Editing File

13

Krebs cycle

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Main text

IMPORTANT

Extra Info

Drs Notes

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Objectives:

- Recognize the various fates of pyruvate
- Define the conversion of pyruvate to acetyl CoEnzyme A (CoA)
- Discuss the major regulatory mechanisms of PDH complex
- Recognize clinical consequences of abnormal oxidative decarboxylation reactions
- Recognize the importance of krebs cycle
- Identify various reactions of krebs cycle
- Define the regulatory mechanisms of krebs cycle
- Asses the energy yield of PDH reaction and krebs cycle's reactions

A helpful video

Fate of pyruvate

Pyruvate can eventually end up as ONE of the FIVE following substrates

- **Lactate**
  in humans and some microorganisms in anaerobic conditions
- **Oxaloacetate (Pyruvate carboxylase)** In Krebs cycle (it's an intermediate) Activated by acetyl CoA
- **Alanine**
  Synthesis of nonessential amino acid using pyruvate + glutamine "essential"
  Done by Alanine transaminase (ALT) & Pyridoxal Phosphate (PLP)
- **Ethanol**
  It occurs in yeast and some Bacteria (including intestinal flora)(Anaerobic)

The route we are focusing on

Glucose
C-C-C-C-C-C *6

Glycolysis

Pyruvate
C-C-C *3

Pyruvate
C-C-C *3

Preparation to krebs cycle

Pyruvate dehydrogenase

Reduces NAD+ to NADH

Acetyl CoA
C-C*2

Krebs cycle

Acetyl CoA + Oxaloacetate —(Citrate synthase)→ Citrate

Irreversible

Citrate
C-C-C-C-C-C *6

Irreversible

Oxaloacetate
C-C-C-C *4

Krebs cycle reactions

After studying glycolysis, we now know that pyruvate is the end product of glycolysis and will produce a net of 8 ATPs, and if we recall, oxidation of one glucose molecule will generate 38 ATPs, where are the other 30 ATPs generated?

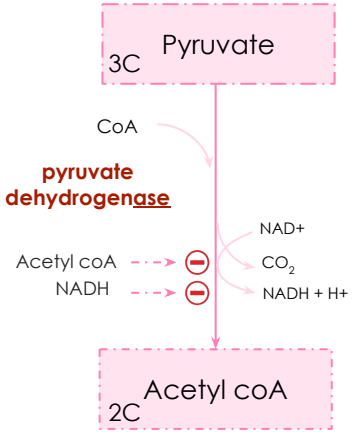
Oxidative decarboxylation of pyruvate

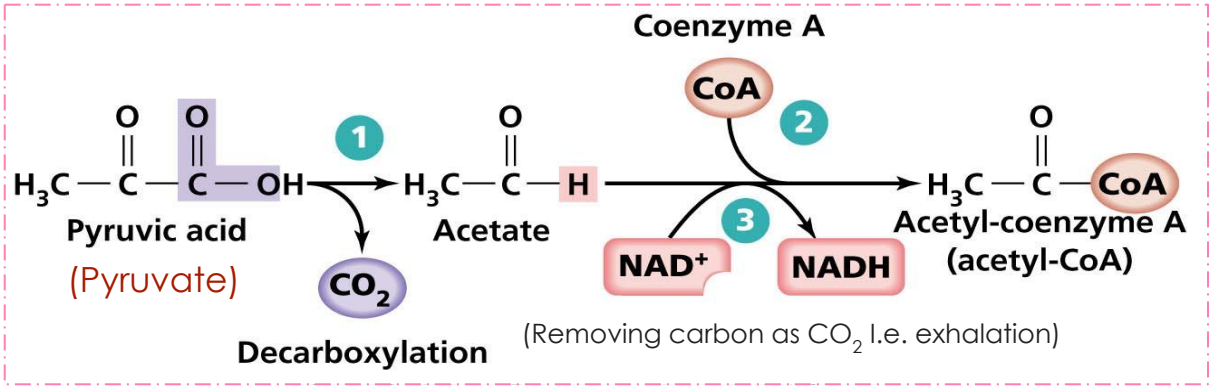
(Preparation phase)

- It's the process of making acetyl Co-A & oxaloacetate from pyruvate by the enzyme **pyruvate dehydrogenase**
- Outcomes of this process : 1 x 2 NADH (6ATP) for two pyruvates

