
السلام عليكم

CARBOHYDRATE CHEMISTRY

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POLYSACCHARIDES

Def.: Carbohydrates of high molecular weight.

Linkage: glycosidic; 1,2 - 1,3 - 1,4 or 1,6.

Hydrolysis:

acid or specific Enz.

Hydrolysis ⟶ Monosaccharides or its derivatives

Polysaccharides

chemically & functionally

Hydrolysis

Homogeneous

Single sugar type

(e.g. glucose units only, or fructose units only)

Heterogeneous

Different sugar types associated with other subs.

Homogeneous		Heterogeneous (mucopolysaccharides)		
Glucosans	Fructosans	Neutral	Acidic	
Starch	Inulin	NANA	Non-sulfated	Hyaluronic a.
Dextrin		Bl. gp subs.	sulfated	Heparin
Glycogen		Gonadotrophins thyrotrophic H		Heparan sulphate
Cellulose		α1 & α2 globulins		Chondoritin sulfate
Dextrans		Ovalbumin		Keratan sulphate
		Fibrinogen		Dermatan sulphate

MUCOPOLYSACCHARIDES (Glycosaminoglycans GAGs)

I. Neutral mucopolysaccharides:

- Formed of **protein & polysaccharides**.
- Contain **acetyl hexosamines but no uronic acid.**
- Present in **mucous secretion.**

II. Acidic mucopolysaccharides:

A. Non-sulfated

B. Sulfated

Heterogeneous (mucopolysaccharides GAGs)		
I. Neutral	II. Acidic	
NANA in tissue of vertebrate & bacteria	A. Non-sulfated	Hyaluronic a.
Bl. gp subs. (L-fucose is important constituent)	B. sulfated	Heparin
Gonadotrophins & thyrotrophic H		Heparan sulphate
α1 & α2 globulins		Chondoritin sulfate
Ovalbumin		Keratan sulphate
Fibrinogen		Dermatan sulphate

N.B. L-fucose is deoxyhexose at C6 ($C_6H_{12}O_5$)

NANA: Pyruvate + mannosamine

Mucopolysaccharides

- Most GAG are present extracellular except heparin
- They act as lubricant and cushion for other tissues as they absorb large amount of water
- On compression of GAG; water is squeezed out and they occupy smaller volume. When the compression is released they return to their original volume. This property is called **resilience** of synovial fluid and vitrous humor of the eye.

Acidic MPS

Formed of (repeated disaccharide units):

1- amino-sugar acids OR amino- sugars

2- Uronic acid (glucuronic or iduronic) OR monosaccharide Linked by glycosidic bond

II. Acidic mucopolysaccharides

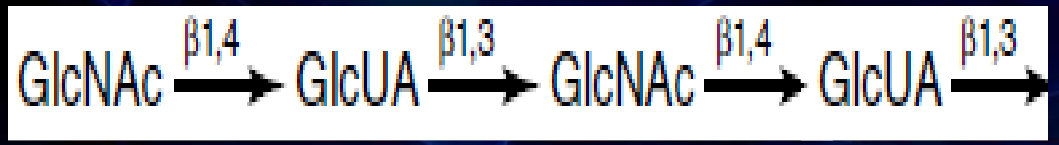
A. Non-sulfated mucopolysaccharides:

1.Hyaluronic acid

•Repeating units of **N-acetyl glucosamine & B-glucuronic a.**

Functions:

- Forms the **cement substance** between tissues.
- Present in **synovial fluid** **(lubricant facilitates joint movement)**
- Makes cartilage **compressible**.
- Makes **ECM loose** (by the ability to attract H_2O).
- Permits **cell migration** during wound repair & morphogenesis.



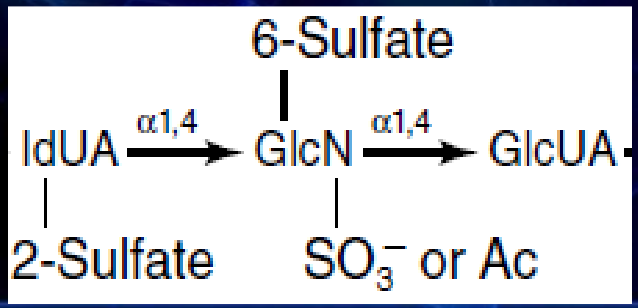
(N.B.)

