COLLAGEN AND CREATINE: PROTEIN AND NONPROTEIN NITROGENOUS COMPOUNDS

Color index:
- Important
- Extra explanation

"THERE IS NO ELEVATOR TO SUCCESS. YOU HAVE TO TAKE THE STAIRS"

435 Biochemistry Team

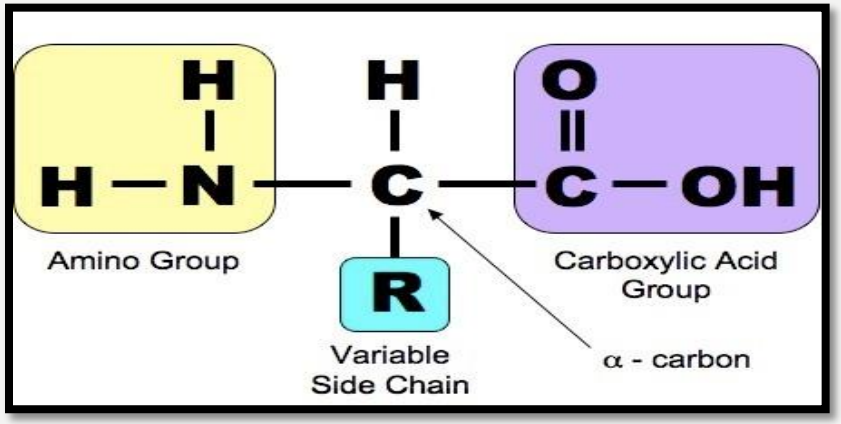
RECALL:

- Amino acid structure.
- Proteins.
- Level of protein structure.

Amino acid structure

Alpha carbon that is attached to:

- 1- hydrogen atom *H*
- 2- side chain *R* — (which is distictive for each amino acid and gives the amino acid a unique set of characteristic)
- 3- two functional groups — - Carboxylic acid group *COOH*
  - Primary amino acid group *NH2* (except for proline which has a secondary amino acid)

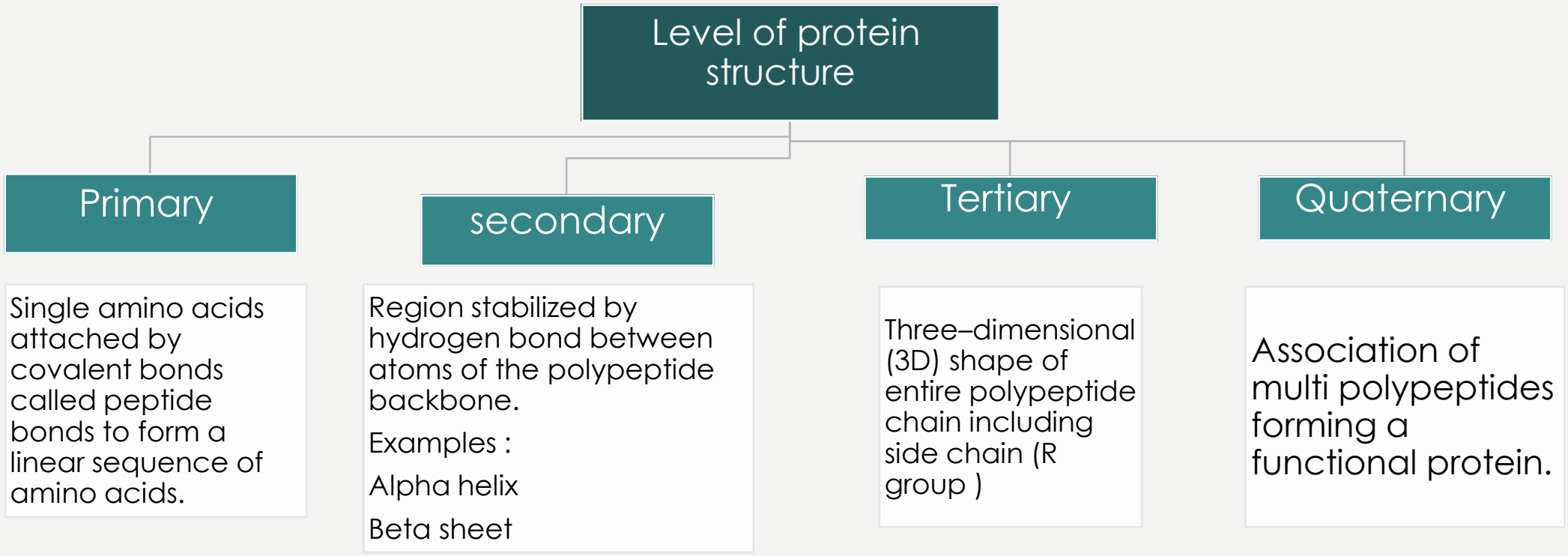


- The amino acid with a free amino Group at the end called "N-Terminus" .
- The amino acid with a free carboxylic group At the end called " C-Terminus"

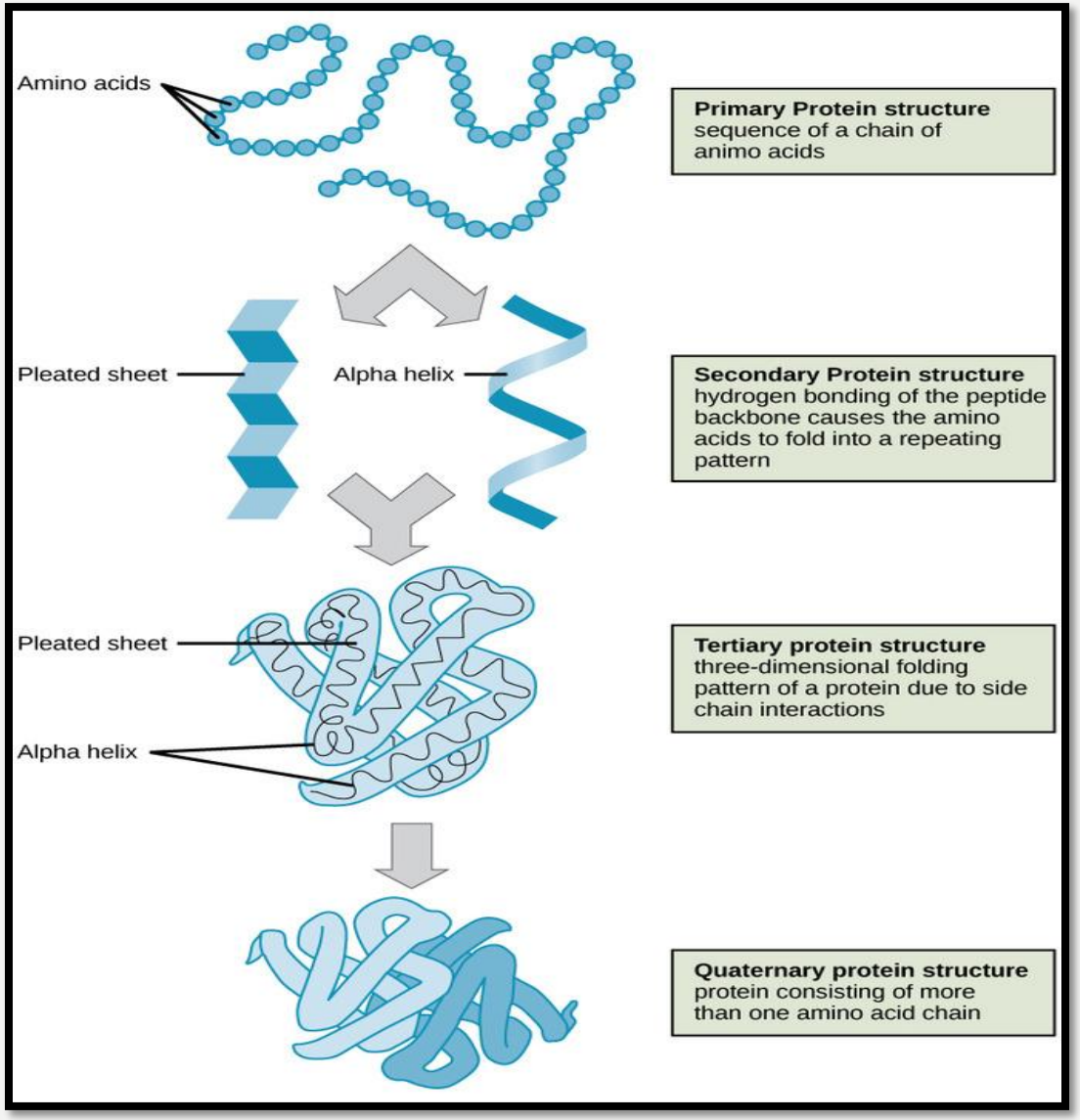
Proteins

Proteins structure :

- Building blocks , made of small molecules unit called amino acid which attached together in long chain by a peptide bond .