  (keep in mind that in every reaction we talk about only one pyruvate, the other will have the same reactions & productions thus we explain one pyruvate and multiply the outcomes by 2)

- Regulated by allosteric regulation of **Acetyl coA and NADH** i.e. Increased amount of Acetyl CoA and NADH act as "Negative Feedback" inhibitors of their respective reactions. Responsible enzyme for this is pyruvate dehydrogenase kinase which phosphorylates and inactivates Pyruvate dehydrogenase





1 NADH = 3 ATP
1 FADH = 2ATP

Kinase= enzyme that adds phosphate group "phosphorylates"
Phosphatase = enzyme that removes phosphate group

PDH complex : covalent regulation

بمعنى اخر كل enzyme لازم يشتغل بطريقه منظمة في جسمنا بحيث مايشتغل طول الوقت ، يشتغل فقط اذا احتجناه بالتفاعل

Regulation of PDH kinase :

Inhibitors of pyruvate dehydrogenase kinase
(induce the deactivation of PDH kinase) :

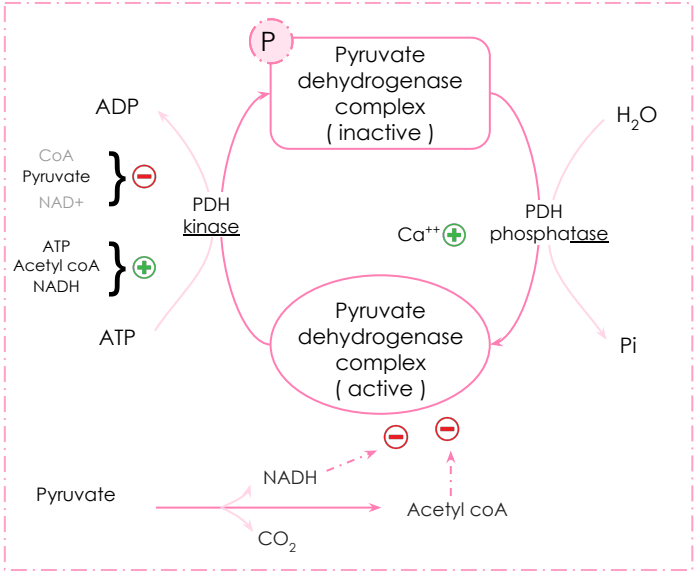
- Pyruvate
- CoA
- NAD+

When there is too much amount of any of them, the enzyme will stop which means it will not add a phosphate group to PDH complex so it will keep PDH complex in the **active form**

Inducers of pyruvate dehydrogenase kinase
(induce the activation of PDH kinase) :

- Acetyl CoA
- NADH
- ATP

When there is too much amount of any of them the enzyme will be activated which means it will add a the phosphate group as a result the PDH complex will be in the **inactive form**



Regulation of PDH kinase

باختصار لو عندي كميه قليله من الـ products اللي تطلع من المرحلة ماقبل الـ kerbs cycle هذا راح يخلي عندي كمية كبيره من الـ co factors اللي تساعدني في التفاعل انه يكمل او النواتج اللي تحتاج نكملها زي الـ pyruvate وجود اللي ذكرناهم راح يأدي الى تحفيز الـ PDH complex عشان يشتغل ويستعملها ويحولهم لـ other products نحتاجهم عشان نكمل وندخل للسايكل (بمعنى اخر يثبط الـ PDH kinase اللي كانت مخلية الـ PDH complex بالصوره الغير نشطة وبالتالي بتخليه نشط ويشتغل) ولو عندي كميه كبيره من الـ products راح يثبط الـPDH complex (بمعنى اخر يحفز الـ PDH kinase اللي راح يخلي PDH complex بالصورة الغير نشطة وبالتالي ماراح يشتغل الـ PDH complex ويوقف التفاعل اللي مفروض يكمل عشان ندخل الـ kerbs cycle)

Regulation of PDH Phosphatase

هذا ماعنده سالفه سوا ان وجود الكالسيوم راح يحفز ان الـ PDH Phosphatase يشتغل وبالتالي معناه راح يشيل مجموعه الفوسفات عن الـ PDH complex وبالتالي راح يزيد عندي الـ CO_2 , NADH and acetyl coA هذي نواتج التفاعل اللي يحدث قبل الدخول لـ kerbs cycle

