacetate

(It gives a methyl group)

End product

Energy source



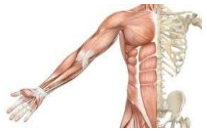
هنا بكل اختصار يتحدون الحمضين جلايسين و الارجينين بوجود انزيم يسمى Amidinotransferase ويعطيني ناتجين :

١- Ornithine : يتم الاستخلاص منه بواسطة kidney

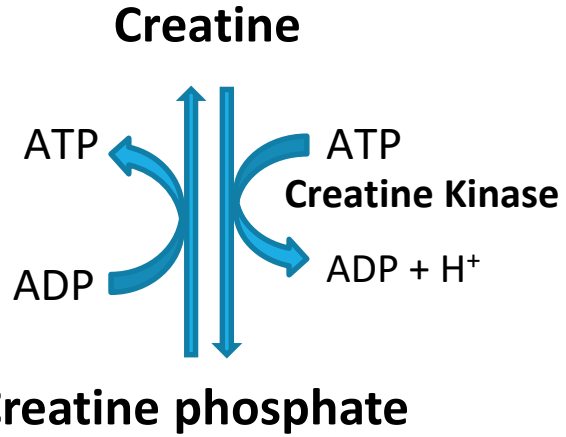
٢- Guanidinoacetate : يروح للكبد ، وهو اللي نبيه عشان يعطيني الكيراتين ولكن بشرط وهو إضافة مجموعة ميثايل بواسطة انزيم Methyltransferase ليعطي الكيراتين.

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 (main storage form for intense and immediate muscular 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.

Why dose the body make creatine phosphate?

Because muscle fibres can't store a lot of ATP
So it stores creatine phosphate so if the body need quick energy creatine phosphate will give it phosphate group to ADP to form ATP.

Creatine degradation :

يقومان بصناعة creatinineبنسب ثابتة تساوي 1-2 % من مجموعهما
it doesn't require enzyme of energy

Creatinine is excreted in the urine

Kidney disease → excretion problems → less creatinine in urine → more creatinine in blood

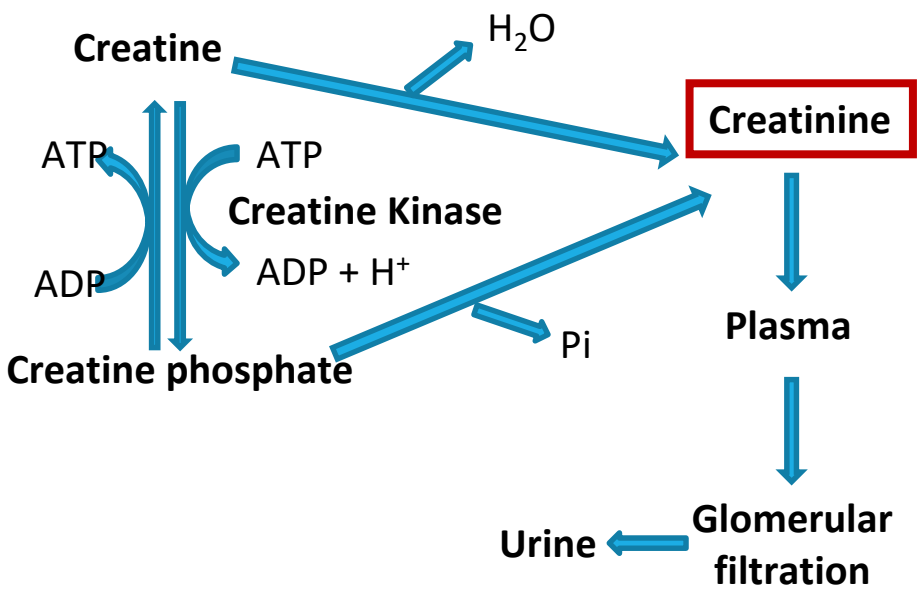
Serum creatinine increases with the impairment of kidney function

Creatine and creatine phosphate spontaneously form creatinine as an end product

Spontaneously: it doesn't require enzyme or energy

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

Its level depends on the muscle mass also.



Urinary **Creatinine**

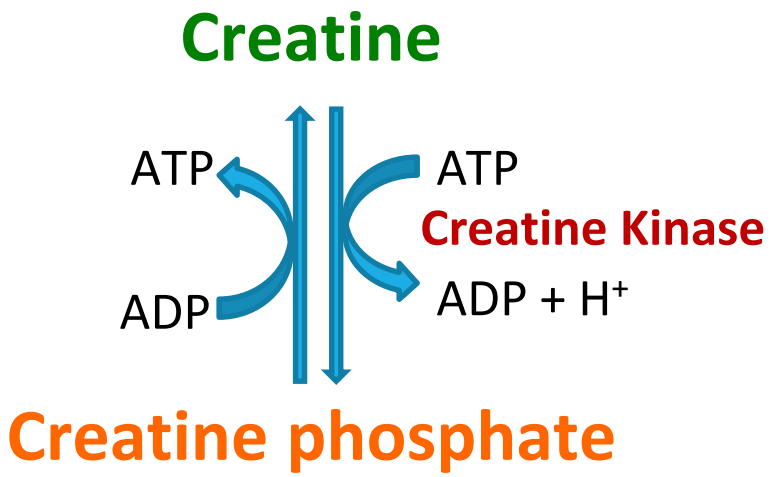
- A typical male excretes about 15 mmol creatinine/day.
- ***Decrease in muscle mass*** (e.g. in muscular dystrophy, paralysis) ***leads to decreased level of urinary creatinine.***
- The amount of creatinine in urine is used as an indicator for the proper collection of 24 hours urine sample.

