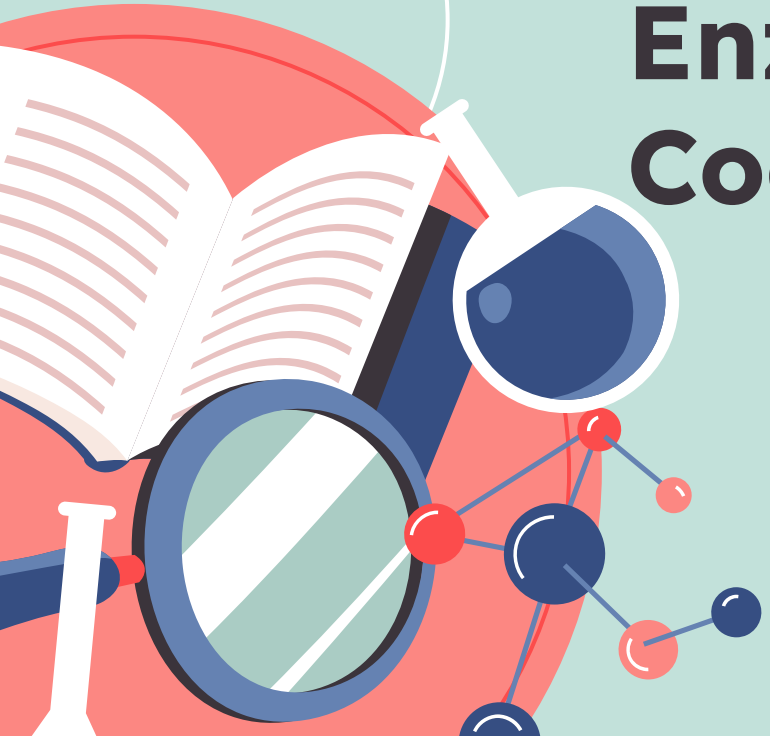


Enzymes and Coenzymes (2)

Editing File

Color Index:
- Main Text (black)
- Female Slides (Pink)
- Male Slides (Blue)
- Important (Red)
- Dr's Notes (Green)
- Extra Info (Grey)

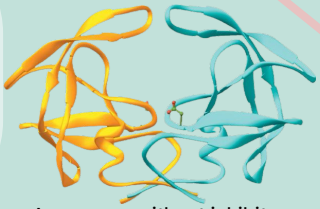
Objectives

- Understand the enzyme kinetics, types of inhibition and regulation of enzyme activity.
- Discuss the clinical role enzymes in the diagnosis of diseases.

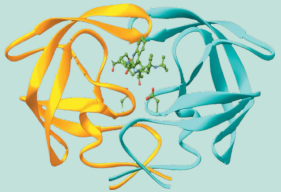
Enzyme Inhibitions

Inhibitions is the process by which the enzyme activity is regulated or controlled or stopped.

To inhibit means to stop the enzyme activity. (the inhibition might be 100% or partial)



An enzyme without inhibitor



An enzyme with inhibitor

Enzymes Inhibitions

- Competitive
- Noncompetitive
- Uncompetitive

Inhibitor constant K_i

- K_i is a measure of the **affinity** of the inhibitor for the enzyme.
- Also known as dissociation constant.

Affinity means attraction. Here we mean the attraction of the substrate to the enzyme.

Not to be confused with K_m
K_m means the substrate concentration that is needed to achieve one-half of the maximum rate (½ V_{max})

Competitive inhibition

Helpful video

1. The inhibitor is a structural analogue (similar) that competes with the substrate for binding at the active site of enzyme

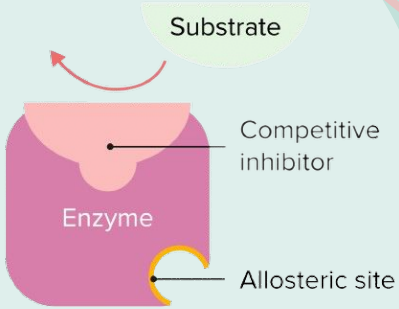
2. Two equilibria/reactions are possible:

$$E + S \rightleftharpoons ES \rightarrow E + P$$

and

$$E + I \rightarrow EI$$

E : Enzyme
S : Substrate
P : Product
ES : enzyme-substrate complex
I : Inhibitor



3. The value of V_{max} is **unchanged** in the presence and the absence of inhibitor

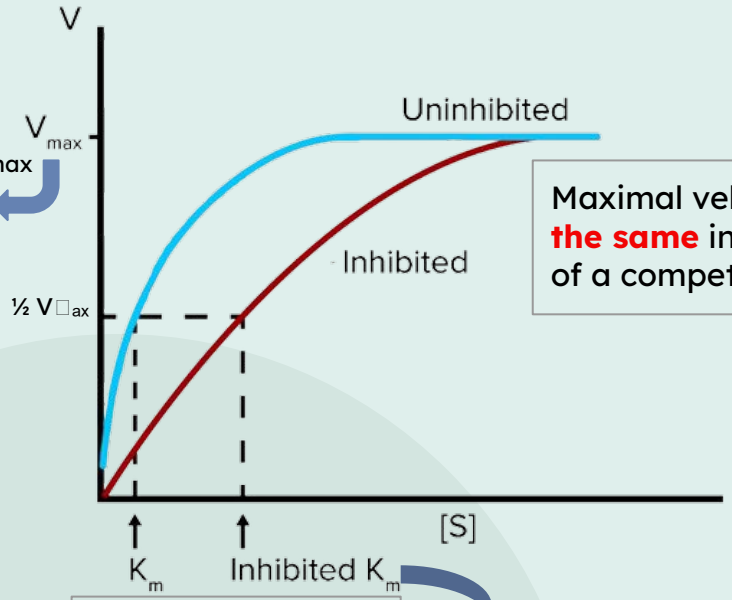
4. The value of K_m is **increased** because substrate and inhibitor compete for binding at the same site (Active site).

5. A higher [S] is required to achieve ½ V_{max} .

Enzyme can bind to substrate or the inhibitor depending on which one has more affinity to the enzyme.

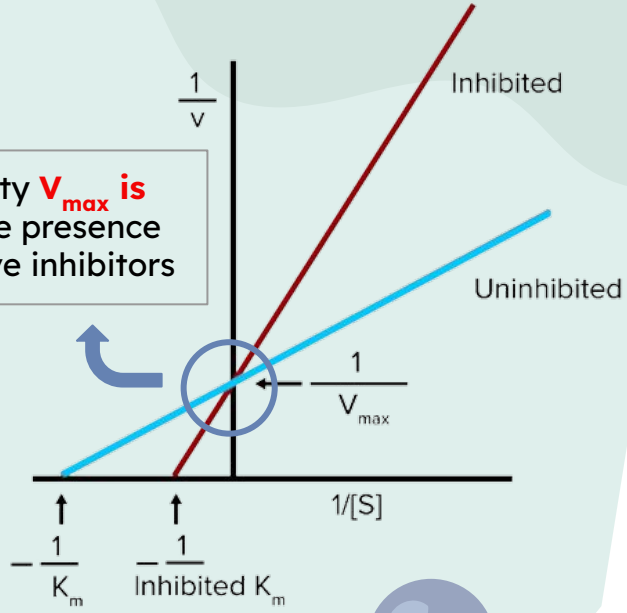
Competitive inhibition

The value of V_{max} is **unchanged**



The value of K_m is **increased**

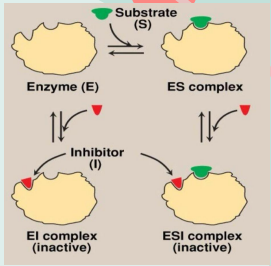
Maximal velocity V_{max} **is the same** in the presence of a competitive inhibitors

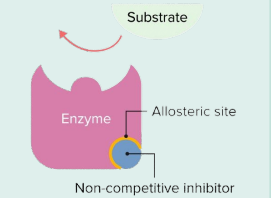


Michaelis constant K_m **is apparently increased** in the presence of a competitive inhibitors

Noncompetitive inhibition

Helpful video





1. The inhibitor does not have structural similarity to the substrate.
2. The inhibitor binds to the enzyme at a site away from the substrate binding site. (at Allosteric site)
3. No competition exists between the inhibitor and the substrate.
4. The inhibitor can bind to a free enzyme or to an enzyme-substrate complex