Direct regulation of PDH complex

مو احنا قلنا قبل ان نواتج مرحله ماقبل الـ kerbs cycle ممكن تأثر بطريقه غير مباشره عن طريق تحفيز PDH kinase برضو هذا النواتج هذي موجوده لكن راح تأثر بطريقه مباشره على PDH complex اللي بالصوره النشطة وبتقلل من فاعليته بانه ينتج لي نفس النواتج يعني كأنه يقول له لعد تنتج نواتج زينا عندنا كثير يكفي يدخل الـ Krebs cycle

Regulation of PDH phosphatase :

Inducer of PDH phosphatase enzyme :

- Ca^2

if PDH phosphatase enzyme activated it will help the PDH complex to be in the active form that will produce a lot of products (NADH , Acetyl coA and CO_2 these are the products of the preparation phase as explained in the previous slide)

Direct regulation of PDH complex :

Inhibitors of PDH PDH complex:

- NADH
- CO_2

PDH reaction: clinical application

- PDH complex plays an important role in CNS, How?
  - Brain cells are unable to produce sufficient ATP if the PDH complex is inactive (no production of acetyl CoA > no krebs cycle > no ATP) Thiamine and niacin are co-factors that helps PDH complex .
  - Deficiencies of them can cause serious CNS problems
- **Congenital Lactic Acidosis :** PDH complex deficiency is the most common biochemical cause (in anaerobic conditions, pyruvate is converted to lactic acid and won't go any further in krebs cycle (accumulate) .
- **Wernicke-Korsakoff** (encephalopathy psychosis syndrome): due to thiamine deficiency, may be seen especially with alcohol abuse. (Thiamine deficiency is Vitamin B1 deficiency).

Tricarboxylic acid cycle: krebs cycle

Properties of the cycle :

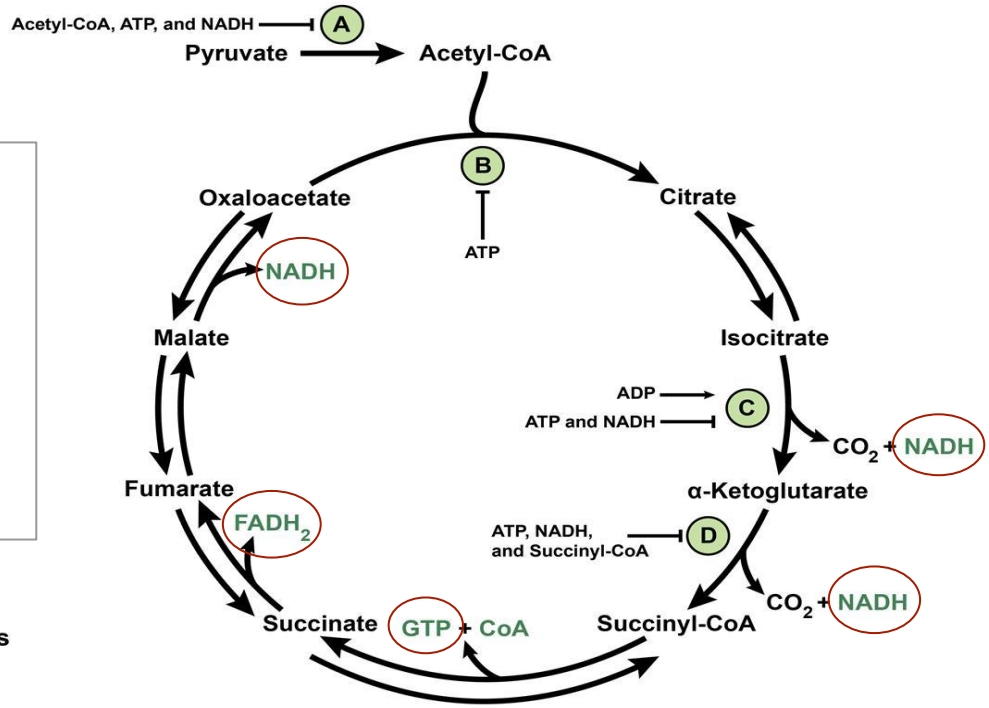
- Final common pathway for oxidation
- Exclusively in **mitochondria** Major source for ATP (24 ATP)
- Mainly catabolic with some anabolic features
- Synthetic reactions (anabolic features):
  - Glucose from amino acids
  - Non-essential amino acids
  - Fatty acids
  - Heme (RBC component, gives blood ability to carry oxygen)