Creatine kinase (ck)

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

Creatine phosphate و Creatine من خلال التحويل بين والعكس

- **CK** levels change in cardiac and skeletal muscle disorders.



Remmeber:
Creatine kinase = in the muscle
Amidinotransferase = in the kidney
Methyle transferase= in the liver

Collagen: Overview

Most abundant protein in the human body.

Collagens are highly stable molecules with half-lives as long as several years.

A fibrous protein that serves structural functions.

It is part of connective tissues, bone, teeth, cartilage, tendons, skin, blood vessels.

It has a long and rigid structure

Collagen structure

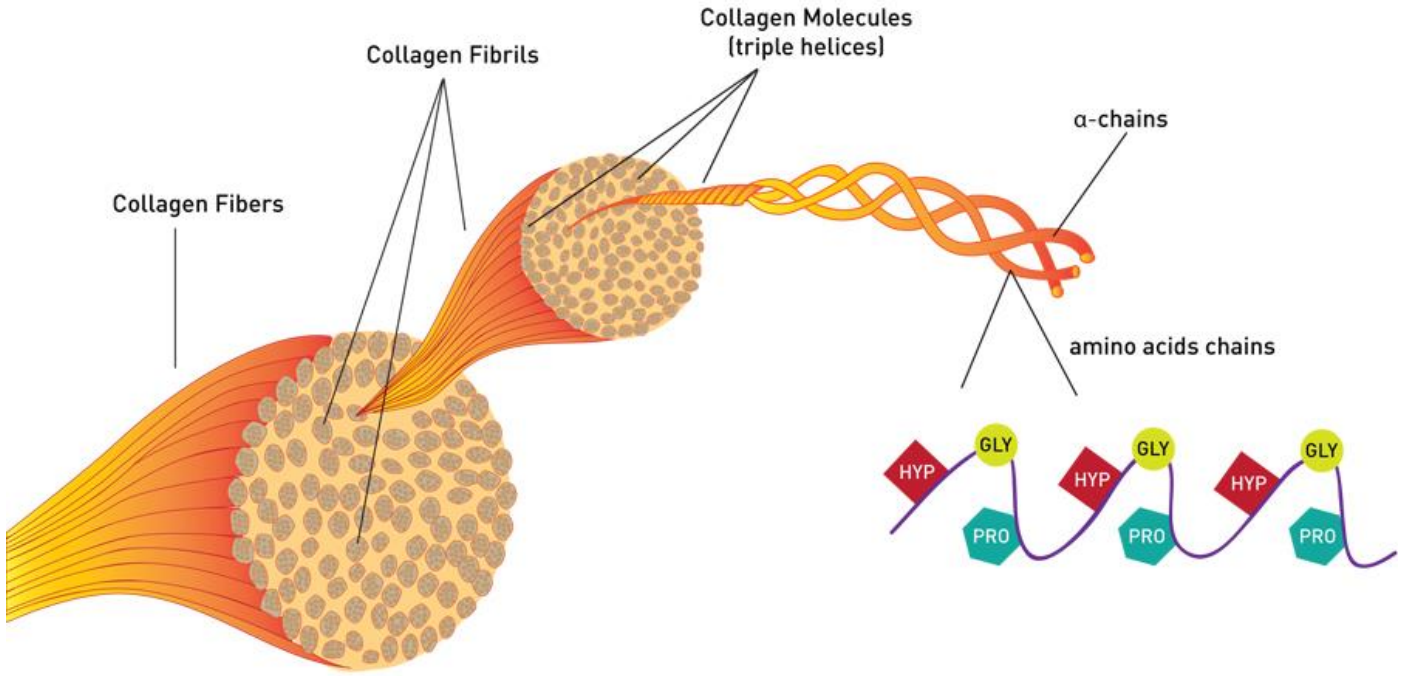
Collagen **α-chain** (~1,000 amino acids long) is rich in **proline** and **glycine**.

