جامعة الملك سعود
King Saud University

Biochemistry437

Cholesterol Metabolism

Biochemistry Team 437

Color index:
Doctors slides
Doctor's notes
Extra information
Highlights

غيداء آل مصمع
عبدالرحمن الحيسوني
Revised by

Cardiovascular block

EDITING FILE

MED437
KING SAUD UNIVERSITY

Objectives

- Understand the structure and functions of cholesterol
- Discuss the regulation of cholesterol homeostasis in the body
- Comprehend the important steps of cholesterol synthesis pathway
- Identify different levels of regulation of cholesterol synthesis
- Discuss the association of hypercholesterolemia with abnormal cholesterol metabolism
- Understand the role of statins in the treatment of hypercholesterolemia

Overview

- Introduction
- Cholesterol structure
- Cholesteryl esters
- Cholesterol synthesis
- Rate limiting step
- Regulation of cholesterol synthesis
- Regulation of HMG CoA reductase
- Excretion of cholesterol
- Hypercholesterolemia and treatment

Cholesterol

Biochemistry437

Cholesterol is not only negative, it has some good roles in the body including:

- Most important animal steroid.
- Maintains membrane fluidity.
- Insulating effect on nerve fibres "involved in the synthesis of myelin sheath".
- Cholesterol is the parent(precursor) molecule for
  - Bile acids and bile salts [1]
  - Steroid hormones [2]
  - Vitamin D3 / A [3]

[1] Components of bile, solubilize lipids and aid in their digestion
[2] e.g. estrogen, cortisol
[3] All fat soluble vitamins

- High levels of cholesterol are harmful to the body, so we need to maintain a proper level of cholesterol (homeostasis) by some mechanisms.
- Liver plays a central role in the regulation of cholesterol homeostasis.

Sources

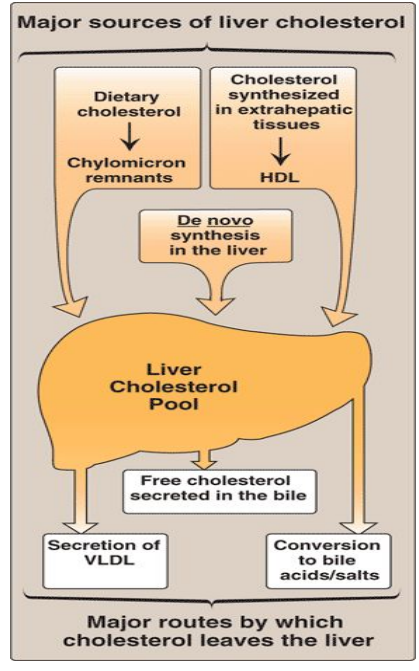
Cholesterol enters the liver's cholesterol pool from

- dietary cholesterol carried by chylomicrons "a lipoprotein"
- synthesized by the liver itself. "De novo" synthesis
- Synthesised in extrahepatic tissue, carried by HDL[1]

Elimination

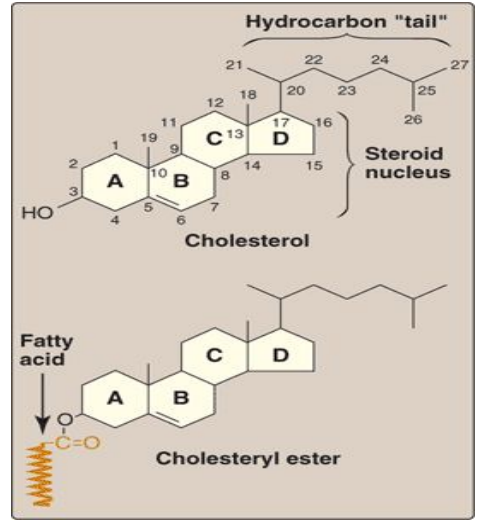
- As VLDL
- Converted to bile salts and acid
- Unmodified cholesterol in bile and feces

[1]This is why we consider HDL a good cholesterol, because it brings all the excess cholesterol from the body to the liver to be metabolized



Cholesterol structure

- Four rings called (Steroid nucleus).
- 27 carbon compounds with two specific features:
  - At carbon no.17 there is a hydrocarbon tail
  - At carbon no.3 there is a hydroxyl group
- The presence of these 2 features makes it a Sterol.
- Meaning cholesterol is a type of sterol and all sterols are steroids. (but not all steroids are sterols)



Cholesterol esters

- Cholesterol is not usually present in the plasma as a sterol, Most **plasma cholesterol** is esterified with a fatty acid.
- CEs “cholesteryl esters” are not present in membranes (only free cholesterol).
- Present in small amounts in most cells.
- More hydrophobic than cholesterol[1].