A helpful video

Tricarboxylic acid cycle: krebs cycle (overview)

Reversible

Irreversible (has induction and inhibition factors)



Let's count together! نعد الدوائر
3 NADH (9 ATPs)
1 FADH (2 ATPs)
1 GTP (1ATP) = 12 ATPs per pyruvate x 2 = 24
+ 6 in the preparation phase
+ 8 in glycolysis = 38 ATPs
(Hey Look Ma, I Made It!)

1 GTP = 1 ATP
1 NADH = 3 ATP
1 FADH = 2 ATP

Mnemonic to memorize the products of krebs cycle :
Citrate Is Krebs Starting Substrate For Making Oxaloacetate
C = Citrate
I = Isocitrate
K = alpha-Ketoglutarate
S = Succinyl CoA
S = Succinate
F = Fumarate
M = L-Malate
O = Oxaloacetate

Irreversible enzyme reactions

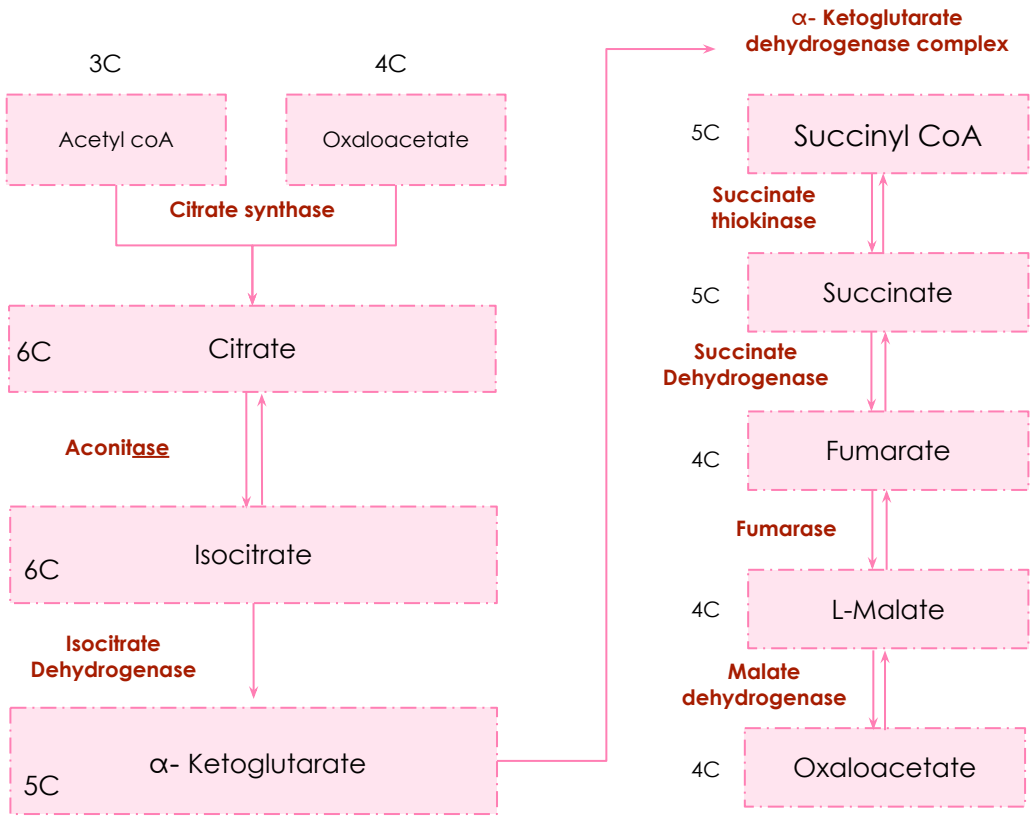
- A — Pyruvate dehydrogenase
- B — Citrate synthase
- C — Isocitrate dehydrogenase
- D — α-Ketoglutarate dehydrogenase

NAD(H) = nicotinamide adenine dinucleotide
GDP = guanosine diphosphate;
P = phosphate
FAD(H_2) = flavin adenine dinucleotide.