- It facilitates cell migration; being produced in **increased amount by tumor cells**; so facilitates migration through ECM & spread of tumor.
- **Hyaluronidase** secreted by **certain bacteria** causes destruction of this cement subs. (hyaluronic a) so help spread of infection **(spreading factor).**
- **Hyaluronidase** is present in **acrosomal cap of sperm** & invades the tissues of the ova causing destruction of hyaluronic a. & its fertilization.
- Morphogenesis: cell differentiation into tissues & organs in the embryo

A. Sulfated mucopolysaccharides:

1-Heparin: repeating units of:

- **Sulfated glucosamine &**
  Sulfated glucuronic a. (or L-iduronic a.)
- linked by **α-1,4 glycosidic bond**.
- Formed by **mast cells (intracelluar), located along the blood vessel wall** in many tissues like heart, lung, liver, kidney, skin & spleen.
- **Its concentration in blood is very low.**



Functions of heparin

1. **Anticoagulant:**

   It activates antithrombin III &

   It Inhibits blood clotting factors II, VII, IX & X.

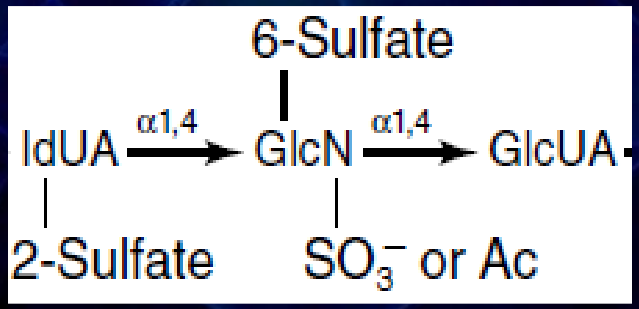
2. **Plasma clearance from lipids:**

   It activates lipoprotein lipase that digests plasma lipids.

(heparin & lipoprotein lipase are clearing factors)

2- Heparan sulphate:

- It differs from heparin in the amount of **uronic a.** & **the sulphate** attached to glucosamine
  (more glucuronic a. but less sulphated glucosamine).
- **It is a component of ECM in the form of proteoglycans. It has a role in:**
  1. **Cell-cell interaction** &
  2. **Cell membrane receptors**.



3- Chondroitin sulfate: repeating units of:

- **N- acetyl galactosamine & β-glucuronic a.** linked by **B-1,3 bond.** **Types: 3 (A, B & C)**

1- Chondroitin sulfate A:

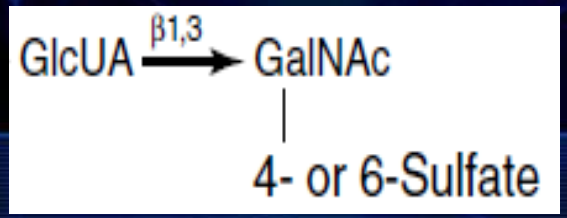
sulfate ester gp of N- acetyl galactosamine

at C4 → *Chondroitin-4-sulfate A*

at C6 → *Chondroitin-6-sulfate C*

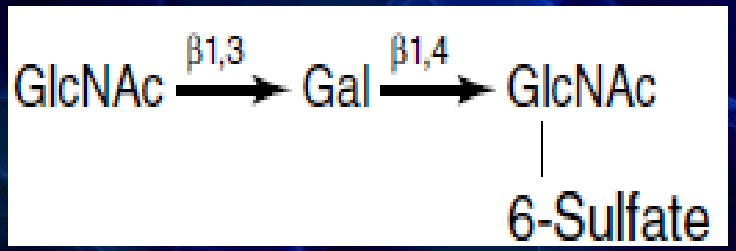
Chondroitin itself is a minor component of ECM but its sulfate ester (A & C) are major component of **cartilage**, **bone**, **cornea** & other connective tissues.