[1] because a hydrocarbon chain was added to it when it was esterified, making it even more hydrophobic.

Cholesterol Synthesis

- Synthesized in all tissues
- Major sites for synthesis: liver, adrenal cortex, testes, ovaries and intestine
- All carbon atoms are derived from acetyl CoA[1]
- Enzymes involved in biosynthesis are partly located in ER[2] and partly in cytoplasm

[1]Just like all fatty acids are broken down into acetyl CoA , a 2 carbon molecule.

[2]Even though the enzyme is present in the ER, synthesis of cholesterol only occurs in the cytoplasm, how? Because the catalytic domain of the enzyme that is present in the ER is found in the cytoplasm.

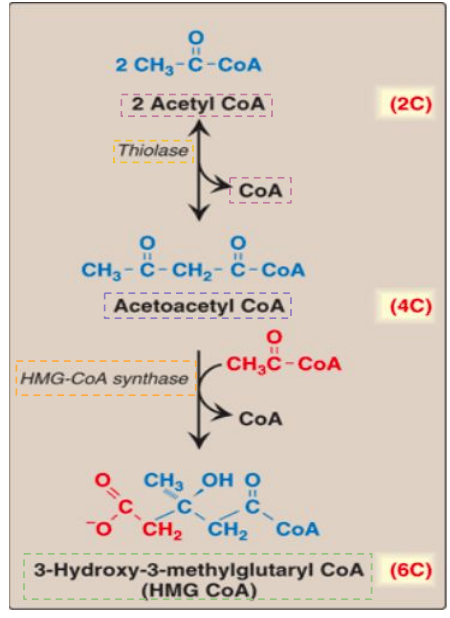
Cholesterol synthesis overview:
1- synthesis of HMG CoA
2- synthesis of mevalonic acid
3- further steps

Synthesis of HMG CoA " HMG-CoA is a molecule that forms cholesterol through certain reactions``

Biochemistry437

3 Acetyl CoA are used to form one HMG-CoA molecule.

- HMG CoA synthase is found within the hepatocytes of the LIVER in either the Cytosol or the Mitochondria and in each place serves a different function.
- In the Mitochondria of hepatocytes- it is used in ketogenesis (the formation of a ketone body)
- In the Cytosol (cytoplasm) of hepatocytes - cholesterol synthesis



Steps:

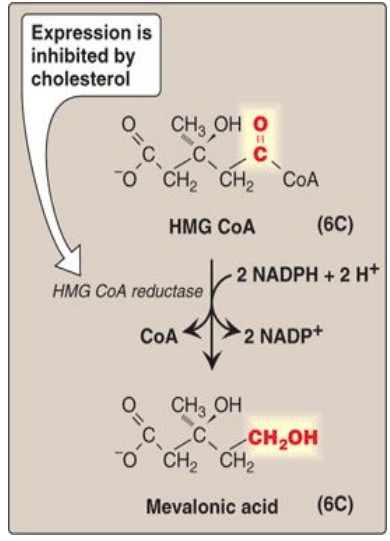
- We start with 2 molecules of Acetyl COA to make a 4 carbon compound called "Acetoacetyl CoA" by the enzyme thiolase.
- Then we add another acetyl CoA to make a 6 carbon molecule called "3-hydroxy-3-methylglutaryl CoA" "HMG CoA" by the enzyme "HMG CoA synthase".

Synthesis of Mevalonic Acid

- The importance of mevalonic acid synthesis
  1. It a the key step in cholesterol synthesis
  2. It rate limits its production.
     (irreversible step that limits production by regulating the whole pathway because it is the target for inhibitors)

- Location of mevalonic acid synthesis.
  It occurs in the cytosol of hepatocytes.

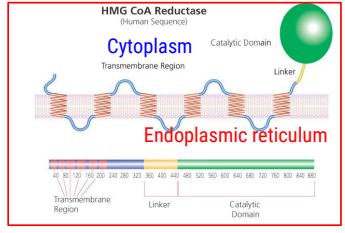
- HMG CoA reductase is an ER membrane enzyme with catalytic unit hanging in the cytosol.



