

الفل يبدأ من دمشق بياضه
ويعطر لها ترتيب الأطياب

“نزار قباني”

nihad.me

Disorders of Carbohydrate metabolism

Diabetes mellitus

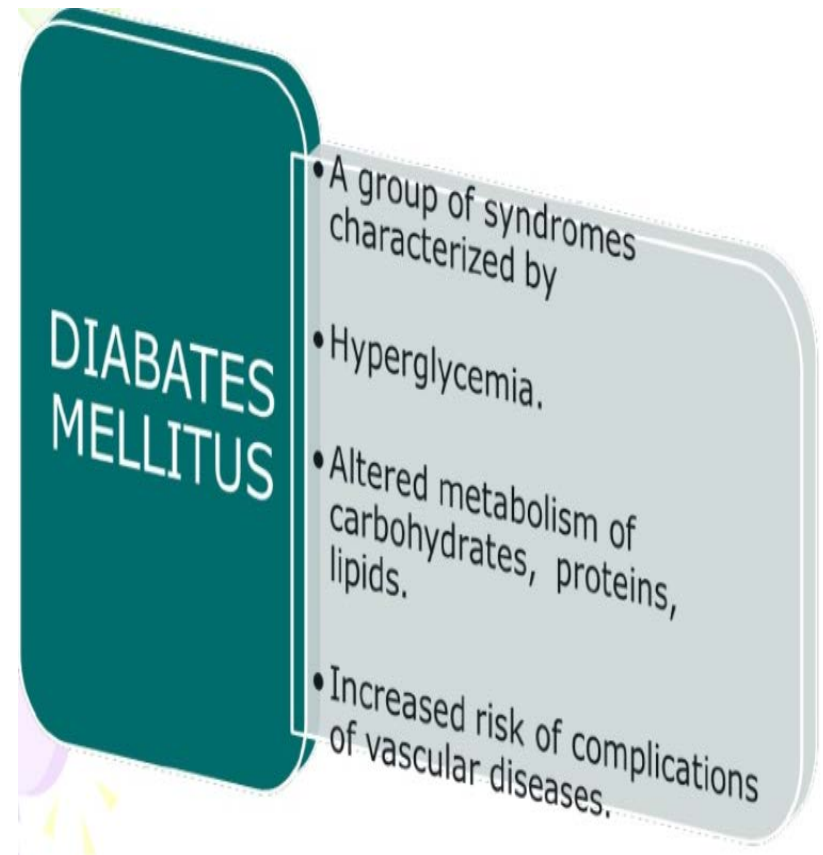
الداء السكري



Diabetes Mellitus (DM)

Diabetes is a group of metabolic disorder sharing the common features of hyperglycemia