2- Chondroitin sulfate B: It yields upon hydrolysis **L-iduronic** a. instead of D-glucuronic a.



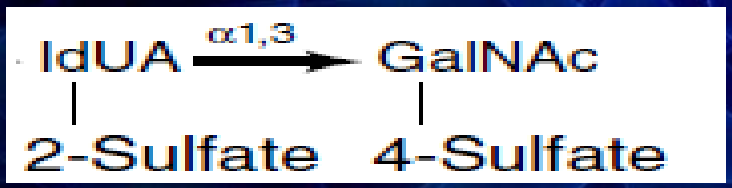
4- Keratan sulphate: repeating units of:

- **Galactose and N-acetyl glucosamine** linked together by β- bond.
- **No uronic acid.**
- **Present in cornea (to make it transparent), cartilage and tendons.**



5- Dermatan sulphate: repeating units of:

- **L-iduronic acid and N-acetyl galactosamine** linked together by α-1,3 bond.
- Present in **blood vessels, heart, cornea, sclera & skin. It maintains the shape of sclera**



Points	Hyaluronic a	Heparin	Heparan S	Chondroitin S	Keratan S	Dermatan S
Amino S.	**Glucosamine**	**Glucosamine**	Glucosamine	Galactosamine	Glucosamine	Galactosamine
Uronic a	**Glucuronic a**	Glucuronic + **Iduronic**	**Glucuronic** + Iduronic	Glucuronic + Iduronic	Galactose (No uronic a)	Iduronic a
Sulfate	Absent	Present	Present	Present	Present	Present
Acetyl	Present	Absent	Absent	Present	Present	Present
Bonds	**β-1,3 & β- 1,4**	**α-1,4**	**α-1,4**	**β-1,3**	**β-1,3 & β- 1,4**	**α-1,3**
Sites	- S.C. tissues - Ovum Wall -Synovial fluid	-CT Mast cells (liver, spleen, kidney, bone marrow) but least conc. in blood.	EXTRA-CELLULAR Matrix (ECM)	- Matrix of cartilage - Tendons - Ligaments - Bone	-**Cornea**. -Cartilage -Tendons	-Blood vessels -Heart. - **Cornea**, - **Sclera** - Skin.
Function	Protective for tissues	Anticoagulant Lipid clearance from plasma	-Cell-cell interaction -Cell membrane receptors	Supportive	Supportive Transparency of cornea	Supportive Maintains the shape of sclera

N.B. **When proteins are connected to acidic mucopolysaccharides →→ proteoglycans**

Mucopolysaccharidosis

Def.

A group of inherited inborn errors of metabolism, progressive lysosomal storage disorders (1:25000 live births).

Age of onset:

initially normal development with the abnormality appear in infancy or later in childhood.

Incidence of subtypes:

- The most common subtype is MPS III, followed by MPS I and MPS II

Inheritance:

- All MPS are autosomal recessive (AR) except MPS II (Hunter syndrome) which is X-linked (occurs in males only).

Cause and pathogenesis

- Mutation in the genes coding for the lysosomal enzymes that degrade GAG →
- variable expression of mutated enzymes →
- variable residual enzyme activity (complete absence, deficiency or malfunction) →
- accumulation of GAG in lysosomes interfering with cell function causing permanent progressive damage in cells, tissues and organs →
- variable severity of disease with characteristic pattern of clinical, radiologic and biochemical abnormalities

N.B.

- Within this pattern, specific diseases can be recognized resulting from intracellular accumulation of different degradation products.

As a general role,

- Impaired degradation of **heparan sulfate** is more closely associated with **mental deficiency**.
- Impaired degradation of **dermatan sulphate, chondroitin sulfate, & keratin sulfate** is more closely associated with **mesenchymal abnormalities**.
- Variable severity of disease is manifest e.g. in MPS I;

➢ homozygous or double heterozygous **non-sense** mutation → severe form of Hurler disease.

➢ **mis-sense** mutation → preserve some residual enzyme activity (mild form of Hurler disease).