Note: It occurs in the cytosol even though HMG CoA reductase is an ER membrane enzyme, because although HMG CoA reductase is an ER membrane enzyme it has a catalytic unit hanging out into cytosol.

(Imagine HMG CoA reductase as being a flag. The base of the pole is grounded on the surface of the ER but the flag waves in the cytoplasm)

Extra picture for understanding the note



Steps:

- HMG CoA is reduced to mevalonic acid " a 6 carbon molecule" by the enzyme HMG CoA reductase. This step requires 2ATP

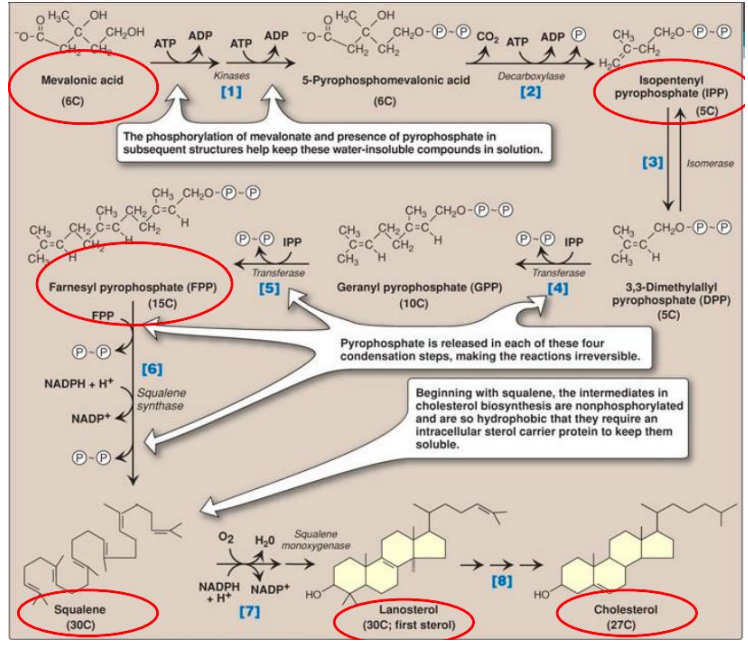
Steps of Mevalonic Acid Synthesis

Biochemistry437

After Mevalonic acid is formed, the complex undergoes a series of reactions to finally become cholesterol.

1. Production of a 5-carbon unit: - Isopentenyl pyrophosphate (IPP) [which is the patent sterol for all sterols, and the building block of cholesterol]
2. IPP is then converted to farnesyl pyrophosphate (FPP) [15 C molecule]
3. 2 molecules of (FPP) are Condensed to a 30C compound: squalene (which is an opened ring molecule)
4. Cyclization of squalene to 30C Lanosterol to form a ring **[the first and parent sterol that is made in the body]**
5. Synthesis of 27-Carbon cholesterol by removal of 3 carbons (defect in this leads to Smith-Lemli-Opitz Syndrome "SLOS")

(SLOS – An autosomal recessive disorder caused by a partial deficiency in 7-dehydrocholesterol-7-reductase)



Here, only know the names circled in red and the number of carbons.
DR.ESSA said the enzyme is important!!

Regulation of Cholesterol Synthesis

- HMG CoA reductase is the rate-limiting enzyme of cholesterol synthesis **(Important!)**

HMG CoA Reductase Regulation

By 4 mechanisms:

- **Sterol-dependent**[1] regulation of **gene**[2] expression
- **Sterol-accelerated** enzyme degradation[3]
- **Sterol-independent** phosphorylation/dephosphorylation
- **Hormonal regulation**