The glycine residues are part of a repeating sequence: **–Gly–X–Y–**

X = Frequently **proline**
Y = Often **hydroxyproline**
$(–Gly–Pro–Hyp)_{333}$
(Y can be also **hydroxylysine**)

Collagen structure

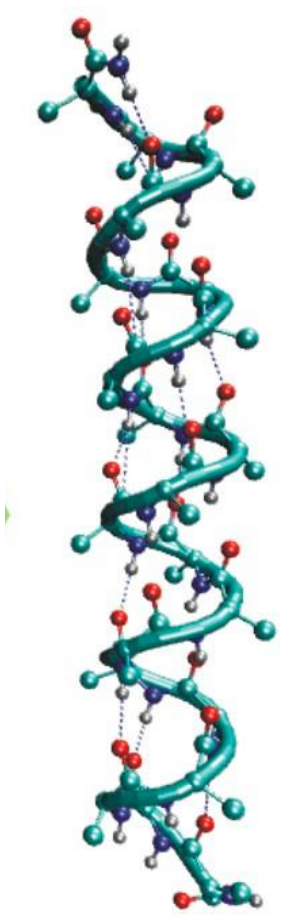
- ***Collagen*** consists of **three α-chains** wound around one another in a rope-like triple helix. "because of the proline, the **α-helix is not stabilized, so it becomes a collagen triple helix"**
- The three polypeptide chains are held together by **hydrogen bonds**.
- Two examples of protein secondary structure: **collagen helix** and **α-helix**.



Collagen structure

- Rich in **proline** and **glycine** amino acids.
- **Proline** prevents collagen chains to form α-helix because:
  - ***Proline*** has no back bone amino group (it is a ring structure with secondary amino group); therefore hydrogen bonding within the helix is not possible.

The secondary structure α-helix is different from collagen helix; in collagen helix the hydrogen bonds are between the chains (intrachain); while in α-helix the hydrogen bonds are within chains (interchain).



α-helix

Collagen helix

Non-standard amino acids in Collagen

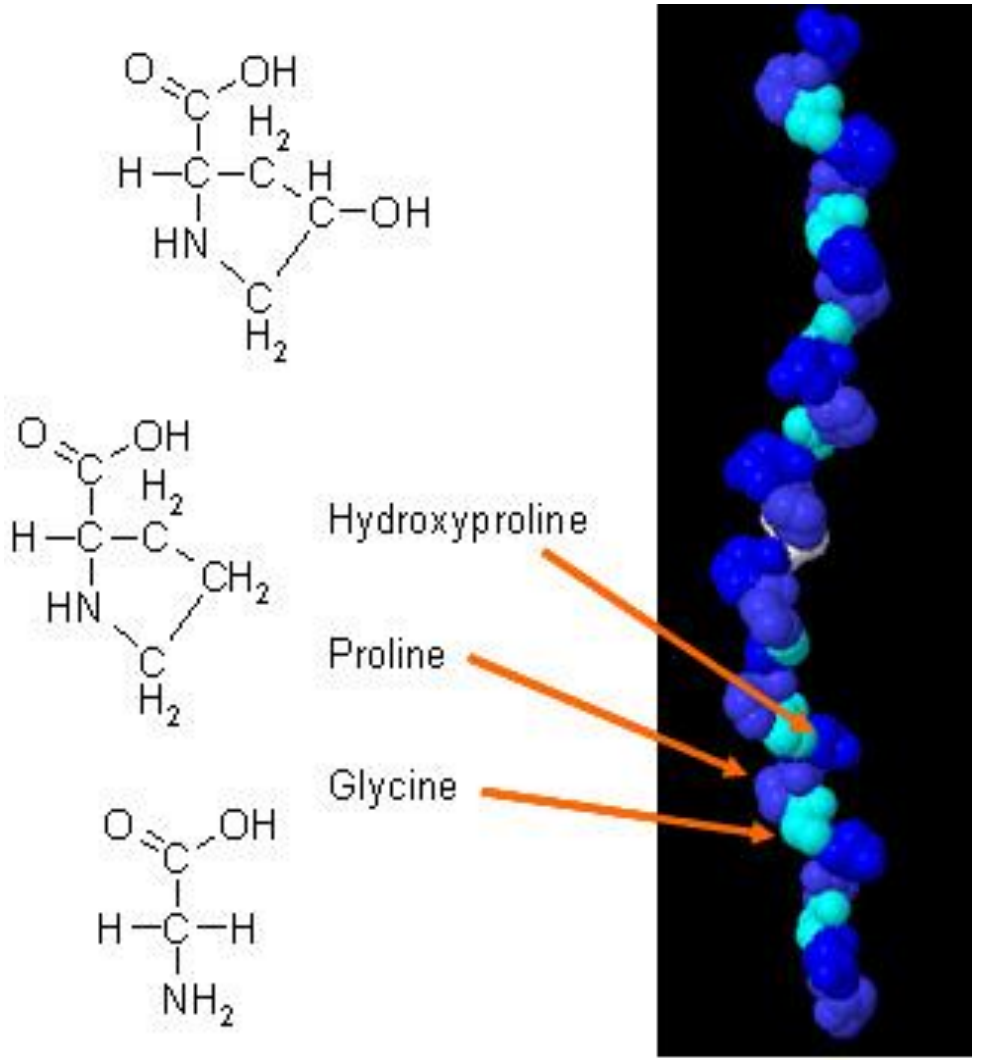
- **Proline** and **lysine** are converted to hydroxyproline and hydroxylysine; by ***hydroxylase*** enzymes during post-translational modifications.