Clinical abnormality

1. Physical features

- Coarse facial features (due to storage of GAGs in soft tissues of the face)
- Skeletal abnormalities: early, prominent feature
- most patients show progressive change in size and shape of bone, involving almost all bones as:
  - short stature with disproportionate short trunk in all MPS except MPS IS
  - spine deformity (kyphosis, scoliosis & lordosis)
- Joint stiffness is common in MPS except MPS IV (hyperlax)

Clinical abnormality

2. Neuologic:

illectual changes & behaviour disability

3. Hepatosplenomegaly

4. Respiratory:

Obstructive airway disease with frequent infections

5. Cardiovascular: valve disease, angina, heart failure

6. Eye: corneal clouding, glaucoma, retinal degeneration

7. Ear: deafness

Generally the patients present in one of three ways:

1. Dysmorphic syndrome (MPS IH, MPS II, MPS VI)

2. Learning difficulties, behavioral disturbance, dementia and mild somatic abnormalities (MPS III)

3. Severe bone dysplasia (MPS IV)

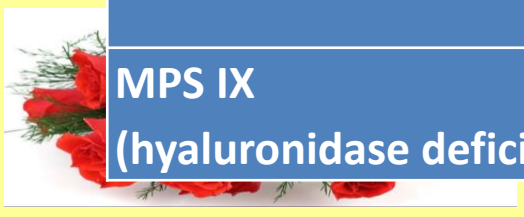
N.B.

1. Heparan sulfate degradation is impaired in MPS types I-H, I-H/S, II, III &VII⟶ Show mental retardation, however mild MPS II may show no mental deficiency.

2. **Absence of corneal opacity in MPS II** & IX & not common in MPS III & Fine in MPS IV

3. MPS VII presents commonly at birth with hydrops fetalis (severe fatal disease usually die at birth)

Subtypes & Disease		Enzyme defect	Urinary MPS
MPS I		α-L-iduronidase	Dermatan sulphate heparan sulphate
MPS I-H (Hurler)		Severe	
MPS I-H/S (Hurler/Scheie)		Moderate	
MPS I-S (V) (Scheie)		Mild (dematan sulfate only in urine)	
MPS II (Hunter)		Iduronate-2-sulfatase	
MPS III (Sanfillipo)	A	Heparan-Sulfate sulfatase	Heparan sulphate
	B	α-N-acetyl Glucosaminidase	
	C	Acetyl transferase	
	D	N- acetyl glucosamine 6- sulfatase	
MPS IV (A and B) (Morquio)		A: N-acetyl galactosamine 6-sulfatase B: β-galactosidase.	A: Keratan sulphate, Chondroitin sulfate B: Keratan sulphate
MPS VI (Maroteaux-Lamy)		N- acetyl galactosamine 4-sulfatase	Dermatan sulphate
MPS VII (Sly)		β-Glucuronidase	Dermatan sulphate, heparan sulphate Chondroitin sulfate
MPS IX (hyaluronidase deficiency)		Hyaluronidase 1	Unknown



Laboratory diagnosis

- 1. Urinary GAG analysis:
  - **Qualitative assay for the total amount of GAG; elevated level in age-matched normal subjects**
  - **Quantitative assay to determine the type of elevated GAG**

2. Enzyme activity assay in WBCs, fibroblast or serum

3. Molecular genetic testing for mutation in the genes coding for the defective enzyme

4. Increased plasma hyaluronan level in type IX

Other tests that may be done

- Prenatal diagnosis using amniotic fluid cells or chorionic villus biopsy.
- Genetic counselling

N.B.

- **Urinary GAG can be used for disease monitoring**
- **When a sibling of MPS patient is identified, the other undiagnosed siblings should undergo the same clinical history & laboratory testing.**

Treatment:

1. Enzyme replacement therapy: used in MPS I & II but can not prevent neurological damage

2. Bone marrow & cord blood transplantation: limited success (macrophage enzymes degrade GAG)

3. Treatment of various clinical manifestations

Mucopolysaccharidosis Case I

A seven year old boy is brought to the physician with severe mental retardation, on asking the mother; several members of the mother‘s and father‘s family had mental retardation. The mother also noticed that this child is very active, restless and frequently get into troubles in his school.