$ES + I \rightleftharpoons ESI$ (Inactive)

and

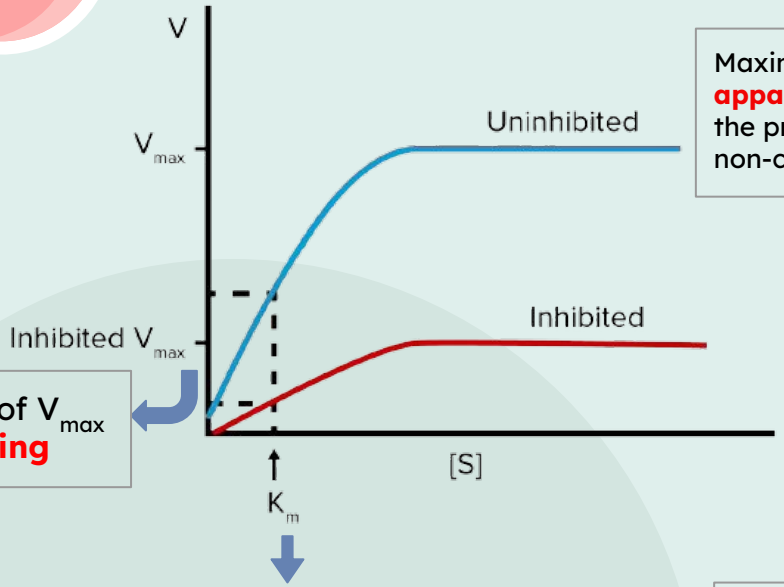
$E + I \rightleftharpoons EI$ (Inactive)

In both cases the complex is catalytically inactive

5. The value of **V_{max} is decreased** by the inhibitor, but **K_m is unchanged** because the affinity of S for E is unchanged.
(because substrate and inhibitor aren't competing for the same site).

when the noncompetitive inhibitor bind to the allosteric site it will change the shape of the active site which will prevent the substrate from binding.
(it can control the active site positively or negatively)

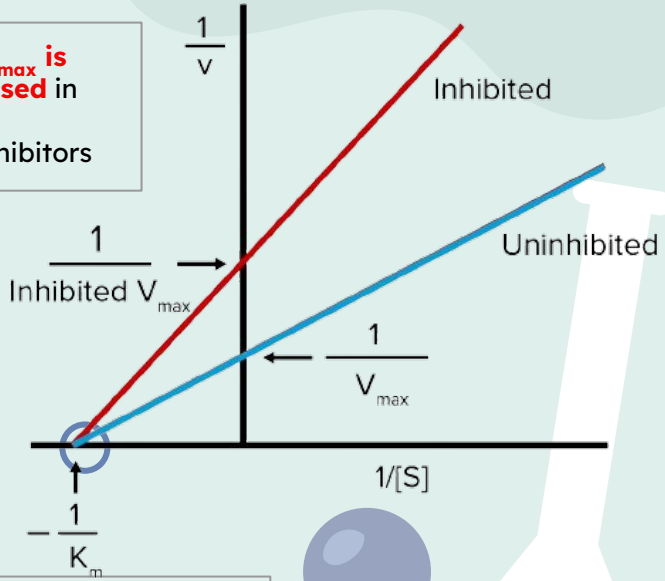
Noncompetitive inhibition



The value of V_{max} is **decreasing**

The value of K_m is **unchanged**

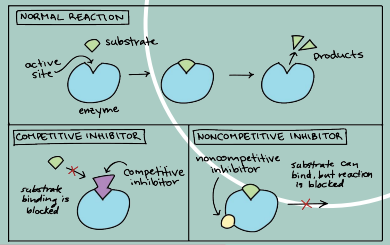
Maximal velocity **V_{max} is apparently decreased** in the presence of non-competitive inhibitors



Michaelis constant **K_m is unchanged** in the presence of a non-competitive inhibitors