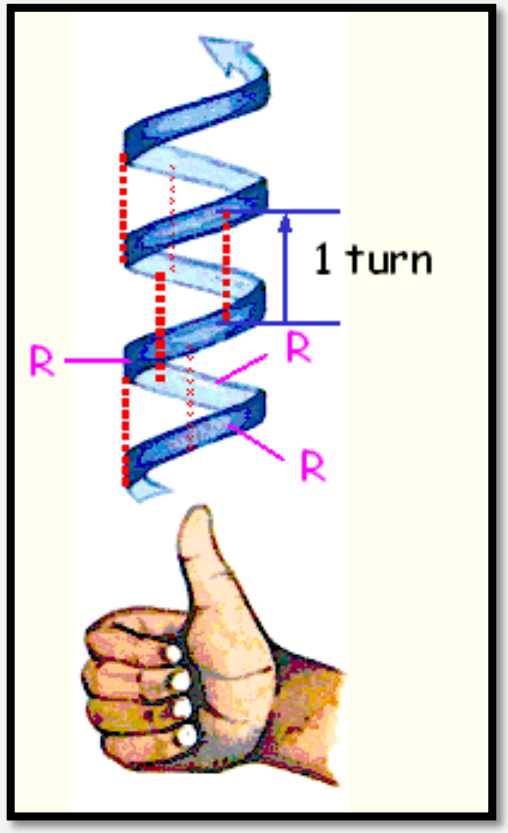
Level of protein structure



Secondary structure

Alpha helix:

- It is right-handed spiral , which side chain extend outward.
- it is stabilized by hydrogen bond , which is formed **between** the peptide bond carbonyl oxygen and amide hydrogen.
- each turn contains 3.6 amino acids.



Amino acid that disrupt alpha helix

- **Proline** → Imino group , interferes with the smooth helical structure .
- Glutamate , aspartate , histidine lysine or arginine → Ionic bond
- **Bulky side chain such as tryptophan**
- Branched amino acids at beta-carbon such as , valine or isoleucine

OBJECTIVES:

- 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 the different diseases associated with collagen

Creatine Metabolism

-Creatine phosphate (phosphocreatine): (Energy source)

It is the **phosphorylated derivative** of creatine found in muscle,is a high-energy compound that act as immediate supply of ATP(small amount) during the first few minutes of intense muscle contraction by transferring its phosphate to ADP.

*العضلة تحتاج طاقة عند انقباضها، مصدر هذه الطاقة في الدقائق الاولى هو كرياتين فوسفات الذي يزودها بكميات قليلة من الطاقة ولكن بسرعة عاليه

- Creatine metabolism(creatine biosynthesis+creatine degradation) overview:

- Creatine is synthesized in liver and kidney tissue, from (1)**glycine** and (2)**arginine**, plus (3)**a methyl group**(CH3) from SAM.

- Creatine and creatine phosphate spontaneously cyclize at a slow but constant rate to form **creatinine**, which is excreted in the urine.

*عند انتهاء انقباض العضلة يتم التخلص من الكرياتين والكرياتين فوسفات بعملية بطيئة وتلقائية بمعدل ثابت يتم فيها تحويل الكرياتين والكرياتين فوسفات إلى كرياتينين ،الذي يتم التخلص منه مع البول

Note: creatine is not the same as creatinine.

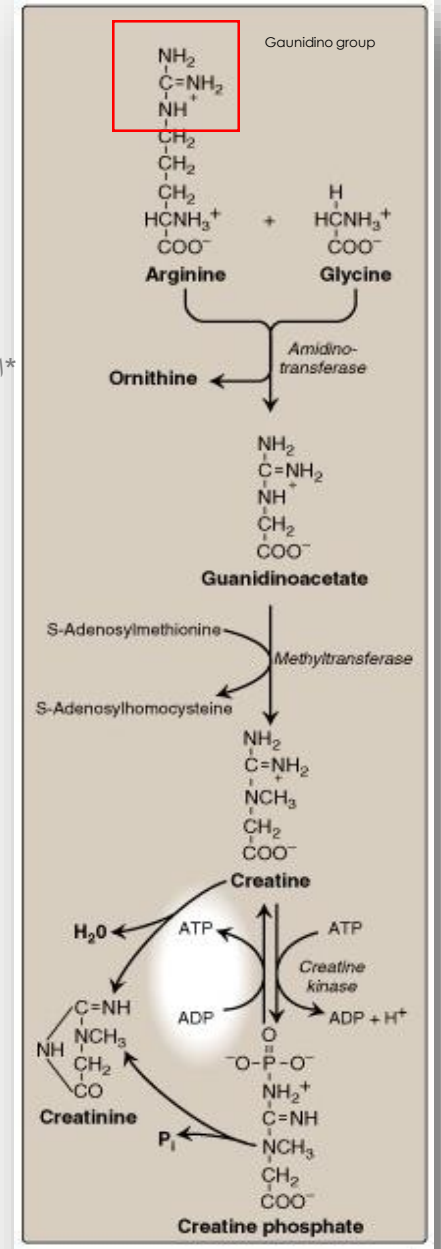


Figure 21.16
Synthesis of creatine.

Creatine Biosynthesis:

-Three amino acids are required:

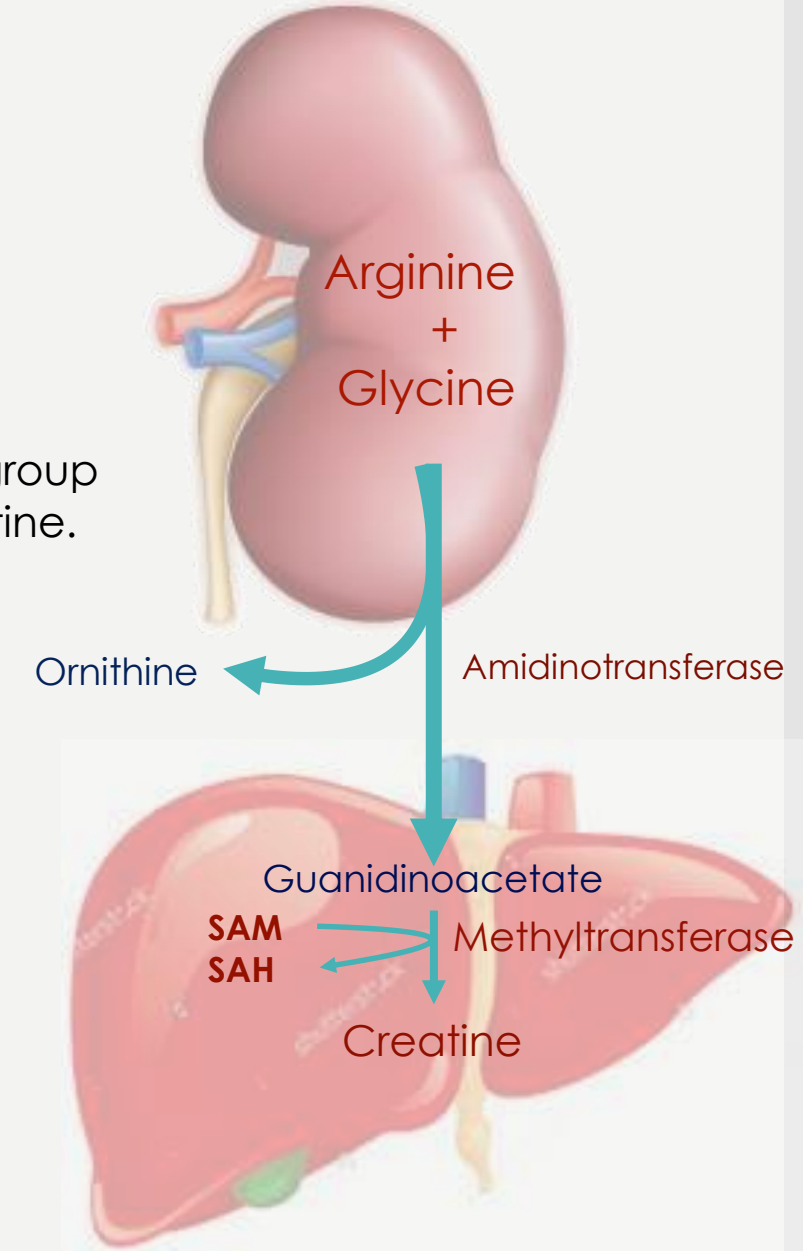
Arginine, Glycine, and methionine(as s-adenomethionine).

