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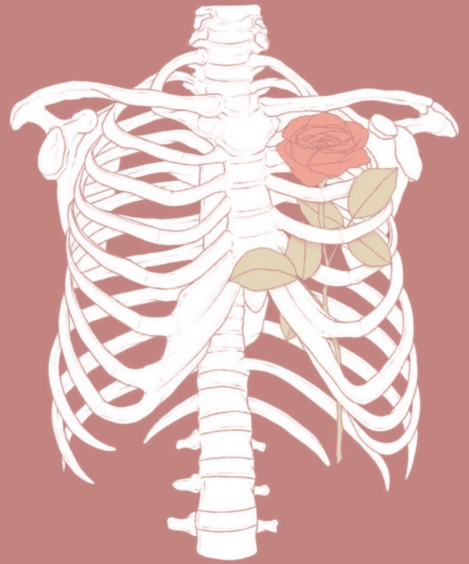
Purine degradation and Gout



Color index :

Main text

IMPORTANT

Extra Info

Drs Notes

Muskuloskeletal Block - Biochemistry Team

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MED439

Objectives:

- Purine degradation, uric acid formation and its association with gout.
- Fate of uric acid in humans.
- Recognize the importance of uric acid in the pathogenesis.
- Overview of Gout classification and treatment.

Purine degradation pathway

- The major source of dietary nucleic acids (purines and pyrimidines) is meat.
- Purine and pyrimidine bases are absorbed by the intestine (small intestine).
- The ingested bases are mostly degraded into different products by degradation pathways.
- These products "product for purine degradation" are then excreted by the body (or it can be utilized if it's useful).
- Adenosine and guanosine (purines) are finally degraded to uric acid by purine degradation pathway.

438 note:
In cells DNA is synthesized via :
1) from primary raw materials "most of DNA"
2) Recycling pathway
3) From food (dietary nucleic acids) "small amount of DNA"

Purine degradation pathway

★ Very important enzymes

1 Degradation of the nucleic acid into its building blocks "Nucleotides (Nitrogenous base + Ribose + PO_4)" with the help of **Pancreatic nuclease** enzyme

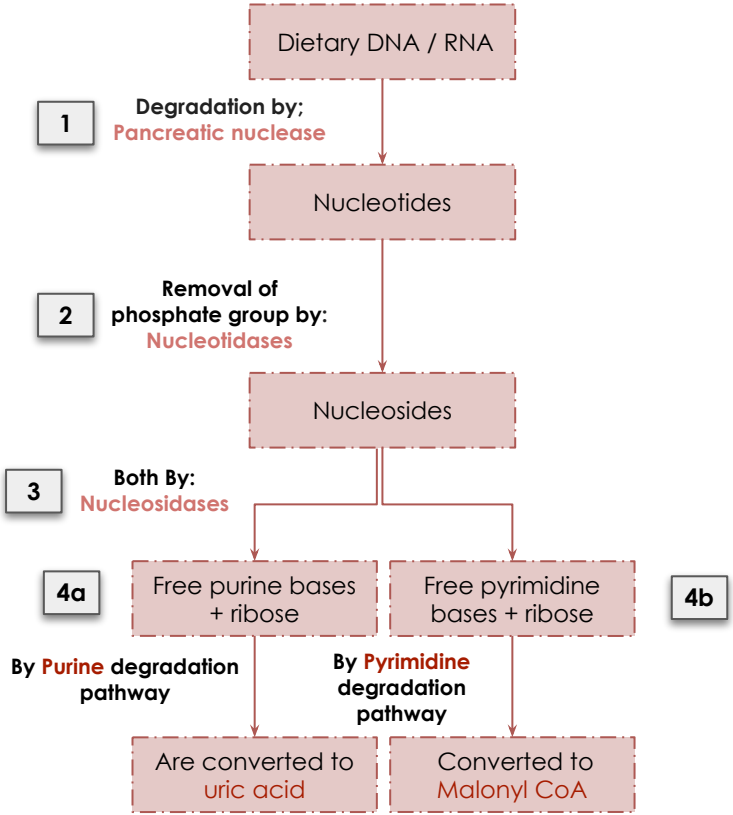
2 Removal of phosphate group from the nucleotides by the enzyme **Nucleotidases** that will give us Nucleosides (Ribose + Nitrogen bases).