  Why is *hydroxyproline* important?

  To stabilize the triple-helical structure.

- The enzyme requires **vitamin C** for its function.

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 their functions.*
- Variations in the amino acid sequence of α-chains result in different properties.

Examples:

- Type I: $(\alpha 1)_2\ (\alpha 2)_1$ (Two α-1-chain + α−2- chain)
- Type II: $(\alpha 1)_3$ (Three α-1-chain)

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

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Types of collagen can be categorized into 3 groups:

1. **Fibril-forming** (Type 1, 2 and 3)
2. **Network-forming** (Type 4 and 7)
3. **Fibril-associated** (Type 9 and 12)

You have to know the types

biosynthesis of collagen

- Collagen is synthesized in fibroblasts, osteoblasts, 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***.

The modifications are:
1-hydroxylation of proline and lysine residues
2- glycosylation of some hydroxylysine residues with glucose or galactose

- Procollagen is 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***. This produces mature collagen

Biosynthesis of Collagen

1- gene of pro-α chains are transcribed into mRNA.

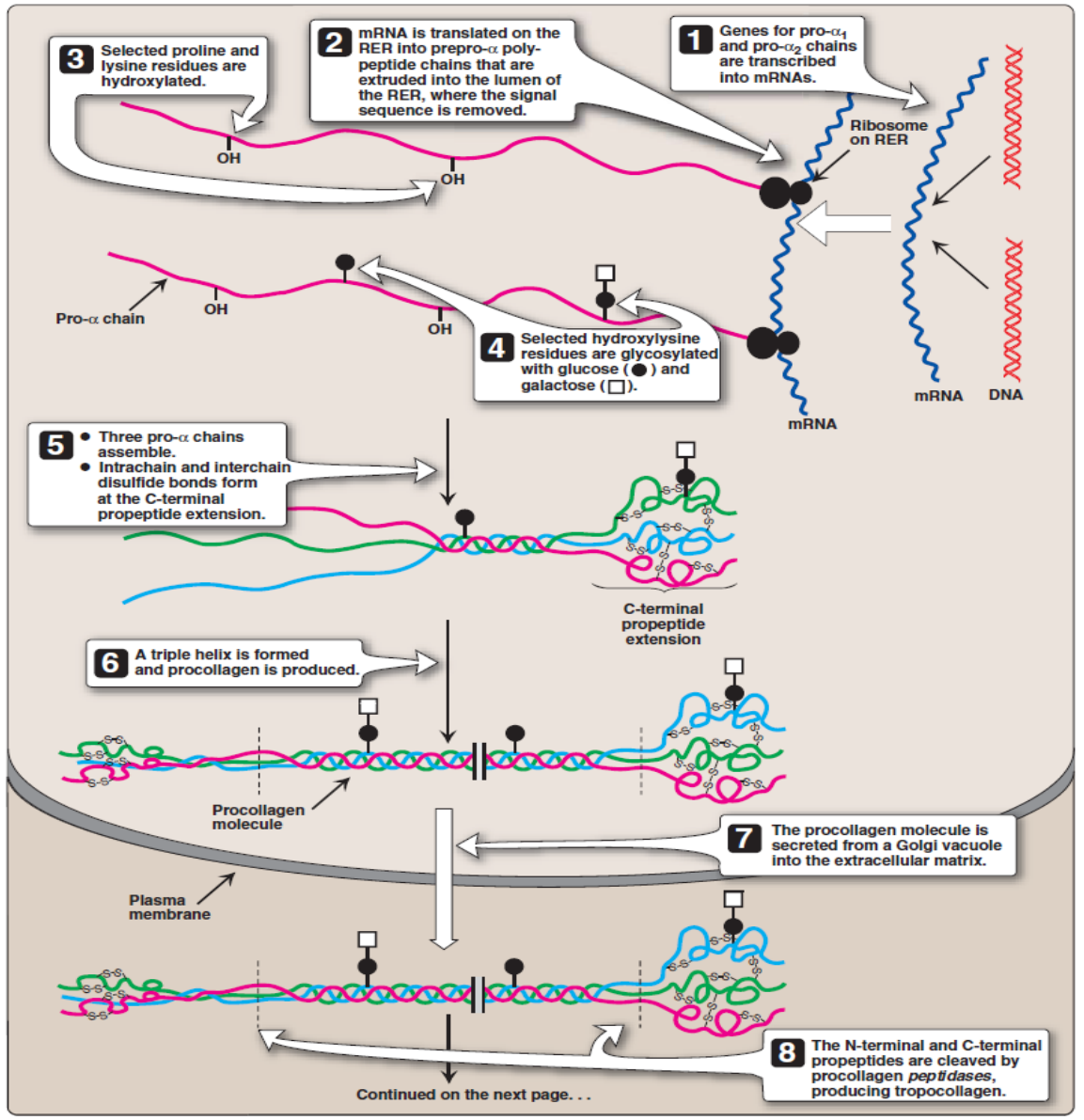
2- This mRNA translated on the RER into prepro-α- polypeptide chains that are extruded (forced out) into RER lumen, where the signal sequence is removed.