-In the kidney:

*Guanidino group of Arginine associate with the Glycine to form Guanidinoacetate by Aminotransferase.

-In the liver:

*SAM contributes by methyl group and comes out as SAH, this methyl group will associate with guanidinoacetate by methyltrasferase to form Creatine.



Note:

-The main organ for creatine biosynthesis is the liver.

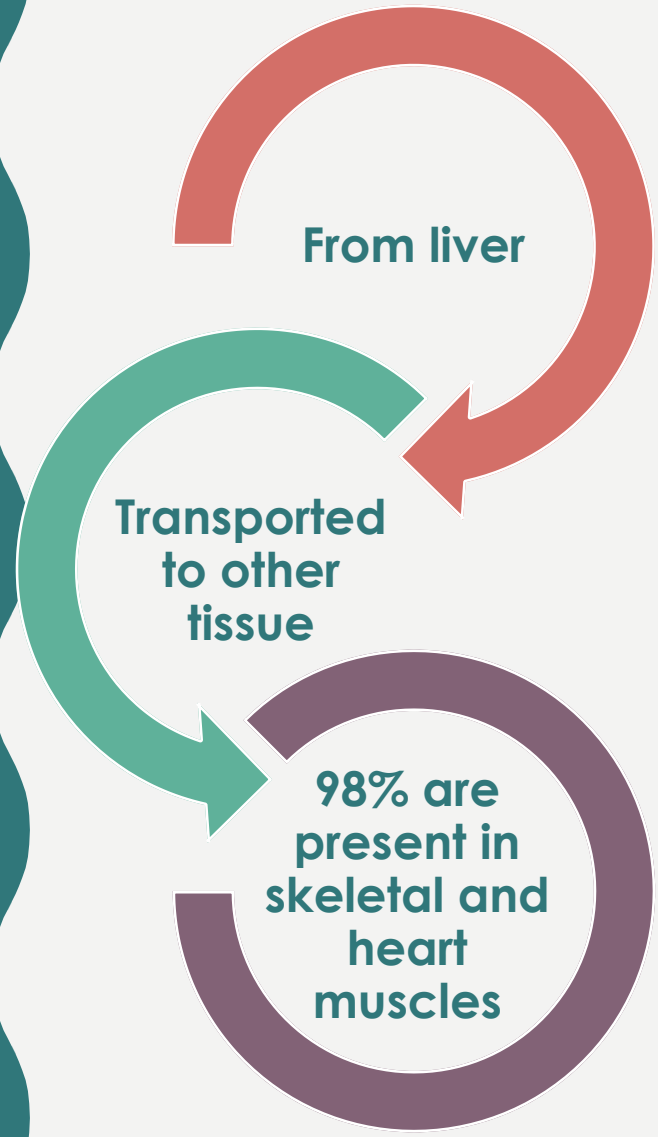
-Arginine and Glycine are amino acids.

-SAM: (S-Adenosylmethionine) "SAM is methyl carrier"

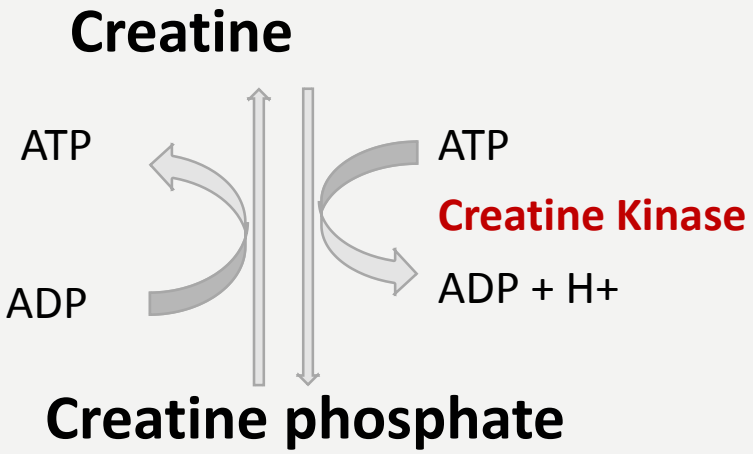
-SAH: (S-Adenosylhomocysteine)

-Arginine converted to Ornithine ,but it does not include in the protein structure.

Distribution of body creatine



- In Muscle, gets converted to the high energy source: **creatine phosphate (phosphocreatine)**



Creatine phosphate (phosphocreatine): is a ready limited source of energy, present in muscles. *At the time of need (low ATP) , creatine phosphate will give its phosphate group to the presenting ADP, converting ADP to ATP. By doing so, it forms creatine. Which can be Re-phosphorylated back into Creatine phosphate.

*بعد تكوين الكيراتين في الكبد سينتقل إلى انسجه أحرى ، ٩٨% منها سيذهب الى العضلات الحركية والى العضلات القلبية.
*في العضلات سيضاف إليه فوسفات وذلك بمساعدة الكيراتين كاينز وسيتحول إلى مصدر طاقة عاليه : كيراتين فوسفات.

Creatine phosphate

- What it creatine phosphate?

Creatine phosphate is high energy compound and acts as **storage form** of energy in the muscles.

Note: Creatine phosphate is not abundant or prolonged source of energy , but it is immediate

- What does it provide?

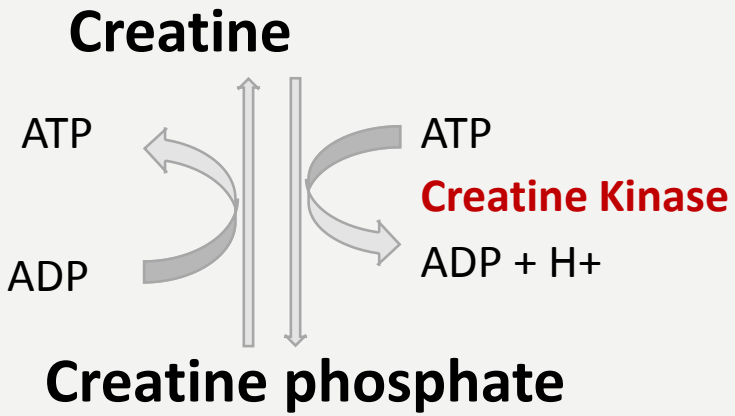
It Provides a small but, ready source of energy during first few minutes of intense muscular contraction.