3 Breakdown of Nucleosides into its original components (Ribose sugar + Nitrogenous bases which in our case either Purine or Pyrimidine)

4a Purine enters the Purine degradation pathway and gives us uric acid.We don't want uric acid so it must be excreted in the urine

4b Pyrimidine enters the Pyrimidine degradation pathway and gives us Malonyl CoA and it is Essential for fatty acids synthesis.

Purine is a nitrogen base.
Nucleo**tide** = N base + Sugar + P_i
Nucleo**sides** = N Base + Sugar



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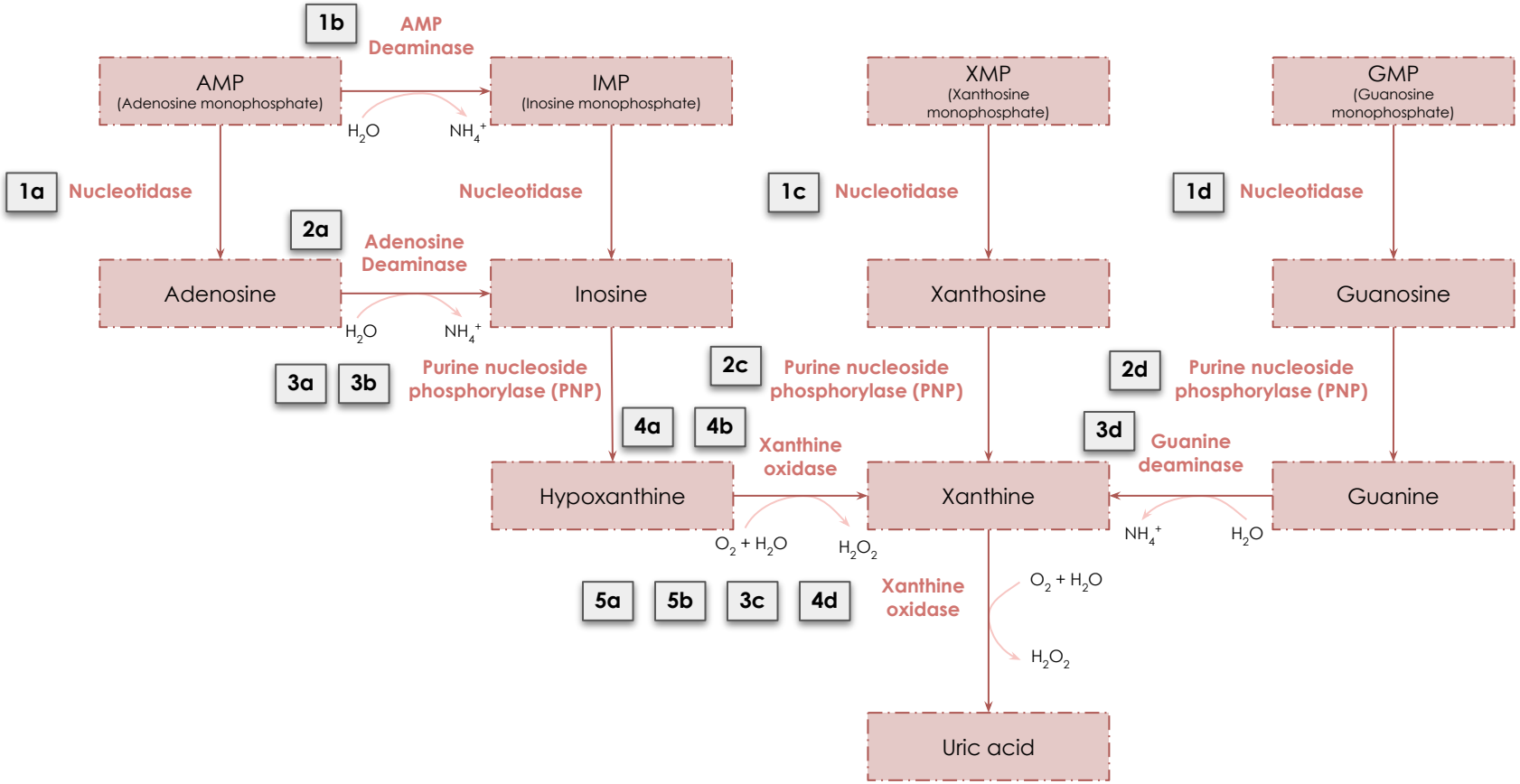
Major Pathway of Purine Catabolism in Animals

A helpful video



Major Pathway of Purine Catabolism in Animals

★ extra explanation

1a AMP gets processed to Adenosine by the help of **Nucleotidase** enzyme, which is an enzyme that gets rid of PO_4 i.e. transforms Nucleotides to Nucleosides.