3-proline and lysine residues are hydroxylated by hydroxylase to form hydroxyproline and hydroxylysine in the presence of vitamin C.

4- hydroxylysine are glycosylated(add carbohydrate to it) with glucose (●) and galactose (□).

5- three pro-α assemble and interchain & intrachain disulfide bonds are formed at the C-terminal propeptide extension.

6- A triple helix is formed and procollagen is produced.

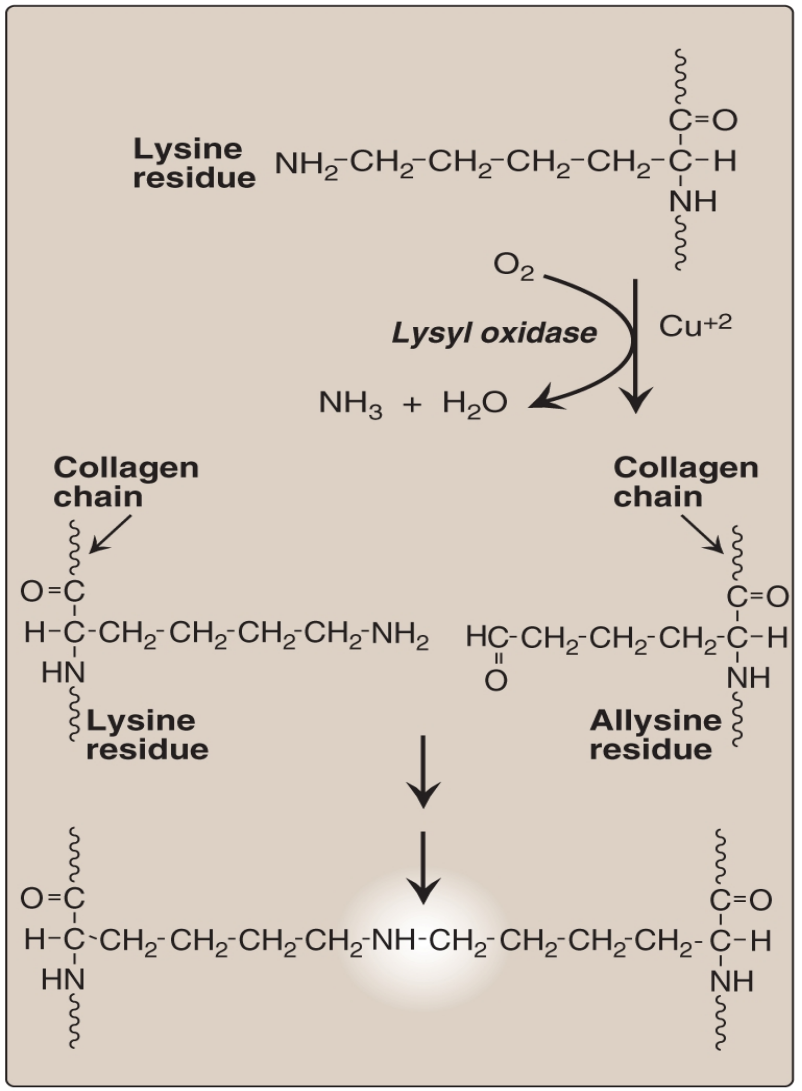


Cross-linking of collagen fibrils

- **Steps**:

1. ***Lysyl oxidase*** oxidatively deaminates some of the lysine and hydroxylysine residues in collagen.

2. The reactive aldehydes – allysine and hydroxyallysine condense with lysine or hydroxylysine residues in neighboring collagen molecules to form covalent cross-links → this produces ***mature collagen fibers***.