#Important:

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

↑ large muscle mass : ↑ amount of creatine

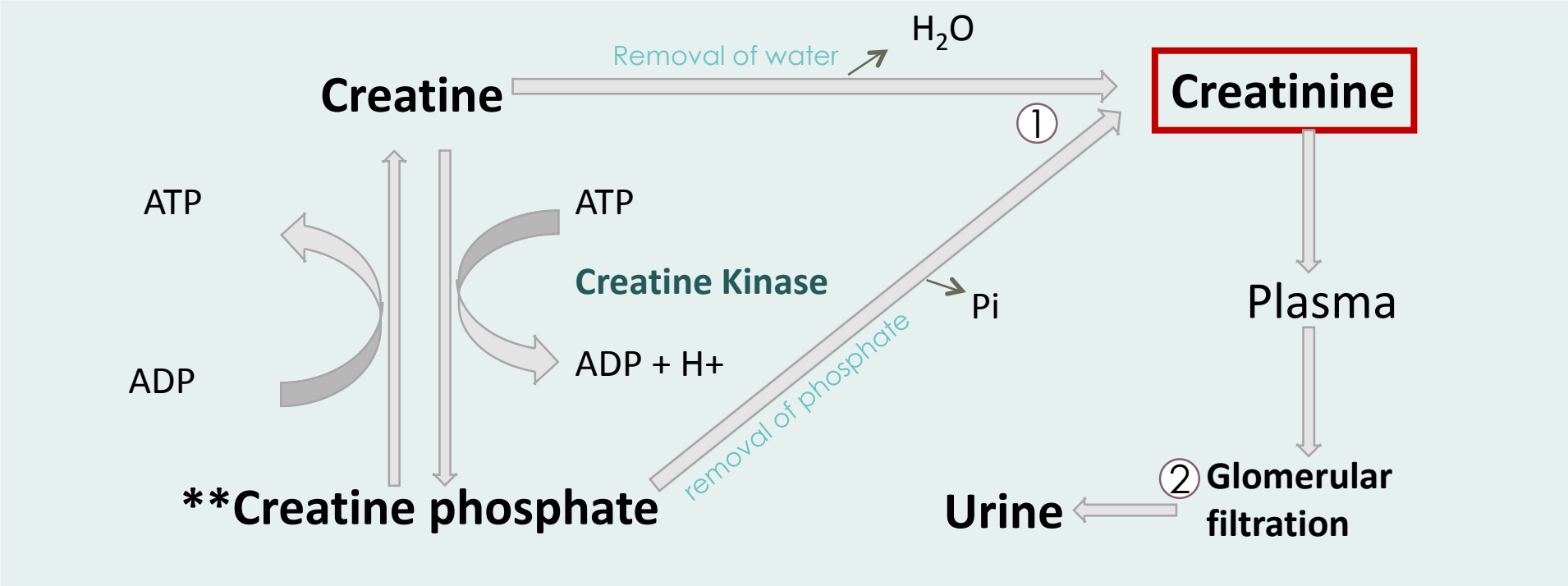
- The amount of creatinine and creatine phosphate are also proportional to muscle mass



Notes:

* reversible reaction
* ATP is used for the synthesis of creatine phosphate. (it gives one of its phosphates)

Creatine degradation



①Creatine and creatinephosphate **spontaneously** (without enzyme) form **creatinine** as an end product.

②Creatinine will leave muscle cell and get excreted in the urine.

#Important: *Serum creatinine is a sensitive indicator of **kidney disease** (Kidney function test) and **increases** with the impairment of kidney function And it means that the excretion of creatinine by the kidney is decreased

*because creatinine normally is rapidly removed from the blood and excreted, so if it doesn't get excreted we can conclude that the kidney has a functional problem (malfunction).
*if you remember we've talked about the creatinine in the foundation block and we said that the cystatin C is a better kidney malfunction biomarker because it Is independent of the age, gender and muscle mass unlike the creatinine which depends on those factors

Muscle's function tests

Urinary Creatinine

The urine creatinine test measures the amount of creatinine in urine.

- A typical **male** excretes about 15mmol of creatinine per day.

- The amount of creatinine in urine is used as an indicator :

1. **For the proper collection of 24 hours urine sample.**

2. Of a **decrease** in the muscle mass due to muscular dystrophy or paralysis, this leads to decreased level of creatinine in urine.

Note: Level of creatinine is constant per day. May increase after a high-protein meal during the day.

Creatine Kinase (CK)

This test measures the amount of an enzyme called creatine kinase (CK) in your blood.

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

- *Thus, CK levels are changed in **disorders of cardiac and skeletal muscle** **(very important)**.

For example, an increased level in serum might be a marker of myocardial infarction, or skeletal muscle injury.

Note: CK is made up of three enzyme forms (isoenzymes): in Brain, Cardiac, and skeletal muscles.

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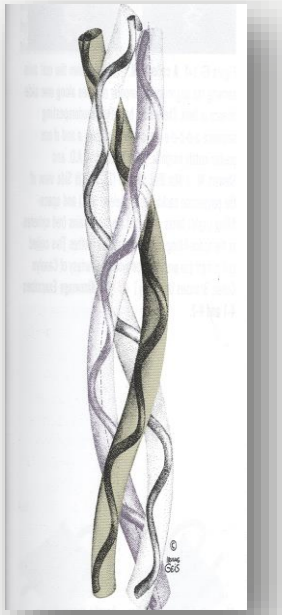
Collagen



- **What is collagen?**

-**Most abundant protein** in the human body.
-highly stable molecules, having half-lives as long as several years.
-*fibrous protein (Row like structure) that serves structural functions.

- **They're part of connective tissues:** bone, teeth, cartilage, tendon, skin, blood vessels.

- Has a long rigid structure.

Collagen Structure (**α-chain):

- 1,000 amino acids long.
- 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 or hydroxylysine

(glycine, proline ,hydroxyproline or hydroxylysine : سلسلة متصلة من)*

- 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).

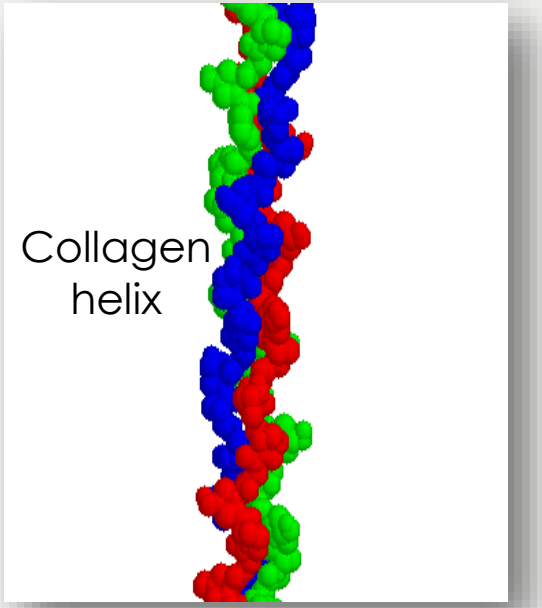
#Important:

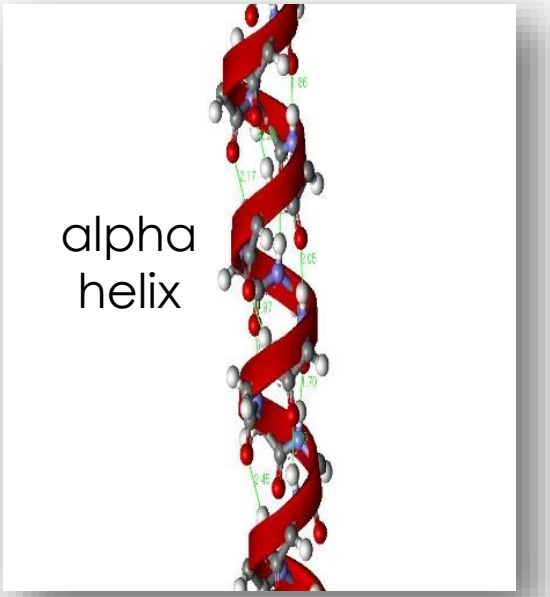
Proline prevents collagen chains to form a-helix because:

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

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





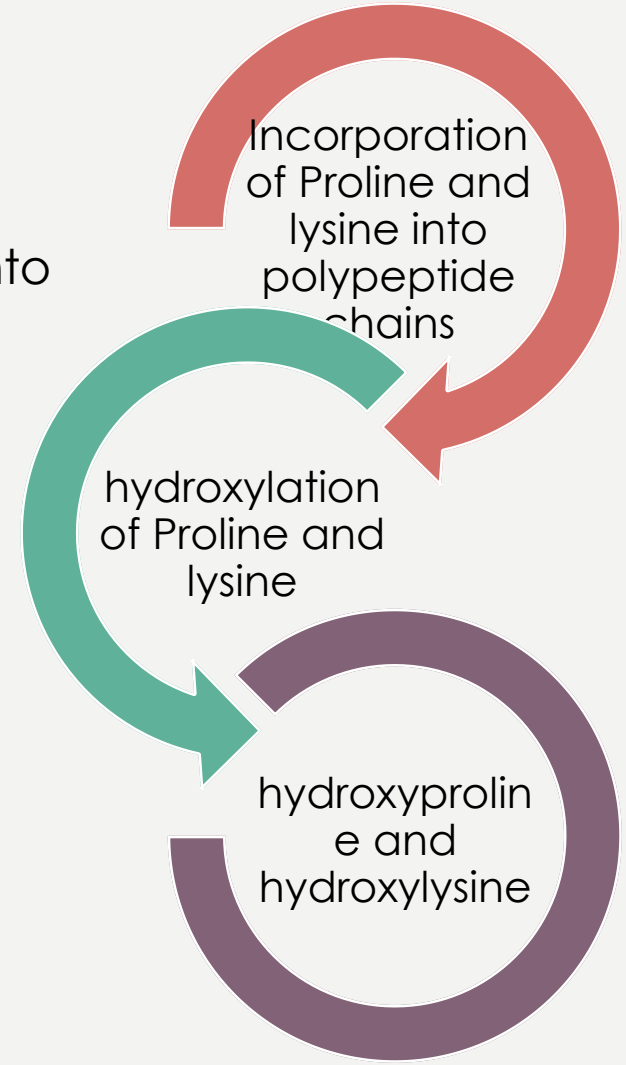
Non-Standard Amino Acids in Collagen

- **The collagen contains :** hydroxyproline and hydroxylysine, **which aren't present in most other proteins.**

- **These residues result from:**

- the hydroxylation of Proline and lysine after their incorporation into polypeptide chains.

- They're converted to hydroxyproline and hydroxylysine by *hydroxylase enzymes during post-translational modification.



Important: These enzymes require vitamin C to function.

Note : Hydroxylase enzymes are :
*Lysyl hydroxylase → lysine
*Prolyl hydroxylase → Proline

Types of Collagen Molecules

As we know, collagen is the most abundant fibrous protein found in our body.
Each fibrous protein exhibits special mechanical properties resulting from its unique structure.

- What's the structure of collagen?

A long rigid structure in which three polypeptides (referred to as a chains) wound around each other to form a triple helix. Those three polypeptides are held together by interchain hydrogen bonds.

The variation of the Amino Acid sequence of the a chains will result in a slightly different structural components. As a result, these different a chains combine together to form various types of collagen.

Important:

- **Most common collagen** is type 1 and it contains two a chains called a1 and one achain called a2. Thus, described by ($\alpha 1_2, \alpha 2$).
- Type two contain 3 chains, thus described by $(a1)_3$

- Collagen can be categorized into three groups, based on their location and functions in the body:

1. Fibril-forming collagens.
2. Network-forming collagens.
3. Fibril-associated collagens.

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Collagen

Fibril-forming collagens.

They have rope–like structure as of a typical collagen molecule. However, they have characteristic binding patterns

- **Type 1 :** Found in supporting elements of high tensile strength like skin, bone, blood vessels. And specially in tendons and cornea.
- **Type 2:** restricted to cartilaginous structures like Cartilage, intervertebral disk and vitreous body.
- **Type 3:** Prevalent (wide–spread) in more distensible tissue like blood vessels, skin and muscles

Network-forming collagens.

Form a three dimensional mesh, rather than distinct fibrils.

- **Type 4:** constitutes a major part in basement membranes.
- **Type 7:** beneath stratified squamous epithelium.

Fibril-associated collagens

Binds to the surface of collagen fibers, linking them to one another and to other components in the extracellular matrix.

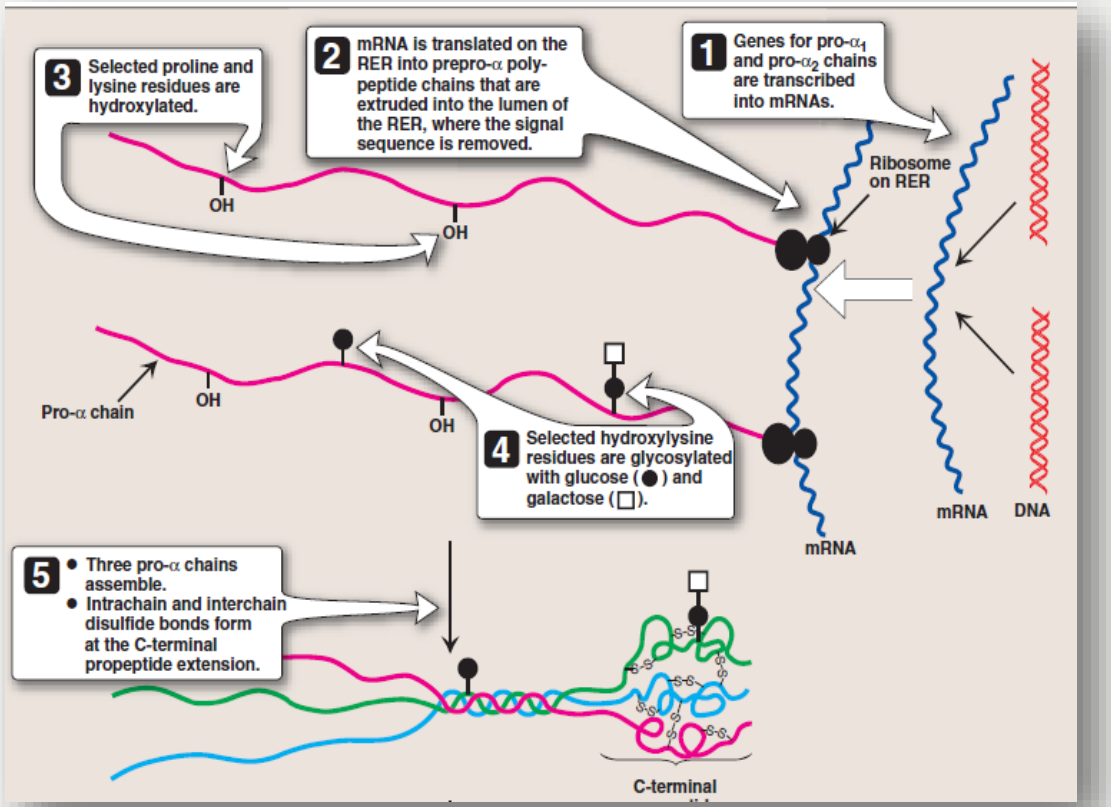
- **Type 9:** Cartalige
- **Type 12:** Tendons, ligaments and other tissue

Biosynthesis of Collagen

- **Collagen is Synthesized in: fibroblasts**, **osteoblasts** and **chondroblasts** (pre-pro- → pro- → mature -collagen)
- Polypeptide precursors are enzymatically modified and form **triple helix** which is secreted into the extracellular matrix as **procollagen.**
- **Glycosylation** of some hydroxylysine residues with **glucose** or **galactose**.
- Procollagen molecules are cleaved by N- and C- procollagen peptidases releasing triple helical **tropocollagen** molecule.
- Tropocollagen molecules spontaneously associate to form **collagen fibrils.**

pre-pro form → pro-form → tropo-form → mature-form

Biosynthesis of Collagen (Explanation):



1) The genes for **pro-achains** are transcribed into **mRNA**.

2) This mRNA translated on the RER into prepro-a-polypeptide chains that are extruded after that *the signal sequence is removed and it is known as **pro-achains** .

3) Proline and lysine are **hydroxylated** to form hydroxyproline and hydroxylysine residues. The hydroxylating enzymes are **prolyl hydroxylase** and **lysyl hydroxylase** + the reducing agent is vitamin C.

4) **Some hydroxylysine residues are modified by ***glycosylation** with glucose or glucosyl-galactose.

5) After hydroxylation and glycosylation, three pro-achains assemble and inter and intra disulfide bonds are formed at the **C-termina**l propeptide estension.