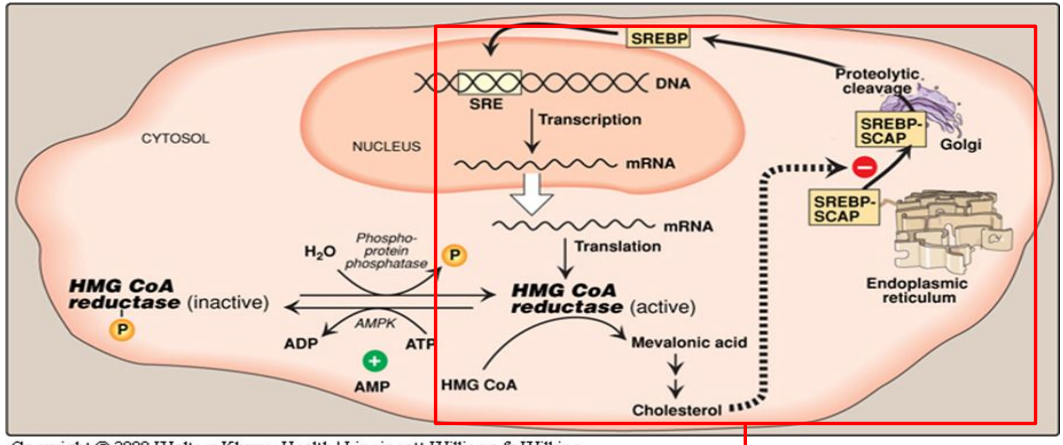
[1]Meaning the amount of cholesterol in your body will determine the regulation
[2]Genes of the enzymes responsible for regulation
[3]The more sterol the faster degradation

Sterol-dependent Regulation of Gene Expression of HMG CoA

- The goal is to regulate transcription, how? By transcription factors. These factors bind before the gene, and either activate or inhibit its transcription
- When sufficient cholesterol is present, transcription is suppressed and vice versa
- Sterol Regulatory Element (SRE) is a recognition sequence in the DNA. (the area that binds with the transcription factor)
- SREBP (SRE binding protein) binding to SRE is essential for transcription of this gene "the transcription factor, present in the ER."
- SREBP cleavage-activating protein (SCAP) is an intracellular cholesterol sensor. so when the levels of cholesterol decrease, SCAP will take SREBP to the ER and cleaves it to synthesize more cholesterol, and if cholesterol levels increase the cleavage will be stopped
- Explained in steps in the next slide.

High Cholesterol	Low Cholesterol
• SCAP binds to insig protein (insulin-induced protein) in ER membrane • SCAP-SREBP is retained in the ER • Down regulation of cholesterol synthesis	• SCAP-SREBP moves to Golgi bodies • SCAP is removed from SREBP • SREBP binds to SRE in DNA • HMG CoA gene is activated

Sterol-dependent Regulation of Gene Expression of HMG CoA



Steps:

Normally or in case of low cholesterol:

- SREBP is present in the ER.
- It needs **SCAP** "cleavage activating protein" to carry it to the golgi bodies.
- Inside the golgi bodies, there are enzyme that remove SCAP and release SREBP.
- SREBP goes the the nucleus, binds to SRE and activates transcription.

In case of high cholesterol:

- Scap senses the raise in cholesterol and binds to another molecule called insig "insulin- induced protein" which prevents it from leaving to the Golgi body, so it remains in the ER along with SREBP, which inhibits the transcription of HMG CoA reductase.

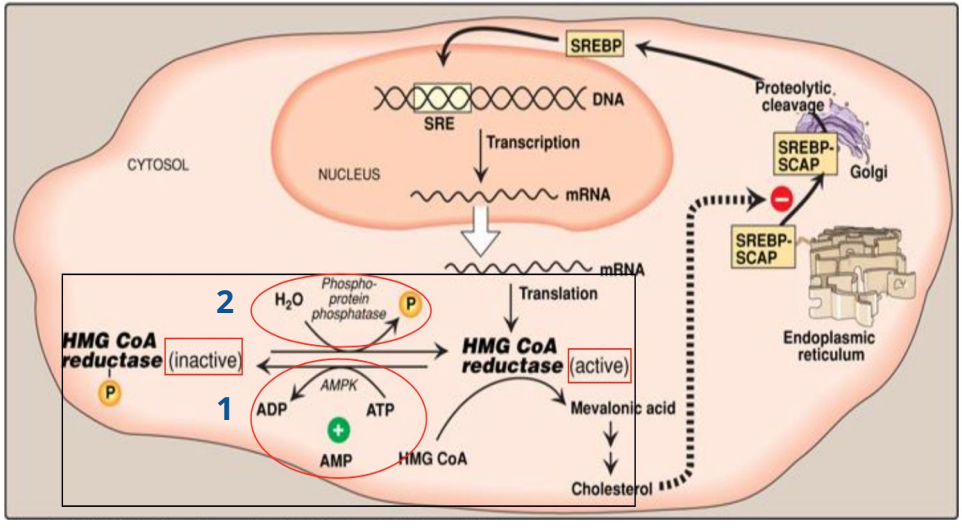
Team436:
اذا صارت كمية الكولسترول كافيه
الكوليسترول نفسه راح يثبط الجين المسؤول
عن تكوين هذا الإنزيم وتوقف عملية تكوين
الكوليسترول بالكامل

Sterol-accelerated Enzyme Degradation

- When cholesterol is high, HMG-CoA reductase itself binds to insigs.
- Leading to (increase) degradation of enzyme.