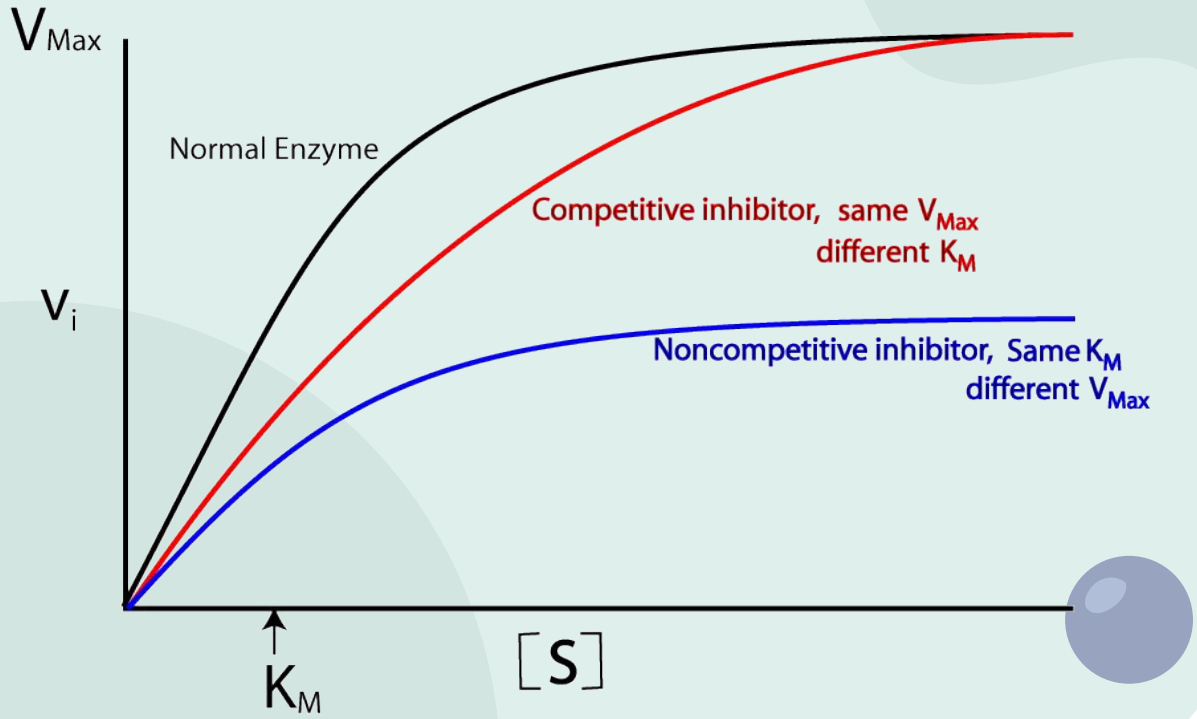
Quick Comparing

Helpful video



	Competitive	Non-Competitive
Structure	Similar to the substrate	Dissimilar to the substrate
Binding site	Active Site	Allosteric Site
Competition	Exists	Nonexistent
Reactions	$E + S \Leftrightarrow ES \Rightarrow E + P$ $E + I \Rightarrow EI$	$ES + I \Leftrightarrow ESI$ $E + I \Leftrightarrow EI$
Maximal velocity V_{max}	Unchanged	Decreased
Michaelis constant K_m	Increased	Unchanged

Competitive and Noncompetitive inhibition



Regulation of enzyme activity

- Regulatory (regulation can be activating or inhibiting) enzymes usually catalyze the first or an early reaction in a metabolic pathway. (The earliest it's stopped the best)
- They catalyze a rate limiting reaction that controls the overall pathway. (It requires energy)
- They may also catalyze a reaction unique to that pathway known as **committed step.**

Med39: Enzymes control the overall pathway by utilizing or giving energy.

Feedback inhibition (Negative)