Tricarboxylic acid cycle: krebs cycle (overview)

reversible

irreversible



More details in the next slides

Krebs cycle (1)

1 Acetyl CoA + Oxaloacetate → citrate (6C)
(Citrate synthase; H_2O In, CoA Out)
2 Cs + 4 Cs

2 Citrate ⇌ Isocitrate (Aconitase)

3 Isocitrate → alpha-Ketoglutarate (Isocitrate dehydrogenase)

- can be regulated (inhibited or activated) :
  - ⊕ ADP, Ca^{2+}
  - ⊖ ATP, NADH

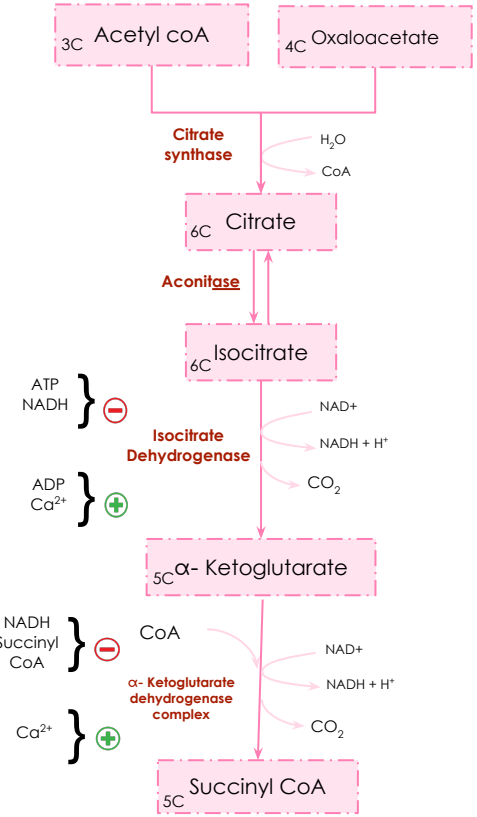
4 *(Oxidation and decarboxylation)

α-Ketoglutarate → Succinyl CoA (α-Ketoglutarate dehydrogenase complex)

- NAD+ is reduced to NADH + H^+
- CO_2 is out
- CoA is in

⊕ **Inducer of this reaction**
- Calcium

⊖ **Inhibitors**
- NADH
- Succinyl CoA
- Acetyl CoA



Citrate Is Krebs Starting Substrate For Making Oxaloacetate

Krebs cycle (2)

5 *(Oxidation and decarboxylation)

Succinyl CoA ⇌ (Succinate Thiokinase) ⇌ Succinate

- Only Substrate-Level phosphorylation in krebs cycle
- GTP is out (Produced)
- CoA is out

6 *(Oxidation)

Succinate ⇌ (Succinate dehydrogenase) ⇌ Fumarate

- FAD is reduced to FADH

7 *(Hydration)

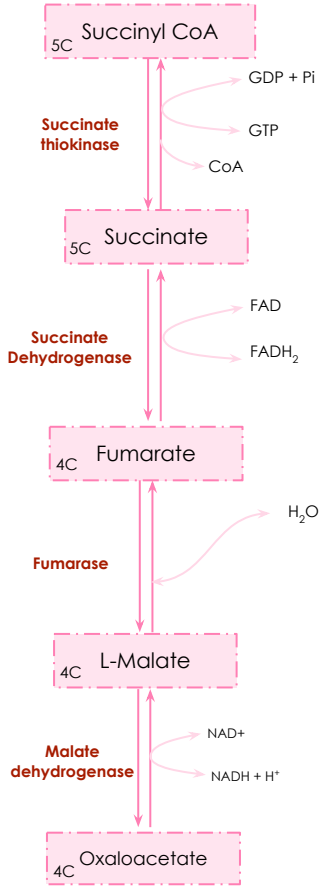
Fumarate ⇌ (Fumarase) ⇌ L-Malate

malate anion is an intermediate in the citric acid cycle

- H_2O is in

8 L-Malate ⇌ (Malate dehydrogenase) ⇌ Oxaloacetate

- NAD is reduced to NADH



Citrate Is Krebs Starting Substrate For Making Oxaloacetate

Since we finally made it to oxaloacetate, if you didn't get it it's totally okay just memorize the **yield** and the **enzymes**. They are extremely important!