Enzyme Phosphorylation and Dephosphorylation

- This is a sterol independent mechanism which depend on the amount energy presented in the cell " no enough ATP, no synthesis".
- High ATP means Low AMP and Low ATP means High AMP.
- AMP- activated protein kinase (AMPK) for phosphorylation.
- Phosphorylated form of enzyme is inactive.
- Dephosphorylated form is active done by (phosphoprotein phosphatase).
- Low ATP or High AMP cholesterol synthesis decreases.



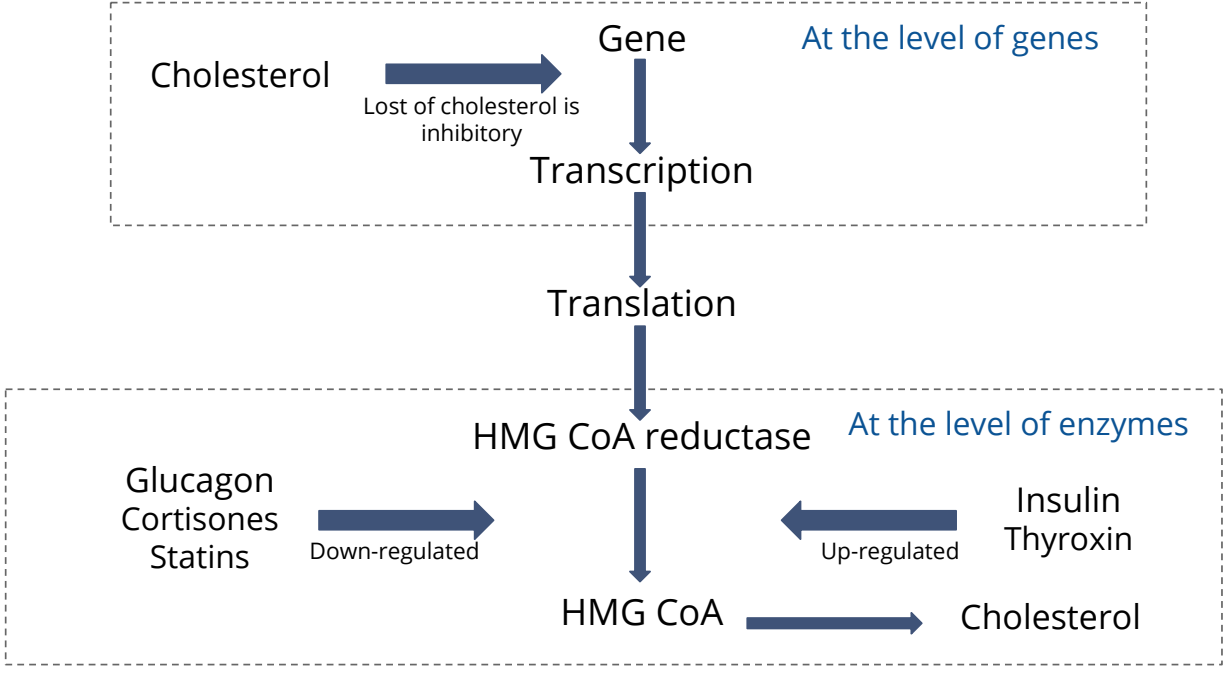
1- When there's high AMP, AMP kinase is activated and then the AMPK will phosphorylate the enzyme and make it inactive and the cholesterol synthesis goes down.

2- When there's high ATP another enzyme which called phosphoprotein phosphatase will remove a phosphate group and make the enzyme active.

Hormonal Regulation

- insulin and thyroxine increase upregulation of enzyme expression
- Glucagon and cortisol have opposite effect

HMG CoA Reductase Regulation



Excretion of Cholesterol

(Normally most of the molecules (protein/carbohydrates) are broken down completely to CO_2 and H_2O , but cholesterol can not be broken down completely because of it big ring structure)

By :

- conversion into bile acids and bile salts excreted in the feces.
- secretion of cholesterol in bile.
- Transported to intestine for elimination.
- In the intestine, some cholesterol is converted by bacteria into coprostanol and cholestanol before excretion.