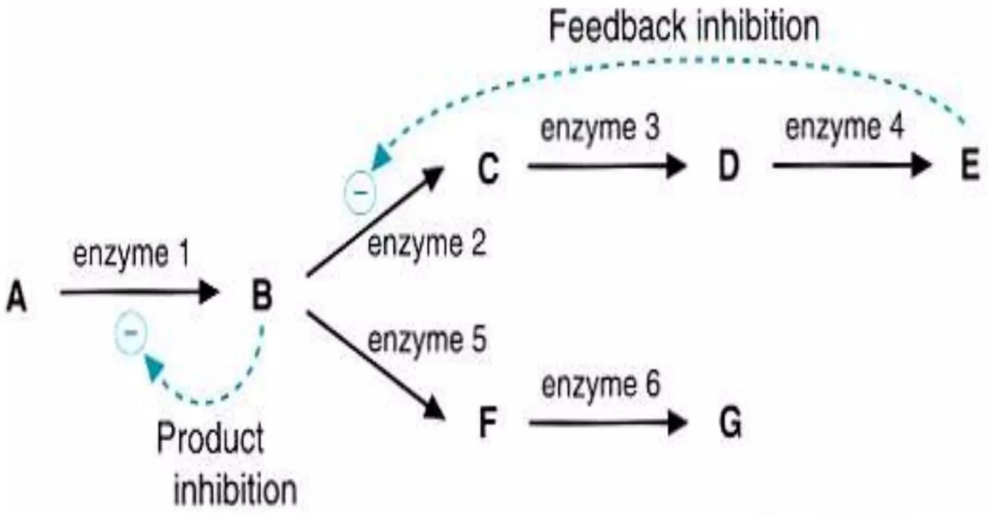
When the end product of a metabolic pathway **exceeds** its concentration limit, it **inhibits** the regulatory enzyme to normalize the pathway. (feedback inhibition)

Feed positive activation

When the end product of a metabolic pathway is **below** its concentration limit, it **activates** the regulatory enzyme to normalize the pathway.

Med439: Cells use feedback inhibition to slow down the production, conserve energy and to maintain a state of homeostasis.

Feedback Inhibition



e.g. If you have enough of **product E** you can't stop enzyme 1 because you will affect **enzyme 5** so the first committed step is stopping **enzyme 2**

Types of regulation

Allosteric enzyme regulation: (Non-Competitive)

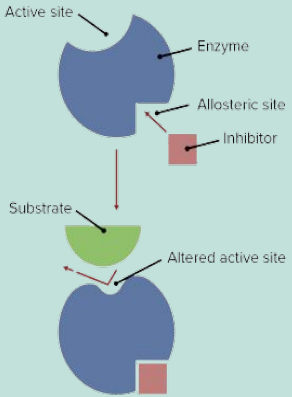
Helpful video until 1:12

- The enzymes in metabolic pathways whose activities can be regulated by certain compounds(Ligand or modulator) that bind to enzyme other than the catalytic site are known as allosteric enzymes.
- These ligands do not bind to active site. They bind to another site (regulatory/allosteric site) on the enzyme(allosteric enzyme).
- The term “ allosteric ” came from Greek word “ allos ” meaning “other”.
- Most allosteric enzymes are **oligomers** (two or more polypeptide chains or subunits).
- The subunits are known as **protomers**.
- The effect of a **modulator (ligands)** may be Positive(activation) OR Negative(inhibition).

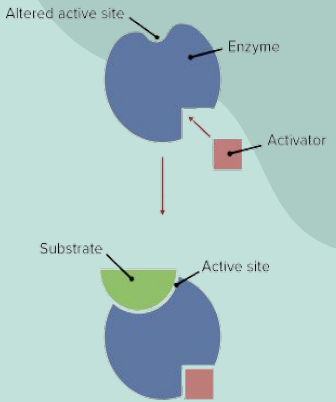
↓	↓
increased E, S affinity	Decreased E, S affinity

Allosteric Inhibition

The active site becomes unavailable to the substrates when a regulatory molecule binds to a different site on the enzyme.



Allosteric Activation



The active site becomes available to the substrates when a regulatory molecule binds to a different site on the enzyme.

Allosteric enzymes Interactions

Heterotropic

Effect of one ligand on the binding of a different ligand

Homotropic

Effect of one ligand on the binding of the same ligand (a regulatory enzyme modulated by its own substrate)

Types of regulation

Cooperative binding:

Helpful video

- The process by which binding of a ligand to a regulatory site affects binding of the same(Homotropic) or of another(Heterotropic) ligand to the enzyme.
- This is called **Cooperative Binding**.
- Binding of an allosteric modulator (ligand) causes a change in the conformation/active site of the enzyme.
- This causes a change in the binding affinity of enzyme for the substrate.

Enzymatic diagnosis and prognosis of diseases

Enzymes are used clinically in three ways:

- **As indicators** of enzyme activity or conc. in body fluids (serum, urine) in the diagnosis/prognosis of diseases.
- **As analytical reagents** in measuring activity of other enzymes or compounds in body fluids.
- **As therapeutic agents**.

Plasma and **Serum** are The most commonly used body fluids for measuring enzyme activity.