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Biosynthesis of Collagen

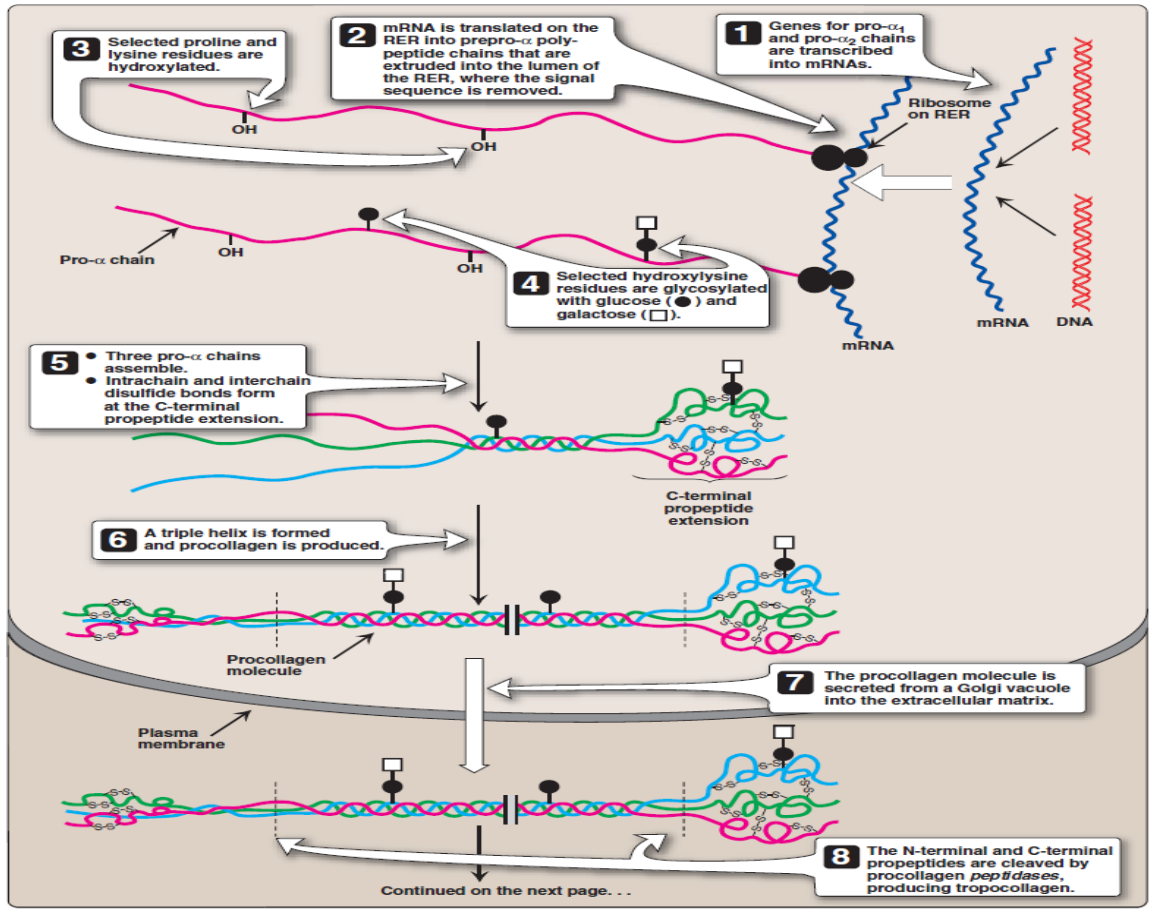
7- the procollagen molecule is secreted through the Golgi apparatus to the extracellular matrix in Golgi vacuole.

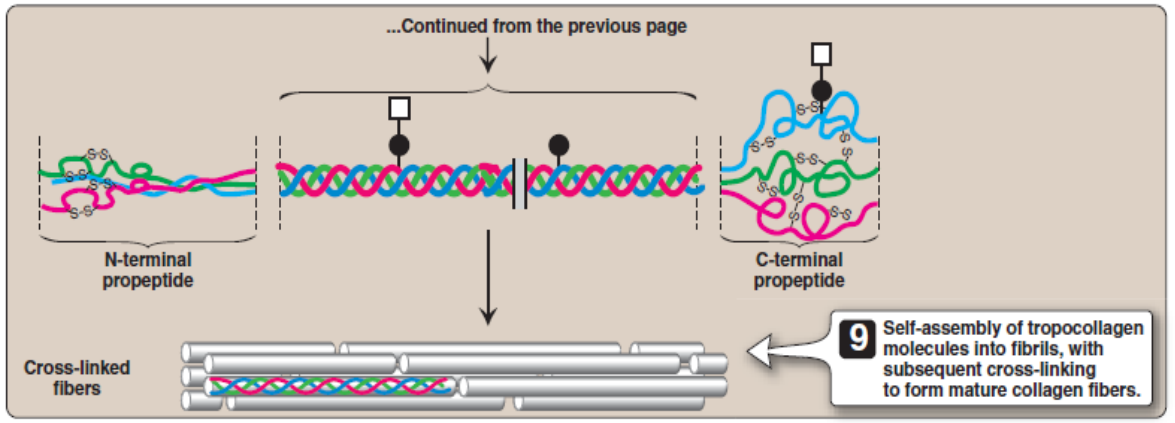
8- The N- & C-terminal propeptides of the procollagen molecule are cleaved by procollagen peptidases, producing tropocollagen.

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.