2a Adenosine gets proceeds to Inosine by the help of **Adenosine Deaminase** enzyme which will remove NH_4^+ "Ammonium ion"

3a Inosine gets processed to Hypoxanthine by the help of **Purine nucleoside phosphorylase (PNP)** enzyme, which is an enzyme that removes the sugar (Ribose-1-Phosphate) and converts it to its basic form e.g. Xanthosine → Xanthine

4a Hypoxanthine gets processed to Xanthine by the help of **Xanthine oxidase** enzyme and produce hydrogen peroxide "H_2O_2"

5a Xanthine can be further processed to Uric acid by the help of **Xanthine oxidase** enzyme and produce hydrogen peroxide "H_2O_2"

1b AMP can also gets processed to IMP by the help of **AMP Deaminase** enzyme which will remove NH_4^+ "Ammonium ion"

2b IMP gets processed to Inosine by the help of **Nucleotidase** enzyme, which is an enzyme that gets rid of PO_4 i.e. transforms Nucleotides to Nucleosides.

3b Inosine gets processed to Hypoxanthine by the help of **Purine nucleoside phosphorylase (PNP)** enzyme, which is an enzyme that removes the sugar (Ribose-1-Phosphate) and converts it to its basic form e.g. Xanthosine → Xanthine

4b Hypoxanthine gets processed to Xanthine by the help of **Xanthine oxidase** enzyme and produce hydrogen peroxide "H_2O_2"

5a Xanthine can be further processed to Uric acid by the help of **Xanthine oxidase** enzyme and produce hydrogen peroxide "H_2O_2"

Major Pathway of Purine Catabolism in Animals, Contd...

★ extra explanation

1c XMP gets processed to Xanthosine by the help of **Nucleotidase** enzyme, which is an enzyme that gets rid of PO_4 i.e. transforms Nucleotides to Nucleosides.

2c Xanthosine gets proceeds to Xanthine by the help of **Purine nucleoside phosphorylase (PNP)** enzyme, which is an enzyme that removes the sugar (Ribose-1-Phosphate) and converts it to its basic form e.g. Xanthosine → Xanthine

3c Xanthine can be further processed to Uric acid by the help of **Xanthine oxidase** enzyme and produce hydrogen peroxide "H_2O_2"

1d GMP gets processed to Guanosine by the help of **Nucleotidase** enzyme, which is an enzyme that gets rid of PO_4 i.e. transforms Nucleotides to Nucleosides.

2d Guanosine can also gets processed to Guanine by the help of **Purine nucleoside phosphorylase (PNP)** enzyme, which is an enzyme that removes the sugar (Ribose-1-Phosphate) and converts it to its basic form.

3d Guanine gets processed to Xanthine by the help of **Guanine deaminase** enzyme which will remove NH_4^+ "Ammonium ion"

4d Xanthine can be further processed to Uric acid by the help of **Xanthine oxidase** enzyme and produce hydrogen peroxide "H_2O_2"

Fate of uric acid in human

- In humans, primates, birds and reptiles the final product of purine degradation is uric acid.
- Uric acid goes to kidney and is excreted in the urine.
- Some animals convert uric acid to other products:

1. **Allantain:**
   - By urate oxidase
2. **Allantoic acid:**
   - By allantoinase
3. **Urea:**
   - By allantoicase
4. **Ammonia:**
   - By Urease

- Humans lack the enzyme urate oxidase " its genes are available but nonfunctional ", which can convert the product to allantoin that can be easily excreted in urine, so instead of excreted in the urine it has a chance to accumulate when the urite find Na+ they will produce monosodium urate crystals which will cause gout if it's in high levels because it will deposit and crystallize in joints
- Uric acid is less soluble in water.
- Reptiles (الزواحف), insects and birds excrete uric acid as a paste of crystals to save water because it needs it to save water.
- Humans excrete uric acid in the urine, they do not have enzymes to further degrade uric acid.
- Excessive production of uric acid causes deposition of uric acid crystals in the joints (mainly) leading to:
  a. Gout
  b. Hyperuricemia is a condition in which the concentration of uric acid is increased in the serum due to overproduction/underexcretion, and it is the most common predisposing factor for gout but does not necessarily lead to it, some individuals may have gout with normal uric acid levels and some may have high uric acid levels and not have gout.

original pic

Fate of uric acid in Animals

★ **Uric acid excreted by:**
- Primates
- Birds
- Reptiles
- Insects

1 Converting Uric acid to Allantoin by the help of **Urate oxidase** enzyme.
- $2\ H_2O + O_2$ In.
- $CO_2 + H_2O_2$ Out.