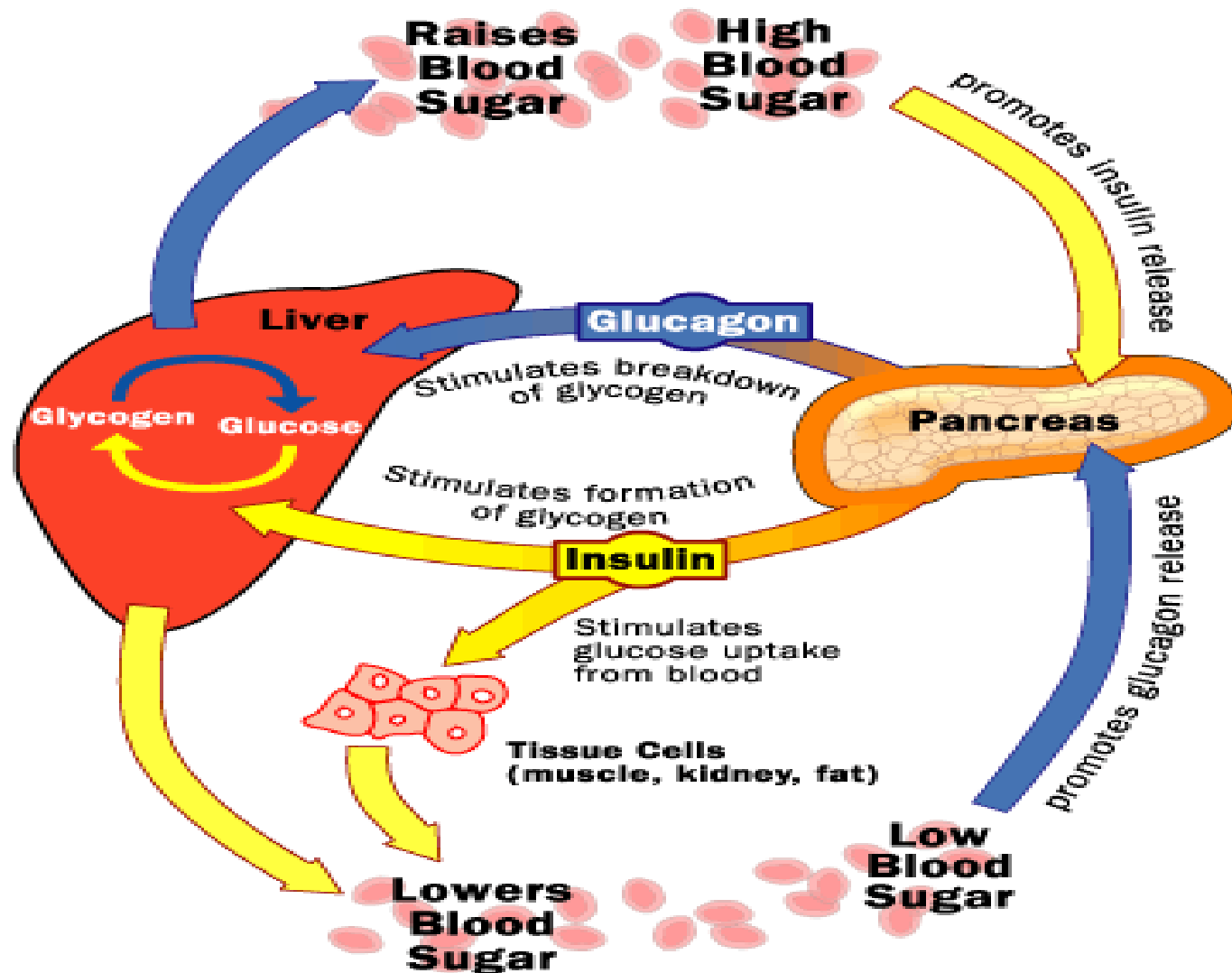
In diabetes there may be a **decrease** in the body's ability to **respond to insulin** and/or a decrease or **absence of pancreatic insulin**.



Symptoms of DM

The most obvious symptom of diabetes is **hyperglycemia**, caused by inadequate uptake of glucose from the blood. Excessive amounts of blood glucose (**>180mg/dl**) results in **glucosuria**. High urinary glucose concentrations produce an osmotic diuresis and therefore **polyuria**. Hyperosmolality due to water loss causes **thirst & polydipsia**. Diabetes is also associated with increased appetite and food consumption (**polyphagia**).

Insulin and Glucagon



Insulin Functions....