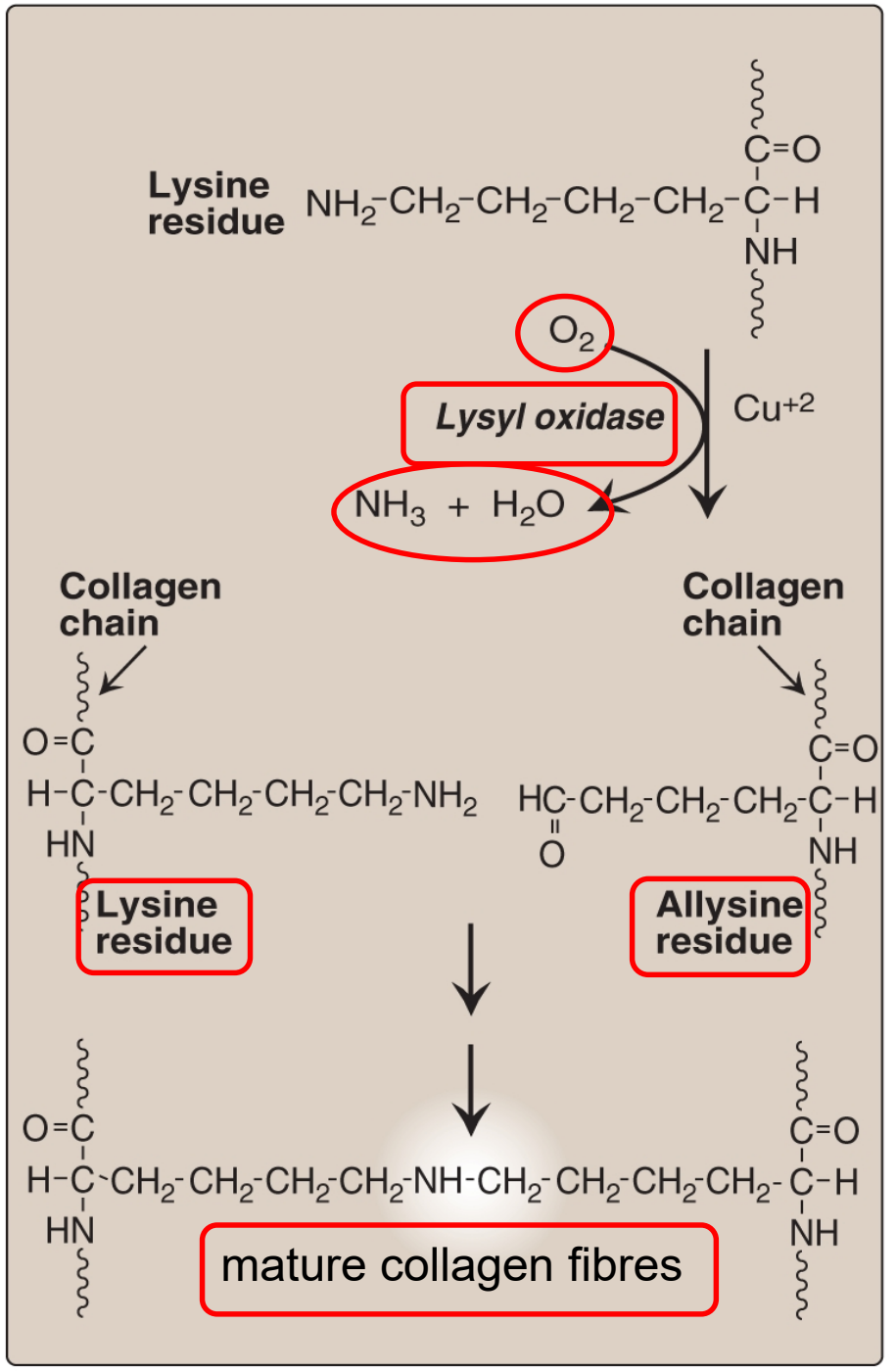


Crosslinking of Collagen Fibrils

1- Lysyl oxidase oxidatively deaminates some of the lysine and hydroxylysine residues in collagen. (by adding oxygen and removing NH_3 and H_2O).

2- The reactive aldehydes – allysine and hydroxyallysine condense with lysine or hydroxylysine residues in neighboring collagen molecules to form covalent cross-links.

3-this produces mature collagen fibres.



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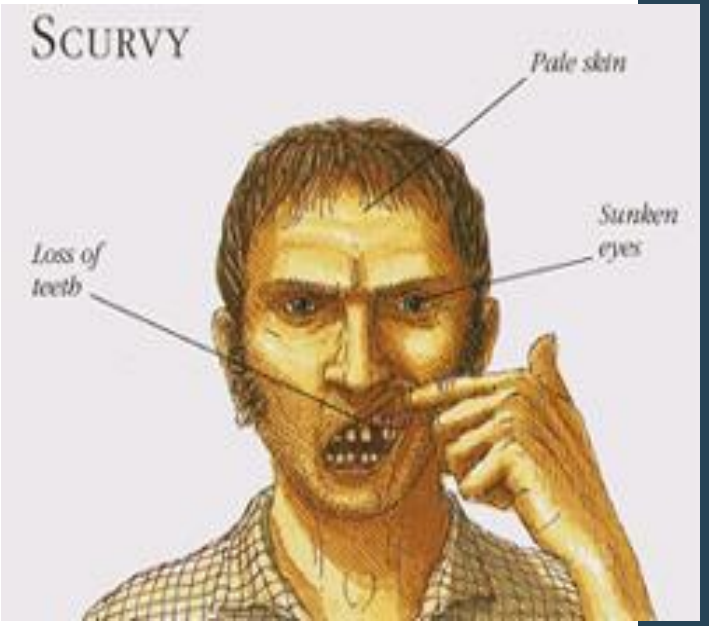
Collagen diseases

we have two types of collagen diseases:

1-Acquired disease:

The deficiency in vitamin C will cause Scurvy disease .