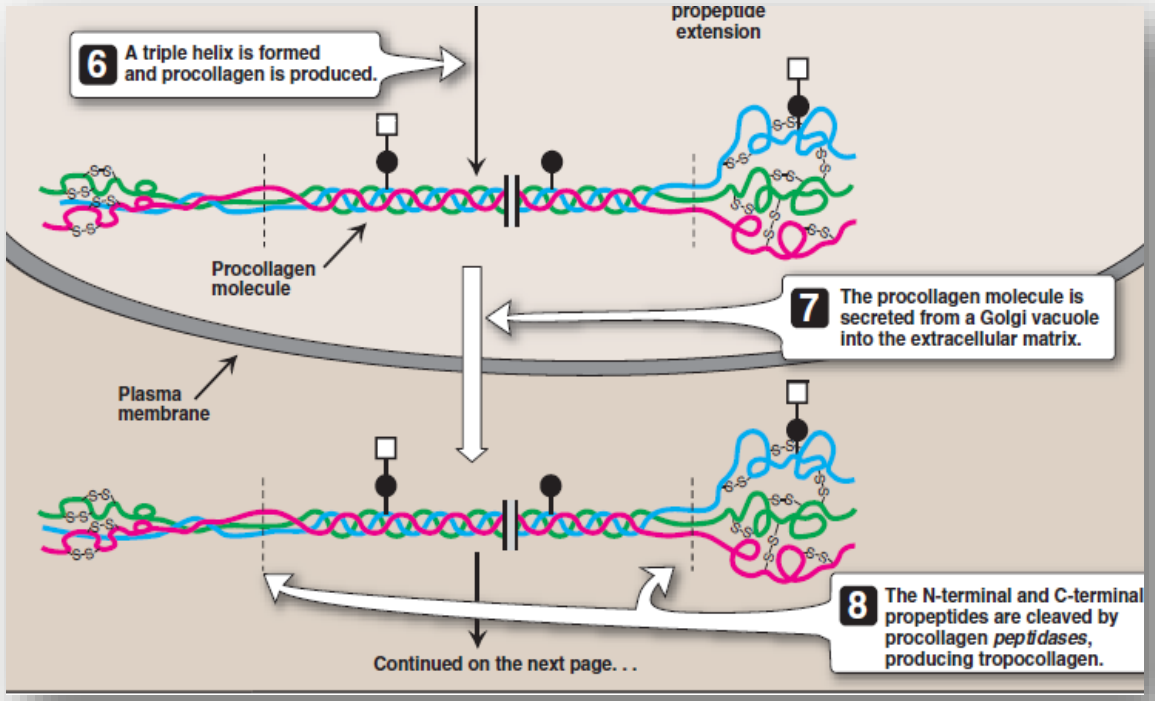
** Step 3 and 4 are post-translational modification steps Which are very important for the proper function of collagen

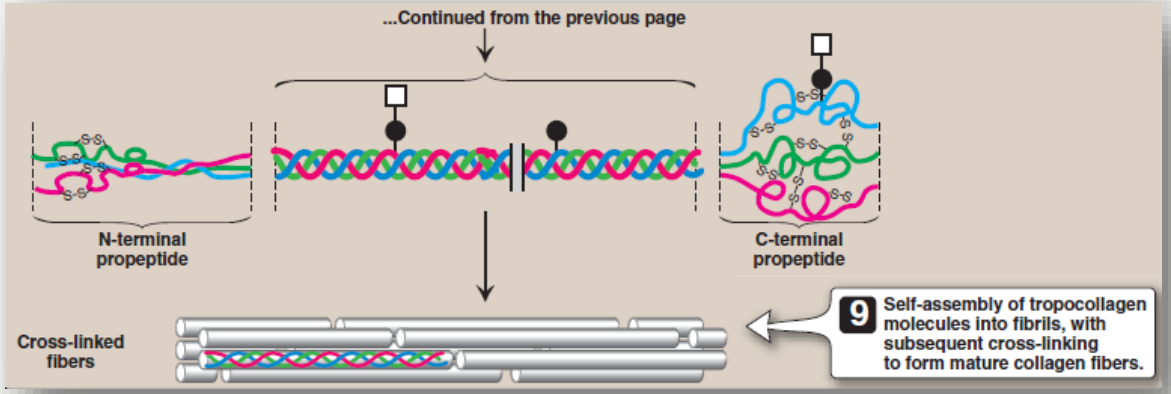
*prepro-a-polypeptide chains special amino acid sequence at their N-terminal ends, this sequence act as a signal that directs the passage of Prepro-achain into the lumen of the RER .

* The pro-achains are processed by a number of enzymic steps within the lumen of the RER while the polypeptides are still being synthesized

*Glycosylation : the attachment of sugar moieties to proteins.

Biosynthesis of Collagen (Explanation):





VIDEO ABOUT THE BIOSYNTHESIS IN DETAILS

VIDEO

6) The formation of **procollagen** begins with formation of interchain disulfide bond between the C-terminal extensions of the pro-a chains, this brings the three a chains into an alignment favorable for helix formation (triple helix formation)

7) The procollagen molecules is secreted through the **Golgi apparatus** where they are packaged in secretory vesicles. The vesicles fuse with the cell membrane causing the release of procollagen molecules into the extracellular matrix .

8) After their release, the N-terminal and c-terminal peptides of the procollagen molecule are cleaved by **N- and C-procollagen peptidase**, producing **tropocollagen** molecules.

9) **Tropocollagen** molecules spontaneously associate to form **collagen fibrils,** then they **cross-link** (will be described later) to form **mature collagen** .

Cross-linking of collagen fibrils

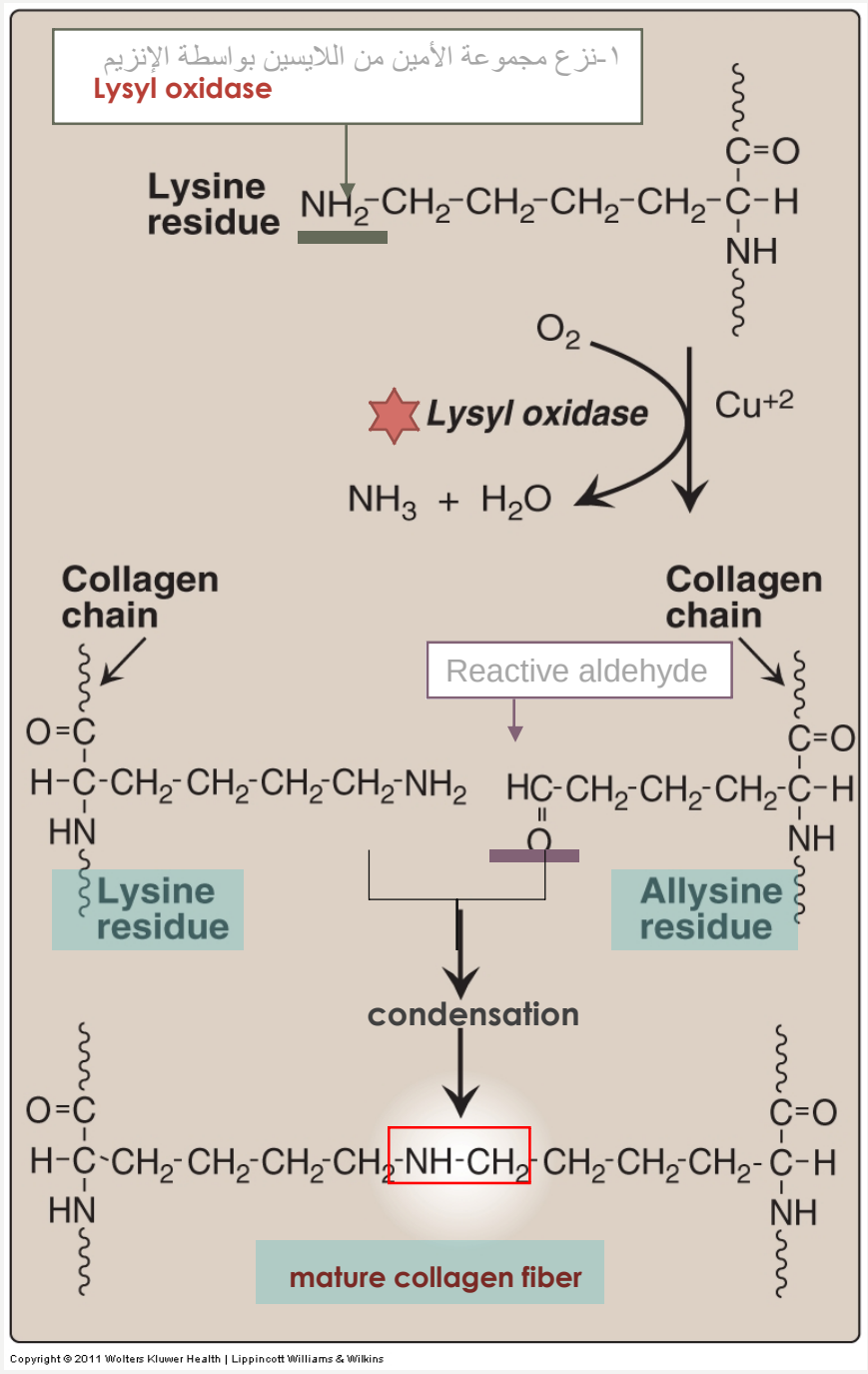
After synthesizing tropocollagen, we have to linked them together to form "mature collagen fibres".