★ **Allantoin excreted by:**
- Other mammals.

2 Converting Allantoin to Allantonic acid by the help of **Allantoinase** enzyme.
- H_2O In.

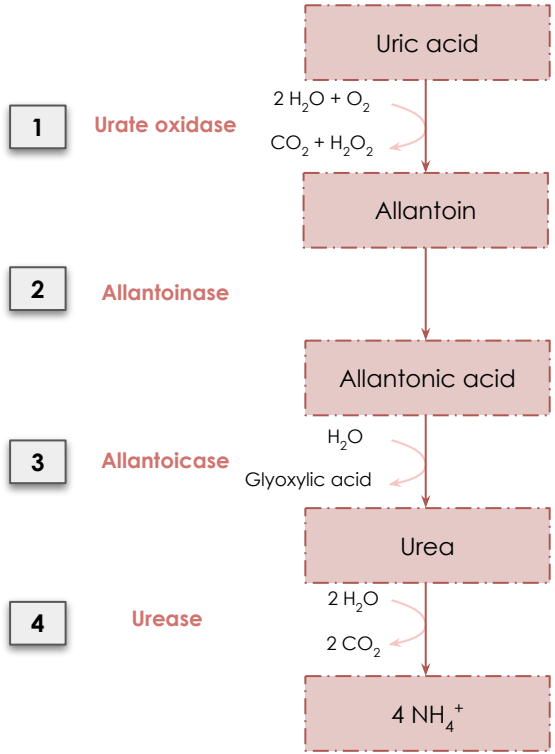
★ **Allantonic acid excreted by:**
- Teleost fish.

3 Converting Allantonic acid to Urea by the help of **Allantoicase** enzyme.
- H_2O In.
- Glyoxylic acid Out.

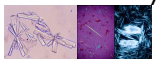
★ **Urea excreted by:**
- Cartilaginous fish.
- Amphibia.

4 Converting Urea to 4 NH_4^+ by the help of **Urease** enzyme.
- $2\ H_2O$ In.
- $2\ CO_2$ Out.

★ **4 NH_4^+ excreted by:**
- Marine.
- Invertebrates..



Gout

- It's a disease due to high uric acid in body fluids.
  - 0 mg/dl and above in male.
  - 6.0 mg/dl and above in female.
- Uric acid accumulates because of:
  1. Overproduction.
  2. Underexcretion.
- Painful arthritic joint inflammation due to deposits of insoluble sodium urate crystals (especially big toe).
- Affects 3 per 1000 people.
- Sodium urate crystals accumulate in kidneys, ureter, joints leading to chronic gouty arthritis.
- Sodium urate crystals in urine → 
  - The needle shaped monosodium urate crystals are KEY FINDING to confirm the diagnosis of gout.
- **Risk factors:**

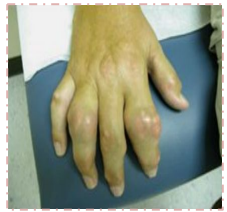
- Gout is Inaccurately associated with overeating and alcohol drinking:

1. Alcohol: is used to be contaminated with lead during manufacture and storage, and lead decreased excretion of uric acid from kidneys causing hyperuricemia and gout.
2. Excessive meat consumption: cause it increases uric acid production in some individuals.