Krebs cycle energy yield

- Number of ATP molecules produced from the oxidation of one molecule of acetyl coenzyme A (CoA) using both substrate-level and oxidative phosphorylation.

Energy - producing reaction	Number of ATP produced
3 NADH → 3 NAD+ FADH2 → FAD GDP + Pi → GTP	9 2 1
——	12 / ATP / Acetyl coA oxidized FOR ONE PYRUVATE HENCE WE MULTIPLY BY 2 = 24 ATP

Net ATP production by complete glucose oxidation

Aerobic Glycolysis	2 ATP 2 NADH	8 ATP
Oxidative decarboxylation (preparation phase)	1 NADH per private 2 NADH total	6 ATP
Krebs cycle	3 NADH 1 FADH 1 GTP Per pyruvate 6 NADH,2 FADH ,2 GTP in total We take one pyruvate and multiply the outcomes by 2	12 ATP per pyruvate 24 ATP in total
Net	38 ATP	

★ Important slide

Regulation of oxidative decarboxylation and krebs cycle

- **PDH complex and the TCA (krebs) cycle are both up-regulated in response to a decrease in the ratio of :**
  - ATP: ADP
  - NADH: NAD+
- **TCA (krebs) cycle activators are:**
  - ADP
  - Ca^{2+}
- **TCA (krebs) cycle inhibitors are:**
  - ATP
  - NADH

- **PDH complex** refers to: Pyruvate Dehydrogenase complex, it converts the **pyruvate** (end product of glycolysis) into **acetyl CoA** (substrate of krebs cycle)

- **TCA** is tricarboxylic acid cycle (aka as **citric acid cycle**, and **Krebs cycle**).
  TCA means Krebs cycle

Take home messages

- Pyruvate is oxidatively decarboxylated by PDH to acetyl CoA inside the mitochondria
- Krebs cycle: Final common pathway for the oxidation of carbohydrates, fatty acids and amino acids
- Occurs in the mitochondria, Aerobic.
- Mainly catabolic, with some anabolic reactions
- The complete oxidation of one glucose molecule results in a net production of 38 ATP molecules

Quiz

Q1 : Krebs cycle occurs in			
A) Mitochondria	B) Nucleus	C) Nucleolus	D) Golgi apparatus
Q2 :The net yield energy of oxidative decarboxylation (preparation phase)			
A) 4 ATP	B) 2 ATP	C) 6 ATP	D) 8 ATP
Q3 : The substrate involved in oxidative decarboxylation and also present in krebs cycle as a final product			
A) Acetyl CoA	B) Oxaloacetate	C) Citrate	D) L-Malate
Q4 : Enzyme responsible for conversion of citrate into isocitrate			
A) Citrate synthase	B) Aconitase	C) Isocitrate dehydrogenase	D) Fumarase
Q5 : net ATP production by complete glucose oxidation is:			
A) 38 ADP	B) 38 ATP	C) 6 ATP	D) 8 ATP
Q6 : The net yield energy of Krebs cycle per pyruvate			
A) 12 ATP	B) 24 ATP	C) 38 ATP	D) 8 ATP

SAQs :

Q1: The enzyme that converts a-ketoglutarate to succinyl CoA?

★ **MCQs Answer key:**

1) A 2) C 3) B 4) B 5) B 6) A

★ **SAQs Answer key:**

1) a-ketoglutarate dehydrogenase complex.

Girls team:

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Nada Babilli
Rania Aqil
Reem alamri
Reema Alomar
Reem Alqahtani
Renad Alhumaidi
Shaden Alobaid
Noura Alsalem
Lama Alahmadi
Sadem Alhazmi
Somow Abdulrahman
Budoor Almubarak
Samar Almohammedi
Nuha Alkudsi
Norah Alsheikh
Muneerah Alssdhan
Mayasem Alhazmi

Boys team:

Mansour albawardi
Hassan alshuraf
Abdulrahman almbki
Mohammed alsayari
Abdullaziz alomar
Abdulaziz alrabiah
Saud alrasheed
Abdullah almazro
Hamad almousa
Ahmad alkhayat

A Bird in the Hand is
Worth Two in the Bush.

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