(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 .

2-Geneticlly inherited diseases:

- Ehlers-Danlos syndromes (EDS) فرط المرونة
- Osteogenesis imperfecta (OI)

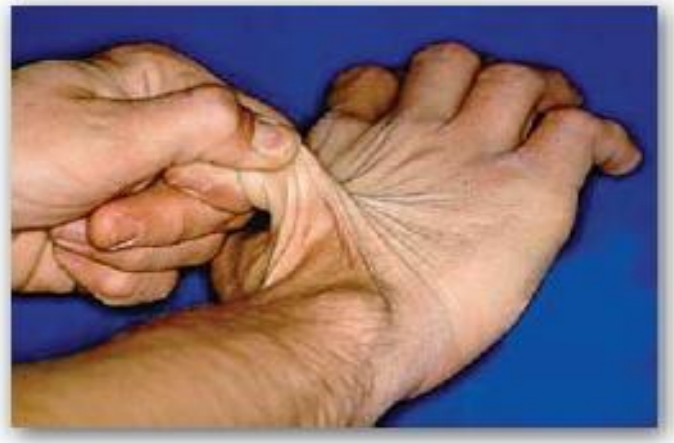
Collagen diseases

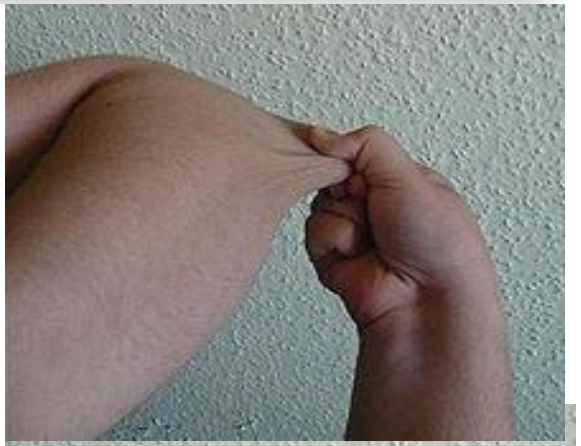
Ehlers-Danlos syndrome
Duo to :

deficiency of lysyl hydroxylase or N-procollagen peptidase

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

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





Collagen diseases

-Osteogenesis imperfecta (brittle bone disease):

Bones fracture easily with minor or no trauma

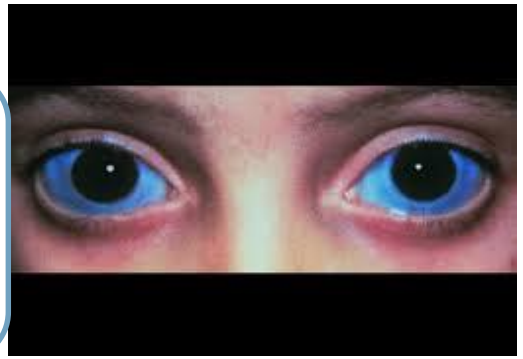
Mutations replace glycine with amino acids having bulky side chains preventing the formation of triple helical conformation.

It has three types :

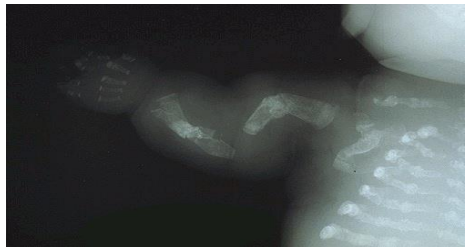
Type I (most common) characterized by mild bone fragility, hearing loss and blue sclerae

بالعادة يكون سميك بس بسبب مشكلة الكولاجين يصير انحف ف يتغير لونها

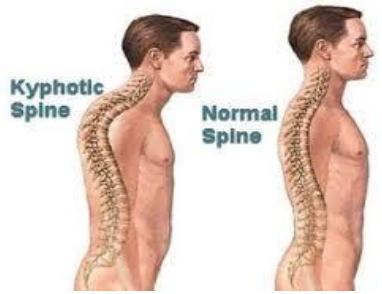
Type I



Type II (most severe) and lethal in the perinatal period (fractures *in utero*) ممكن يجيه الكسر في بطن امه



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



MCQ

- ***1- where Guanidinoacetate synthesized ?***
- A- liver b- kidney
  c- muscle d- blood
- ***2- how many amino acid required for glycine?***
- A- one b- two c- three d-five
- ***3- Collage consists of***
- A- one α-chains b- two α-chains and one beta c- three α-chains
  d- one α-chains and one beta
- ***4 -creatine is a sensitive indicator of kidney disease***
- a- true b-false
- ***5-collagen structure rich in glycine and arginine***
- A- true b- false
- ***6- Collage consists of***
- A- one α-chains b- two α-chains and one beta c- three α-chains
  d- one α-chains and one beta

answers :
1-b
2-c
3-c
4-b
5-b
6-c

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