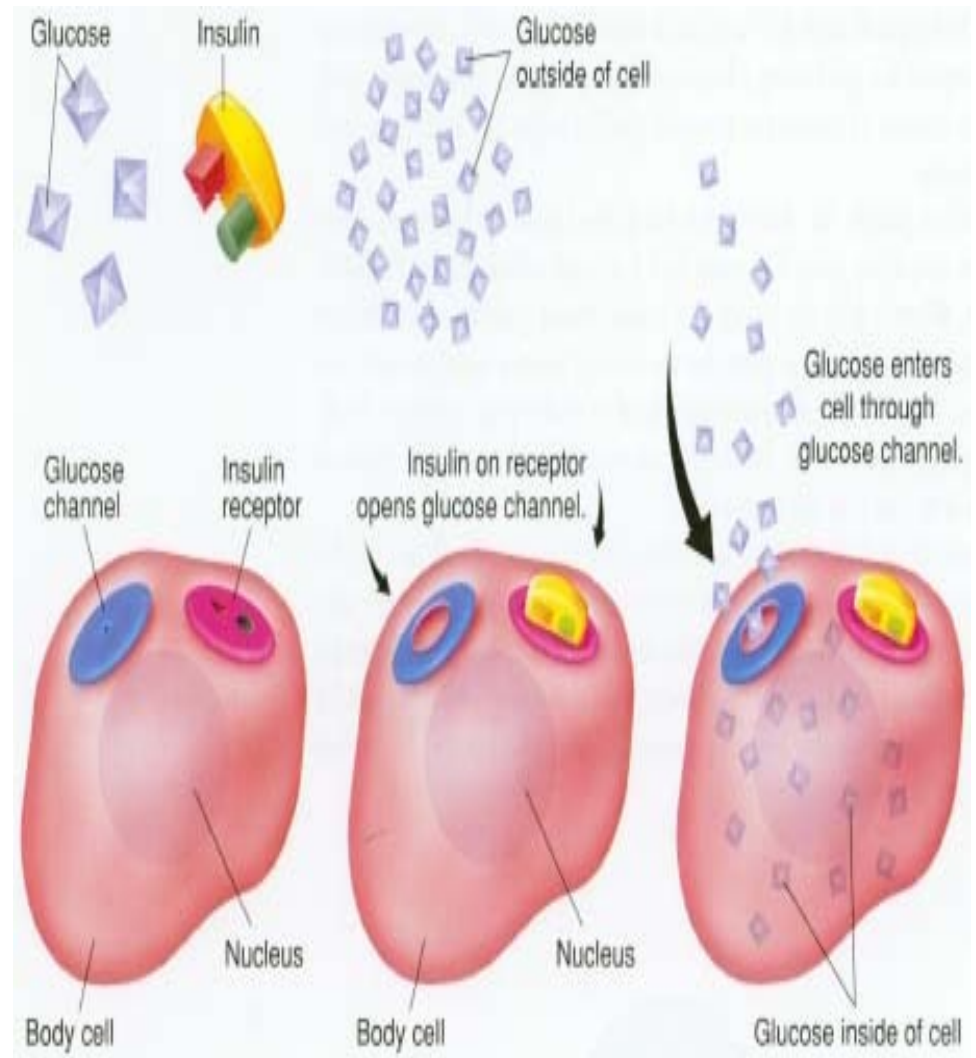
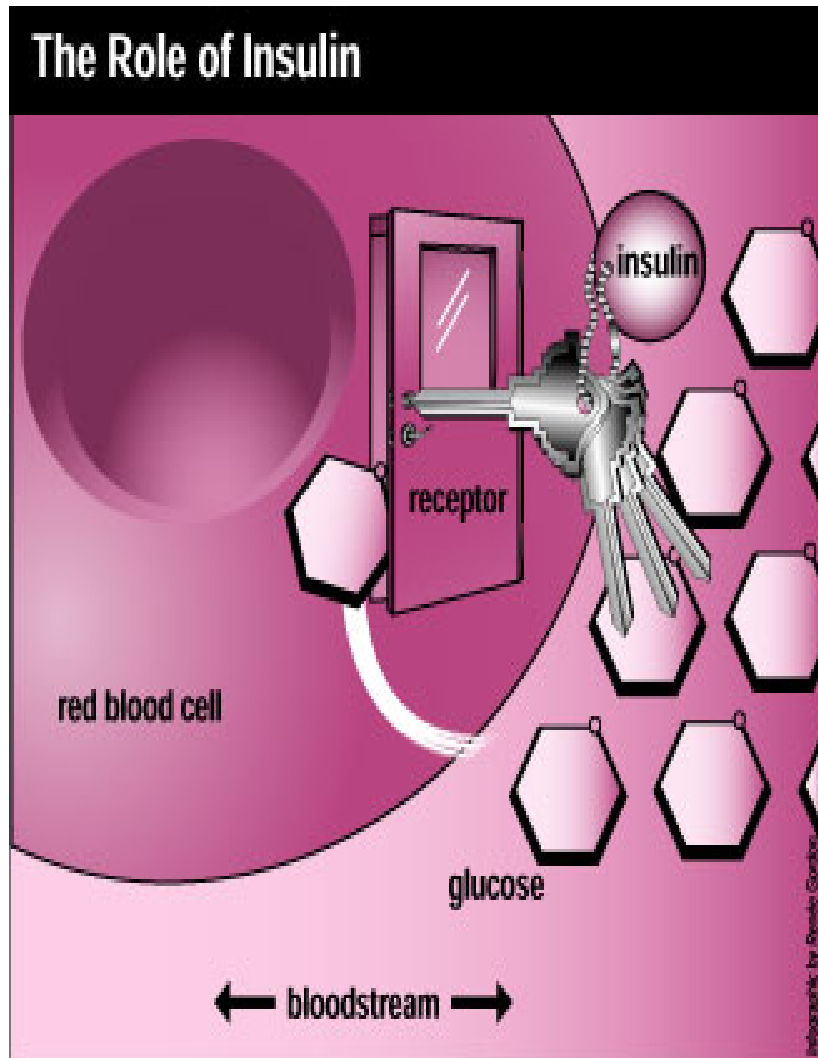
- ❖ Stimulates **storage of glucose** in the liver and muscle (in the form of glycogen).
- ❖ Enhances **storage of dietary fat** in adipose tissue.
- ❖ Accelerates transport of amino acids (derived from dietary protein) into the cells.