- **On examination**; he appeared restless with delayed incomprehensive speech, coarse facial features and normal other examination. The lab tests showed elevated heparan sulphate.

- Summary: A 7 years old boy with severe mental retardation, family history of mental retardation, language delays and behavioral problems, with coarse facial features.

Questions

- What is the most likely diagnosis?
- What is the inheritance pattern of this disorder?
- What are the other causes of MPS?

Answers

1. MPS III (Sanfillipo syndrome)
2. Autosomal recessive (AR)
3. **Write all other types of MPS;**

   Hurler (MPS I), Hunter (MPS II), Morquio (IV), Maroteaux-Lamy (VI), Sly (VII), hyaluronidase deficiency (IX)

*** The first explanation for diagnosis;**

MPS present in one of three ways:

1.As a dysmorphic syndrome (e.g. MPS IH, MPS II, MPS VI).

2.With learning difficulties, behavioral disturbance and dementia and mild somatic abnormalities (MPS III)

3.As a severe bone dysplasia (MPS IV)

*** The second explanation presence of heparan sulfate in urine (the only metabolite present)**

Case 2:

- An infant presented with corneal clouding. His urine examination showed dermatan sulphate and heparan sulphate. He was diagnosed as Hurler syndrome.
- One of the following enzymes has decreased activity to confirm the suspected diagnosis:

a. α-L-iduronidase b. α-glucuronidase

c. Glycosyl transferase d. Iduronte sulfatase

Answers:

a. α-L-iduronidase

Case 3

- A fifteen month old white **female** was brought to the paediatrician because of upper respiratory tract infection. On examination; the girl was noticed to have short stature, some corneal clouding, coarse facial features, some hearing loss, developmental delay. It was suscpected to has MPS. Which of the following is the least likely to affect her:

a. Hurler syndrome (MPS I)

b. Hunter syndrome (MPS II)

C. Morquio syndrome (MPS IV)

d. Sly syndrome (MPS VII)

e. Sanfillipo syndrome (MPS III)

Answers

b. Hunter syndrome (MPS II)

Explanation: All are autosomal recessive except hunter syndrome. Hunter syndrome is X linked recessive and thus is almost exclusively seen in males. This case is female and thus not expected to have an X linked disorder.

Case 4

A 3-year-old male with coarse facial features, progressive loss of motor skills, hepatosplenomegaly & chronic diarrhea is suspected of having **Hunter syndrome (MPS II).** Which of the following monosaccharide residues would be expected to be found at the non reducing end of GAGs in this patient urine.

a) N-acetyl glucosamine.

b) N-acetyl galactosamine.

c) Glucuronate.

d) Iduronate.

e) Iduronate **2- sulfate.**

Answers:

e. Iduronate 2- sulfate

Explanation: Since the patient is suspected of having Hunter syndrome (MPS II) with deficiency of iduronate 2- sulfatase, iduronate 2- sulfate would be expected to be found at the non reducing end of GAGs in this patient urine.

Case 5

An 11-year-old boy was referred to the outpatient department for routine examination. Medical history reported that he had frequent respiratory infections and generalized weakness with easy fatigability. On examination, the patient had retarded growth with a short stature with mild mental retardation and hepatomegaly. Bony deformities, including kyphosis and rotated legs. The case was diagnosed as **MPS II** after the suitable lab investigations were done.

a) What do you think the laboratory investigations were done to diagnose MPS II and their results?

b) What is the treatment of this case?

Answers:

a) Lab. investigations for MPS II and their results:

1. Urinary GAG analyses:

- **Quantitative GAG assay**: revealed elevation of GAG compared to GAG levels in age-matched normal subjects.
- **Qualitative GAG assays:** revealed the type of GAG excreted (dermatan sulfate and heparan sulfate).

2. Enzyme activity assays: Iduronate-2-sulfatase enzyme activity in WBCs, fibroblasts or serum was decreased.

3. Molecular genetic testing: of mutation in the gene coding Iduronate-2-sulfatase enzyme was found.

Treatment of this MPS II case:

1) Enzyme replacement therapy.

2) Treatment of different clinical manifestations


Thank you