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

2) The produced **reactive aldehydes** (allysine and hydroxyallysine) condense with lysine or hydroxylysine residues in neighbouring collagen molecules to form **covalent cross-links**.

3- This produces mature collagen fiber.

Note: lysine condense with allysine .
Hydroxylysine condense with hydroxyallysine.



Collagen diseases

Acquired	inherited
- Scurvy (due to vitamin C deficiency)	- Osteogenesis imperfecta(brittle bone). - Ehlers-Danlos syndrome.

1)Scurvy:

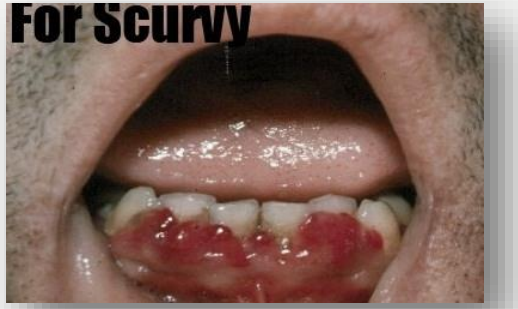
-Cause :

deficiency of vitamin C

-Symptoms:

Gums are swollen, ulcerated, and bleeding → due to vitamin C-induced defects in oral epithelial basement membranes and periodontal collagen fiber synthesis

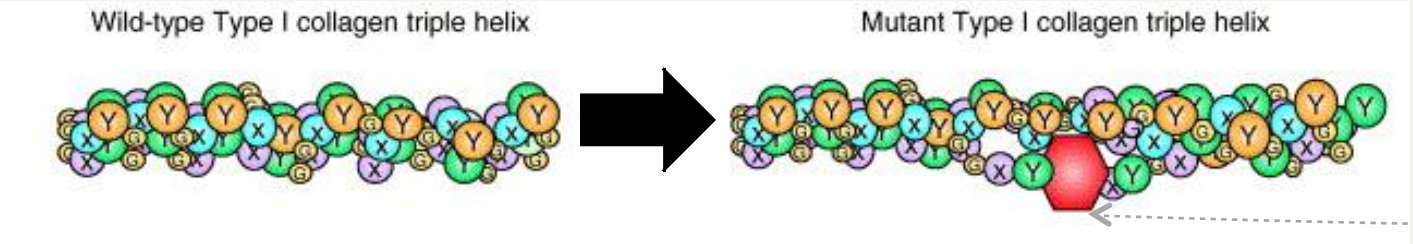
-Diagnosis : by vitamin C level (ascorbic acid) in serum.



2)Osteogenesis imperfecta(OI) Brittle bone disease:

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

Note:
*OI is autosomal dominant disease (in most cases) and it can be autosomal recessive.



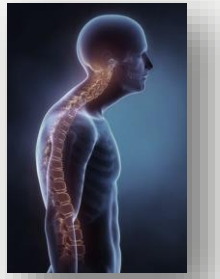
Extra information: it is caused by mutation(defect) of type 1 collagen gene.
On the triple helix, glycine is substituted by another amino acid , breaking Glycine , X,Y pattern of collagen.

types

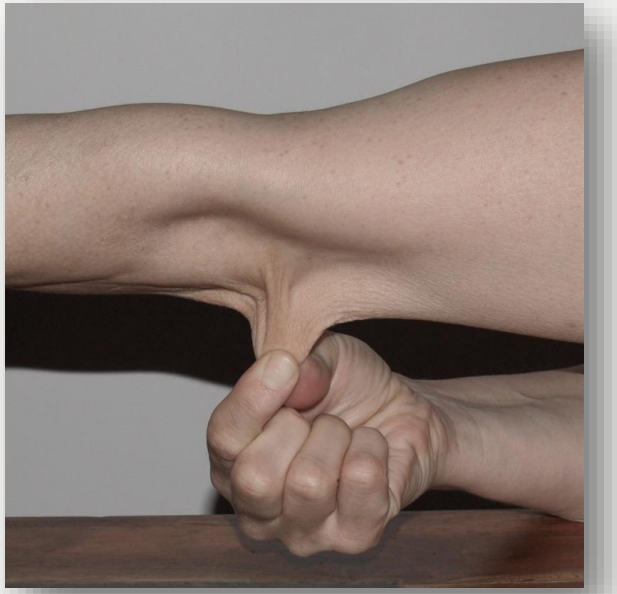
Type1 symptoms: *most common*
#blue sclera
#hear loss
#bone fragility.

Type2 : most severe form and typically lethal in the perinatal period.
Fractures are seen **in utero**.

Type3 symptoms:
#blue sclera.
short stature.
#multiple fractures at birth .
#kyphosis.



3)Ehler danlos syndrome (EDS)



Causes:

-deficincy of **N-procollagen peptidase enzyme**.

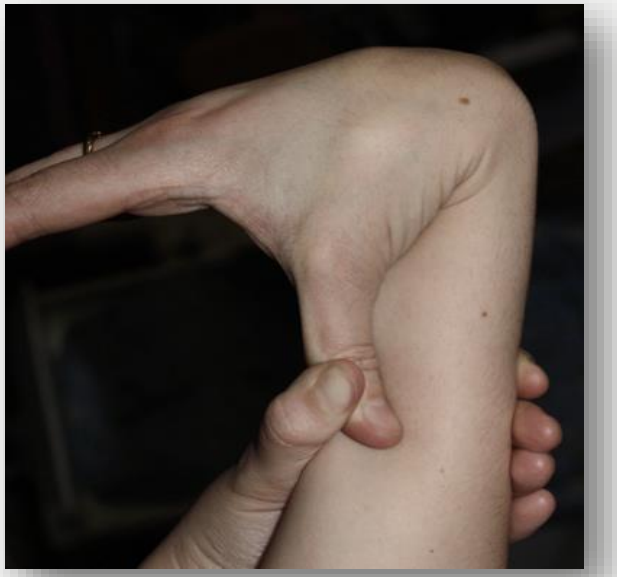
-deficency of **lysyl hydroxylase enzyme.**

- Mutations in the amino acid sequences of collagen I, III and V

Symptoms:

-hyper-extensibility of joints and skin

Remember: EDS is inherited = the cause is defected genes



Extra Information:

*ADAMTS2 is the gene of the N-procollagen enzyme.
*PLOD1 is the gene of lysyl hydroxylase enzyme.
*COL1A2 (type1 collagen),Col3a1(type 3 collagen),COL5A1(type 5 collagen) and TNXB gene mutation cause Ehler-danol syndrome.