Insulin also *inhibits the breakdown* of stored glucose, protein, and fat.



The Role of Insulin

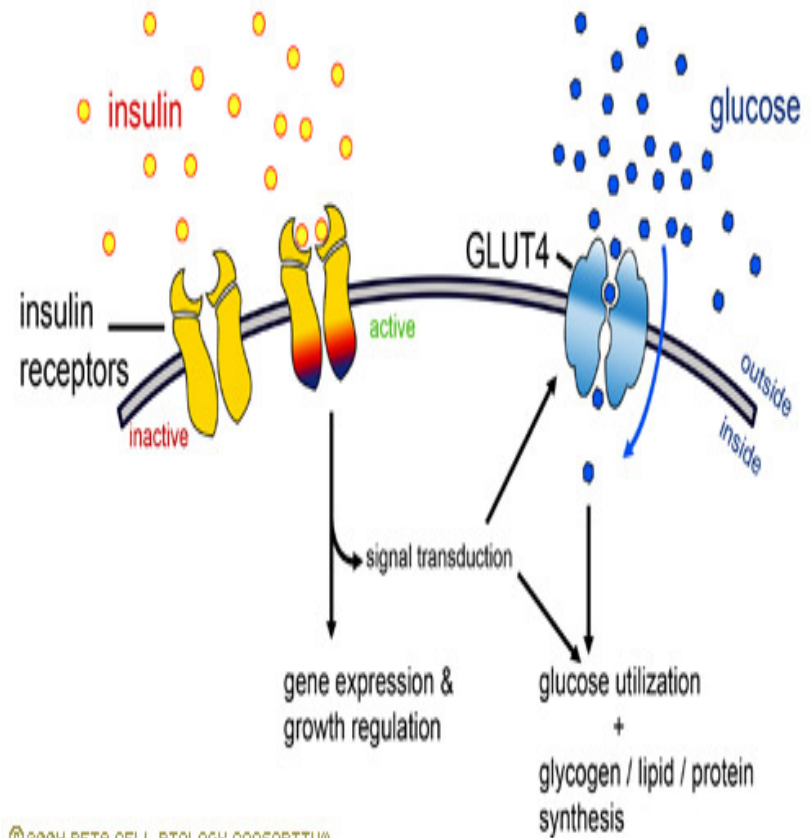


How Insulin Works!!

When Insulin molecules bind to their receptors, the **insulin receptors** promote the uptake of glucose into various tissues that contain type 4 glucose transporters (GLUT4). Such as skeletal muscles (which burn glucose for energy) and fat tissues (which convert glucose to triglycerides for storage).