There are 4 forms of which cholesterol can be excreted:

- bile salts
- bile acids
- cholestanol
- coprostanol

Hypercholesterolemia

- High concentration of cholesterol in blood leads to atherosclerosis
- Statin drugs are used to decrease plasma cholesterol levels
- Statins are structural analogs of HMG CoA reductase
- Statins inhibit enzyme activity by competitive inhibition
  (because statins and HMG CoA reductive are structurally similar, they competitively bind to the active site of the enzyme and when they're bound , HMG CoA synthesis drops)

β-sitosterols / phytosterols

- Plant sterols and are poorly absorbed by humans (Poorly absorbed in the intestine)
- Block the absorption of dietary cholesterol
- Clinically useful in the dietary treatment of hypercholesterolemia

Take Home Messages

- Cholesterol is important various body functions
- Liver plays a major role in the cholesterol
- homeostasis in the body
- HMG CoA reductase is a rate-limiting enzyme for cholesterol synthesis

Cholesterol

1) Structure:
Sterol: 4 rings with a hydrocarbon tail and a hydroxyl group.
Cholesteryl ester: have a fatty acid tail

2) Function:
- Most important animal steroid.
- Maintains membrane fluidity.
- Insulating nerve fibers.
- Parent molecule for bile acids, bile salt, steroid hormones, vitamin D3.

3) Synthesis:
- In all tissues mainly in liver, intestines, adrenal cortex, testes, ovaries.
- Carbon atoms are derived from acetyl CoA.
- Biosynthesis enzymes are located in ER and cytoplasm.

4) HMG CoA Reductase Regulation:
It is the rate limiting enzyme of cholesterol synthesis.

HMG CoA Synthase enzyme:
In cytosol: cholesterol synthesis
In mitochondria of liver: ketogenesis
1) It makes HMG CoA from acetyl coA.

Mevalonic acid synthesis: in cytosol. Rate limiting step.
2) HMG CoA is reduced into mevalonic acid by **HMG CoA Reductase.**

HMG CoA Reductase: ER membrane enzyme with catalytic unit hanging in cytosol.
3) Synthesis of IPP (5C unit) from mevalonic acid.
4) Synthesis of FPP by putting 3 IPPs together.
5) Condensing to squalene, a 30C compound by squalene synthase.
6) Cyclization of squalene to 30C lanosterol.
7) Synthesis of 27 C Cholesterol (defect leads to Smith Lemli Oplitz syndrome)

1) Sterol dependent regulation of HMG CoA gene expression
Important molecules:
- SRE –SREBP – SCAP –Insig
Know what happens to SCAP when cholesterol is high or low.

2) Hormonal regulation
Important molecules:
Insulin, thyroxine, cortisol, glucagon.

3) Sterol accelerated enzyme degradation
Important molecule: Insigs

4) Sterol independent phosphorylation/dephosphoryltion
Important molecule:
ATP levels, AMP Kinase

MCQs:

1) Which of these is not a major site for cholesterol synthesis?

a. Liver
b. Brain
c. Ovaries
d. Adrenal cortex

2) HMG CoA synthase is present in?

a. Mitochondria
b. Cytosol
c. Both a and b

3) Which of these is the rate limiting enzyme of cholesterol synthesis?

a. HMG CoA reductase
b. HMG CoA synthase
c. Thiolase

1. B
2. C
3. A

Biochemistry437

Team leaders

- رهام الحلبي
- معاذ الحمود

Boys team

- محمد الصويغ
- فيصل الطحان
- طارق العميم
- انس القحطاني
- صالح الوكيل
- عبد الملك الشرهان
- سعيد القحطاني
- محمد الاصقه
- نواف اللويمي
- عدنان المقبل
- عبدالرحمن التركي
- عبدالله الحربي

Girls team

- رهف الشنيبر
- شهد الجبرين
- لينا الرحمة
- منيرة المسعد
- ليلى الصّباغ
- العنود المنصور
- أرجوانة العقيل
- ريناد الغريبي
- رزان الزهراني
- ليان المانع
- مشاعل القحطاني
- ريما الديحان

@biochemistry437

teambiochem437@gmail.com