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Summary

Creatine

Biosynthesis (step1= in kidney) (step2= in liver)			
Reactant	Enzyme	Byproduct	Product *
Glycine + arginine	Amidino-transeferase(kidney)	Ornithine	Guanidinoacetate
Guanidinoacetate + S-adenosylmethionine (SAM)	Methyltransferase(liver)	S-adenosylhomocysteine (SAH)	Creatine

Distribution of body creatine (liver → other tissues)

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

Reactant	Enzyme	Product	ATP
Creatine	Creatine Kinase (CK) • responsible for the generation of energy in muscles. • Its levels are changed in cardiac/skeletal muscle disorders • Serum CK is increased in MI and crush injuries	Creatine phosphate (CP) • high-energy phosphate compound • storage form of energy in the muscle • Provides a small but, ready source of energy. • ↑ Muscle mass = ↑ CP	1 ATP is consumed

Creatine Degradation

Reactant	Enzyme	Product
Creatine or Creatine phosphate (CP)	No enzyme required (spontaneously)	Creatinine • Excreted in the urine (so normally its level is high in urine) • ↑ creatinine in serum = impairment of kidney function • ↓ creatiniine in urine = ↓ muscle mass due to muscular dystrophy or paralysis

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Summary

collagen

overview

- Most abundant protein.
- Highly stable.
- serves structural functions.
- Part of connective tissue.
- Has a long rigid structure.

Non-standard amino acids in collagen

Reactant	Enzyme	product
Proline	Hydroxylase • during post-translational modification • The enzyme requires vitamin C for its function	hydroxyproline
lysine		hydroxylysine

Collagen structure

- 3 a-chains wound around one another (each a-chain= ~ 1000 amino acids long)
- Rich in proline and glycine.
- Proline prevents collagen chains to form a-helix (It does not have back bone amino group → hydrogen bonding <u>within</u> the chain <u>is impossible</u>)
- Hydrogen bonds are <u>between</u> the chains
- The glycine residues are part of a repeating sequence Gly-X-Y
  - X= proline
  - Y= hydroxyproline or hydroxylysine

Types of collagen molecules

- Type and organization of collagen depends on its function
- Variations in the amino acid sequence of a-chains result in different properties. "type I = $(a1)_2a2$" and "type II = $(a1)_3$"

Fibril-forming	I	Skin, bone, tendon, blood vessels, cornea
	II	Cartilage, intervertebral disc, vitreous body
	III	Blood vessels, fetal skin
Network-forming	IV	Basement membrane
	VII	Beneath stratified squamous epithelium
Fibril-associated	IX	cartilage
	XII	Tendon, ligaments

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Summary

collagen

Biosynthesis (in fibroblasts, osteoblasts and chondroblasts)	
1	Chains genes are transcribed into mRNA
2	mRNA is translated on the RER into prepro-a-polypeptide chain
3	Lysine and proline are hydroxylated by hydroxylase
4	Hydroxylysines are glycosylated with glucose and galactose
5	Three pro-a-chain assemble. intrachain and Interchain disulfied bonds form at C-terminal
6	Triple helix is formed and procollagen is produced
7	Procollagen is secreted from golgi vacuole → extracellular matrix
8	N-terminal and C-terminal propeptides are cleaved by procollagen peptidase → tropocollagen
9	Self assembly of tropocollagen into fibrils with subsequent cross-linking(lysyl oxidase) → mature collagen fiber

Collagen Diseases			
Scurvy	Acquired	vitamin C deficiency	Gums are swollen, ulcerated, and bleeding
Ehlers-Danlos syndrome	Congenital	• Deficiency of lysyl hydroxylase or N- procollagen peptidase. • Mutations in the amino acid sequences of collagen I, III and V.	hyperextensibility of joints and skin
Osteogenesis imperfecta (brittle bone disease)	Congenital	Mutations replace glycine with amino acids having bulky side chains preventing the formation of triple helical conformation	bones that fracture easily, with minor or no trauma

MCQs:

1- What is the name of the enzyme that have this function (oxidatively deaminates some of the lysine and hydroxylysine residues in collagen)?

A – hydroxylase. B - Lysyl oxidase. C - procollagen peptidases.

2 – If we cross linking tropocollagen that gives us mature collagen fibres. (T or F)

3 – When lysine is deaminates it makes allysine and when hydroxylysine deaminates it makes hydroxyallysine. (T or F)

4- what is the site of creatine synthesis?

A-stomach B-kidney C-liver D-Muscle

5-Which enzyme is used for Guanidinoacetate formation?

A-methyltrasferase B-amidinotrasferase C-creatine kinase D-dehydrogenase

6- amino acids that disrupt an alpha helix because of bulky side chain is :

A-Proline B-Tryptophan C-Valine D-Lysine

7- in the amino acids the alpha carbon attached to :

A-Two functional groups and H only B-Primary amino acid only

C-R and H only D-R , H and two functional groups.

1- B
2- T
3 – T
4- C
5- B
6- B
7 - D

MCQs:

8-What is the primary site of synthesis of creatine?

A-Liver
B-Kidney
C-Skeletal muscle
D-Cardiac muscle

9-Decreased level of creatinine in urine is an indication of:

A-decrease in muscle mass.

B-myocardial infarction

C-Muscle injury

D-Renal failure

10-Responsible for the generation of energy in contractile muscular tissues:

A-Creatine kinase

B-Creatinine

C-Creatinine Kinase.

D-Collagen

11-What s the most abundant protein in our bodies?

A- collagen

B- Tyrosine

C-Amyloid

D- Hemeprotien

8-A
9-A
10-A
11-A

MCQs:

12-collagen found in tendons is :

A- Network forming
B- Tyrosine
C-Fibril-Associated

13-Which of the following is not present in most proteins:

A- proline
B- Hydroxyproline
C-lysine
D- Hemoglobin

14-Facilitates the formation of the helical conformation:

A- Lysine
B- Tyrosine
C- Cytosine
D- Proline

15-Which of the following is a part of a repeating sequence regarding the structure of collagen?

A- Glycine
B- Tyrosine
C- Arginine
D- Histadine

12-C
13-B
14-D
15-A

MCQs:

16-Which one of these enzyme convert creatine to creatine phosphate:

A-Pyruvate kinase B-Creatine Kinase C-Phospho kinase D-Creatinine kinase

17-Large mass of muscle contain:

A-High amount of creatine

B-Low amount of creatine

18-In kidney diseases the amount of ..... increase :

A-Creatine

B-Creatinine

19-The mRNA translated in the :

A-Nucleus B-smooth endoplasmic reticulum C-rough endoplasmic reticulum

20-Proline and lysine found in the Y-position of the –Gly –X –Y– sequence will be :

A-Hydrogenated B-glycosylated C-hydroxylated

21-The procollagen molecules are cleaved in the :

A-RER B-EC matrix C-cytoplasm

22-the reducing agent in hydroxylation of proline and lysine :

A-Vitamin B B-Vitamin C C-Vitamin A

16-B
17-A
18-B
19-C
20-C
21-B
22-B

MCQs:

23-A patient came to the clinic with fracture in his arm and a history of a pervious fractures. After examination we noticed he has blue sclera and kyphotic spine. He mostly likely has:

A. Brittle bones
B. Osteoarthritis
C. Scurvy

24-A patient was diagnosed with Ehler-Danol syndrome. What are the signs that will be noticed during examination:

A. Very dry skin
B. Blue sclera
C. Joint hypermobility

25-Scurvy is due to the deficiency of:

A. Vitamin A
B. Vitamin D
C. Vitamin C

26-collagen a chin is rich in:

27-The 3 poly peptide chains are held together by :

A. Hydrogen bond. B. ionic bond. C. coolant bond. D. polar bond

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

A. Gly–X–Y–,
B. pro-x-y.
C. gly-x-y-y.
D. pro-x-y-

23-A
24-C
25-C
26-proline and glycine
27-A
28-A

SAQs

1) **A 4-year old boy came for consultation with swollen, ulcerated and bleeding gum. He was the 12th born in a poor family where one previous child died from malnutrition and dehydration in the period of infancy.**

A. What is the probable diagnosis for this child.
B. What causes the problem?
C. Name one enzyme that might get affected and Explain its rule in collagen biosynthesis,

SAQs Answers

1)

a- Scurvy.

b– deficiency of vitamin C, the swollen, ulcerated and bleeding of the gum was due to vitamin C-induced defects in oral epithelial basement membranes and periodontal collagen fiber synthesis

C- hydroxylase enzymes (Lysyl hydroxylase and proly hydroxylase) , they convert Proline and lysine to hydroxyproline and hydroxylysine during post-translational modification.

Videos:

- The Process Of Collagen Formation
- creatin kinase
- very useful
- creatin phosphate
- Osteogenesis Imperfecta
- Collagen

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