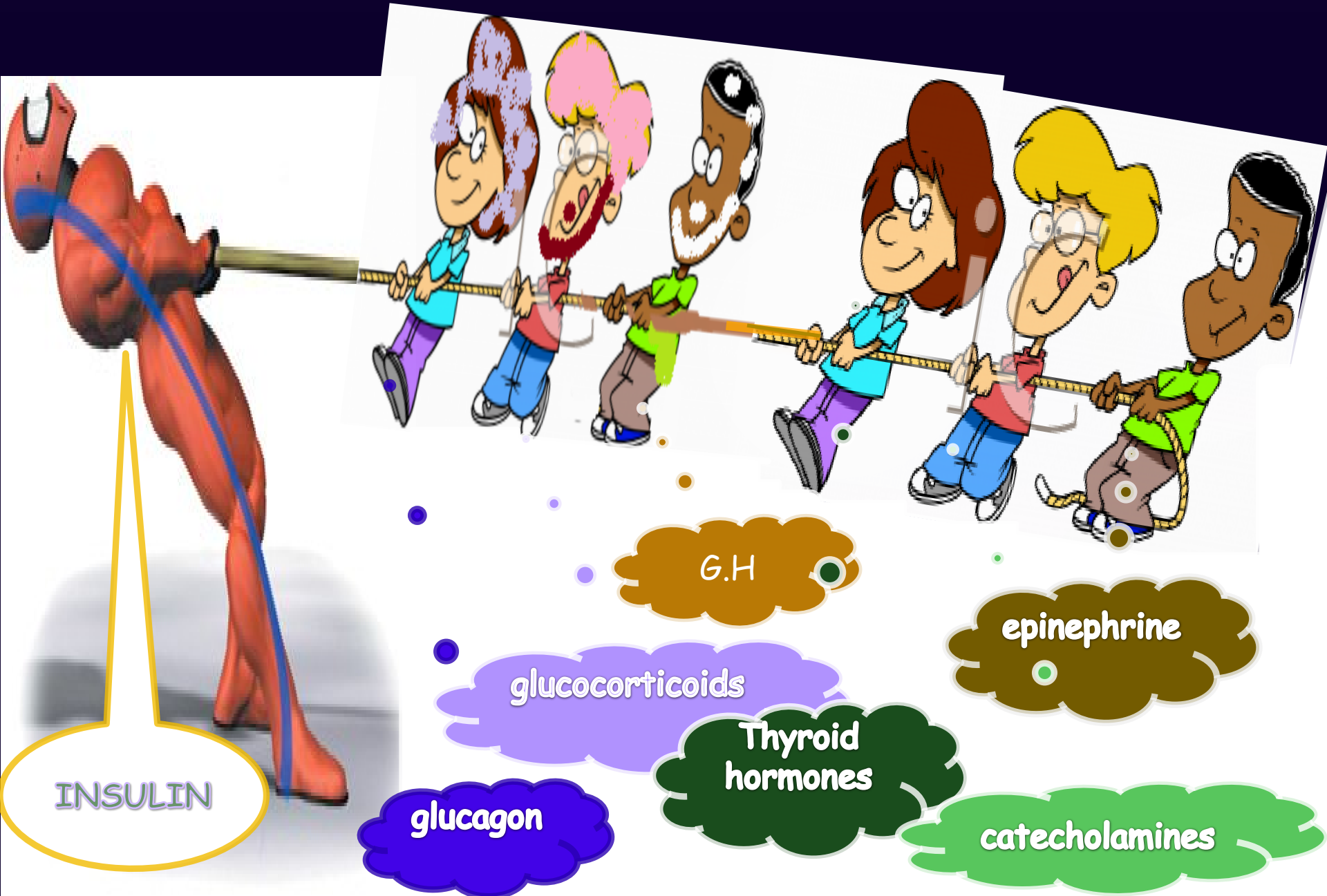
Remove glucose from blood

The “key step” in glucose metabolism is: the ***immediate activation and increased levels of GLUT4 glucose transporters***



©2004 BETA CELL BIOLOGY CONSORTIUM

War between Insulin & other hormones



Hormonal control on Blood Glucose

	Insulin	Glucagon	Catecholamine	Glucocorticoids	Growth hormone	Thyroid hormones
Absorption of glucose	✗	✗	✗	✗	✗	↑
Peripheral uptake	↑	↓	✗	✗	↓	↓
Glycolysis	↑	↓	↓	↓	↓	↓
Gluconeogenesis	↓	↑	↑	↑	↑	↑
glycogenesis	↑	↓	↓	↑	↑	↓
Glucogenolysis	↓	↑	↑	↓	↓	↑
Lipogenesis	↑	↓	↓	↓	↓	↓
Lipolysis	↓	↑	↑	↑	↑	↑
Protein catabolism	↓	↑	✗	↑	↑	↑
Net effect on blood glucose	↓↓	↑↑	↑↑	↑↑	↑↑	↑↑

Hormonal control on Blood Glucose

	Insulin	Glucagon	Catecholamine	Glucocorticoids	Growth hormone	Thyroid hormones
Absorbtion of glucose	✗	✗	✗	✗	✗	↑
Peripheral uptake	↑	↓	✗	✗	↓	↓
Glycolysis	↑	↓	↓	↓	↓	↓
Gluconeogenes is	↓	↑	↑	↑	↑	↑
glycogenesis	↑	↓	↓	↑	↑	↓
Glucogenolysis	↓	↑	↑	↓	↓	↑
Lipogenesis	↑	↓	↓	↓	↓	↓
Lipolysis	↓	↑	↑	↑	↑	↑
Protein catabolism	↓	↑	✗	↑	↑	↑
Net effect on blood glucose	↓↓	↑↑	↑↑	↑↑	↑↑	↑↑