- **2 Main causes of gout:**

1. Overproduction of uric acid.
2. Under excretion of uric acid

Swollen joints (tophi)



Classification of gout

★ Very important

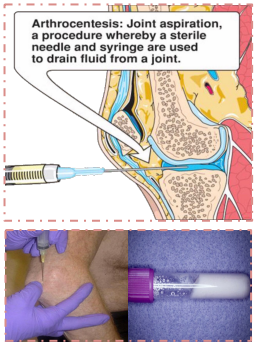
Clinical Category	Metabolic defect
Primary Gout (90% of cases) "Genetic and direct cause"	
1. Enzyme defects-Unknown (85% to 90% of cases).	• Overproduction of uric acid - Normal excretion (Majority). - Increased excretion (Minority). • Underexcretion of uric acid with normal production.
2. Known enzyme defects – e.g., Partial Hypoxanthine-Guanine Phosphoribosyltransferase "HGPRT" deficiency (rare). - Hypoxanthine-guanine phosphoribosyltransferase (HGPRT) converts xanthine and guanine to nucleotides but if it's not existed they will be converted to uric acid.	• Overproduction of uric acid
Secondary Gout (10% of cases)	
1. Associated with increase nucleic acid turnover – e,g. Leukaemia	• Overproduction of uric acid with increase urinary excretion.
2. Chronic renal disease	• Reduced excretion of uric acid with normal production.
3. Inborn errors of metabolism e.g Complete HGPRT deficiency (Lesch-nyhan syndrome)	• Overproduction of uric acid with increased urinary excretion. - Uric acid in serum (S-UA) is produced by the breakdown of the cellular nucleic acids of leukemia cells

Biochemical Diagnosis

- **Joint Fluid test:**
  - The definitive diagnosis of gout requires aspiration and examination of synovial fluid from an affected joint (or material from a tophus) using polarized light microscopy to confirm the presence of needle-shaped monosodium urate crystals. Sensitive and Specific for gout but it's only used on patient with affected joint

- **Blood test:**
  - To measure: blood levels of uric acid. high level of uric acid in the blood test means that the patient at high risk of gout or he already have it.

- **Urine test:**
  - To see the crystals



Sample results. Actual results may vary.

PATIENT INFORMATION

REPORT STATUS: FINAL

SPECIMEN INFORMATION
SPECIMEN:
REQUISITION:
LAB REF NO:

COLLECTED:
RECEIVED:
REPORTED:

DOB:
AGE:
GENDER:
FASTING:

Clinical Info:

ORDERING PHYSICIAN

CLIENT INFORMATION

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Test Name	Result	Flag	Reference Range	Lab
FASTING: UNKNOWN				
URIC ACID				
URIC ACID	9.5	HIGH	4.0-8.0 mg/dL	01
Therapeutic target for gout patients: <6.0 mg/dL				

Treatment

- **To reduce pain and inflammation:**
  - Analgesic.
  - Anti-inflammatory drugs.
- **To increase uric acid excretion:**
  - Uricosuric agents (Used in cases of renal problems for example).
- **To reduce uric acid production:**
  - Allopurinol (Xanthine oxidase inhibitor) Which is a competitive inhibitor of this enzyme and can be used in cases of overproduction.

Take home messages

- The biochemical causes that contribute to the development of gout and hyperuricemia are defects in purine degradation pathway and impaired excretion of uric acid.
- Hyperuricemia does not always cause gout.

Quiz

Q1 : Purine and pyrimidine bases are absorbed by the:			
A) Stomach	B) Intestine	C) Liver	D) Kidney
Q2 : Nucleotidase is an enzyme that:			
A) Remove the sugar and convert it to its basic form	B) Convert Hypoxanthine to xanthine	C) Helps to get rid of Phosphate	D) Change the Adenosine to Inosine by removing NH_4
Q3 : What's the end product for purine degradation pathway?			
A) Uric acid	B) Xanthine	C) Adenosine	D) Malonyl CoA
Q4 : Choose the wrong sentence about gout?			
A) Over production of uric acid	B) Affects 3 per 1000 people	C) Painful arthritic joint inflammation	D) Over excretion of uric acid
Q5 : What's the first target that Sodium urate crystals deposits in ?			
A) Joint	B) Kidney	C) Urter	D) Liver

SAQs :

Q1: What's the substrate that causes gout? and mention the two causes of gout

Q2: How What are the ways of diagnosing gout? With explaining both of them.

★ **MCQs Answer key:**

1) B 2) C 3) A 4) D 5) A

★ **SAQs Answer key:**

1) High level in Uric acid (Monosodium urate crystals), overproduction orunderexcretion Uric acid

2) Slide 12

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Renad Alhomaidi
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Abdullaziz Alrabiah
Abdullah Almazro
Mishal Alhamed
Omar Alsuliman
Abdullah Alanzan
Abdullaziz Alomar
Ahmed Alkhayyat
Hamad Almousa

Mishal Althunayan

"One small positive thought can change your whole day"

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