There is:

-Plasma-specific enzymes (present in blood)

– Non Plasma-specific enzymes

Serum markers in the diagnosis of diseases:

- Heart disease (troponin)
- Pancreatic diseases (Lipase and amylase)
- Liver diseases (ALT & AST)

You don't need to memorise these enzymes

Take Home Messages

- Enzymes are essential for all biochemical reactions in the body.
- A number of diseases are treated by inhibiting specific enzymes.
- Many enzymes are used as biomarkers for diagnosis of diseases .

Question 1

Which one of the following types of inhibitors requires more substrate to reach ½ V_{max}?

A Non-Competitive

C All of them

B Competitive

D None of them

Question 1

Which one of the following types of inhibitors requires more substrate to reach ½ V_{max}?

A Non-Competitive

C All of them

B Competitive

D None of them

Question 2

Which of these mechanisms increases the k_m:

A. Competitive inhibition

C. Competitive activation

B. Non-competitive inhibition

D. Non-competitive activation

Question 2

Which of these mechanisms increases the k_m:

A. Competitive inhibition

C. Competitive activation

B. Non-competitive inhibition

D. Non-competitive activation

Question 3

Known as dissociation constant :

A V_{max}

C K_m

B [S]

D K_i

Question 3

Known as dissociation constant :

A V_{max}

C K_m

B [S]

D K_i

Question 4

What happens to V_{max} in the case of non-competitive inhibition?

A. Decreased

C. Stay the same

B. Increased

D. All of them

Question 4

What happens to V_{max} in the case of non-competitive inhibition?

A. Decreased

C. Stay the same

B. Increased

D. All of them

Question 5

Most allosteric enzymes are :

A Monomers

C Protomers

B Oligomers

D Enantiomers

Question 5

Most allosteric enzymes are :

A Monomers

C Protomers

B Oligomers

D Enantiomers

Question 6

The effect of a positive modulator :

A. Increase E,S affinity

C. Decreased E,S affinity

B. Increased E and Decreased S affinity

D. Decreased E and increased S affinity

Question 6

The effect of a positive modulator :

A. Increase E,S affinity

C. Decreased E,S affinity

B. Increased E and Decreased S affinity

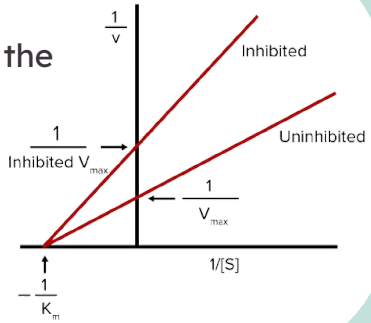
D. Decreased E and increased S affinity

SAQ Question 1

1) What kind of inhibition is seen in the diagram?

1) How does it affect V_{max} ?

1) How does it affect in K_m



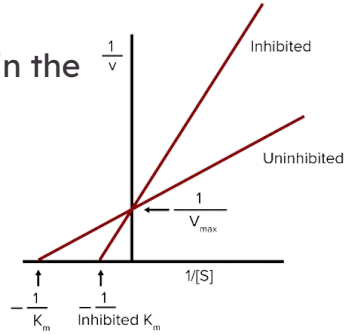
1) **Non-competitive inhibition**
2) **Decreases it**
3) **It doesn't change** because the affinity of S for E is unchanged
(because the substrate and inhibitor aren't competing for the same site).

SAQ Question 2

1) What kind of inhibition is seen in the diagram?

1) How does it affect V_{max}?

1) How does it affect in K_m?



1) **Competitive inhibition**
2) **It doesn't change**
3) **Increases it because the substrate and the inhibitor compete for bending to the same site**

SAQ Question 3

Which type of feedback occurs when the metabolic pathway is **below** it's concentration limit?

Feed positive activation

SAQ Question 4

In which diseases can you use enzymes as a markers?

Heart disease - Pancreatic disease - Liver disease

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- Abdullah Almutlaq

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- Huda Bassam
- Manar Alqahtani
- Marwa Fal
- Jenan Al-Sayari
- Rahaf Aldawood
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Lura Almusaeeb

- Shaden Alotaibi
- Aljawharah Alyahya
- Norah Albahdal
- Ghaida Alotaibi
- Ghida Alkahtani
- Lama Alhayan
- Shaden Alshammari

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