Classification of Diabetes

- Type 1
- Type 2
- Gestational
- Other specific types (genetic)



diabetics
are naturally
sweet

Comparison of Type I and Type II diabetes

IDDM

NIDDM

Feature	Type 1 diabetes	Type 2 diabetes
Onset	Sudden	Gradual
Age at onset	Mostly in children	Mostly in adults
Body habitus	Thin or normal ^[5]	Often <u>obese</u>
<u>Ketoacidosis</u>	Common	Rare
<u>Autoantibodies</u>	Usually present	Absent
Endogenous insulin	Low or absent	Normal, decreased or increased
<u>Concordance</u> in <u>identical twins</u>	50%	90%
Prevalence	~10%	~90%

Classification of DM

Insulin-Dependent Diabetes Mellitus (IDDM)	Non-insulin-Dependent Diabetes Mellitus (NIDDM)
Also called type I diabetes or juvenile onset diabetes (usually occurs before the age of 20).	Also called type II diabetes or maturity-onset diabetes (usually occurs after the age of 40).
It represents 10-20% of diabetic patients.	It represents 80-90% of diabetic patients.
Prone to ketosis	Resistant to ketosis
Endogenous insulin low/absent	Endogenous insulin present but insufficient
Very low serum C-peptide levels <10mg	Normal or increased C-peptide levels
Low/normal weight	Mostly obese
Treatment by exogenous insulin	Diet control and exercise. Oral hypoglycemics are used when necessary.

Gestational diabetes

- ▶ A form of **glucose intolerance** that is diagnosed in some women **during pregnancy**.
- ▶ Gestational diabetes occurs more frequently among African Americans, Latino Americans, and American Indians. It is also more common among obese women and women with a family history of diabetes.
- ▶ During pregnancy, gestational diabetes requires treatment to normalize maternal blood glucose levels to avoid complications in the infant.
- ▶ After pregnancy, 5% to 10% of women with gestational diabetes are found to have **type 2 diabetes**.
- ▶ Women who have had gestational diabetes have a 20% to 50% chance of developing diabetes in the next 5-10 years.

Late Complications of Diabetes Mellitus

- Microangiopathy اعتلال الأوعية الدقيقة
- Retinopathy اعتلال الشبكية
- Nephropathy اعتلال الكلية
- Neuropathy اعتلال الأعصاب
- Macroangiopathy اعتلال الأوعية الكبيرة
- Dyslipidaemia خلل الشحوم

Diabetic Foot Ulcer



Measuring Units: Converting between mmol/l and mg/dl

$\text{mg/dl} \times 0.0555 = \text{mmol/L}$

mg/dL	mmol/L
40	2.2
45	2.5
50	2.8
55	3.1
60	3.3
65	3.6
70	3.9
75	4.2
80	4.3
85	4.7
90	5.0
95	5.3
100	5.6

mg/dL	mmol/L
110	6.2
120	6.7
130	7.2
140	7.8
150	8.3
160	8.9
170	9.4
180	10.0
190	10.6
200	11.1
220	12.2
240	13.3
260	14.4

← Formula for calculation →

- Formula for calculation of mg/dl from mmol/l: **$\text{mg/dl} = 18 \times \text{mmol/l}$**
- Formula for calculation of mmol/l from mg/dl: **$\text{mmol/l} = \text{mg/dl} / 18$**



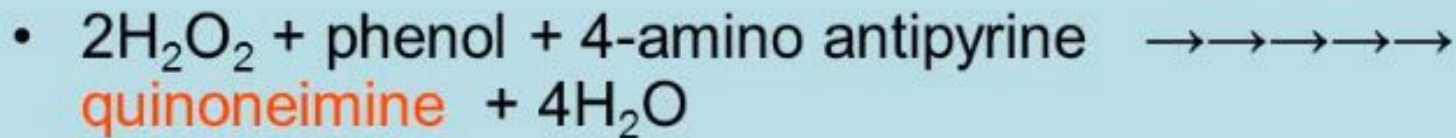
The Common Glucose Measuring Method is:

- **Glucose Oxidase- peroxidase- chromogen sequence (Glucose Oxidase Method)**

Glucose oxidase



peroxidase



- **quinoneimine** measured at 505 nm.



Diabetes Testing

1- The **Fasting plasma Glucose test (FPG)** after at least 8-10 hours of fasting, is the preferred method for diagnosing diabetes, because it is easy, convenient, and less expensive than other tests.

What Do the Results of the Glucose Test Mean?

Normal fasting blood glucose is between **70 and 110mg/dl** for people who do not have diabetes. The standard diagnosis of *diabetes* is made when two separate blood tests show that your fasting blood *glucose level is greater than or equal to 125 mg/dL*.

2- Random blood glucose (or 2 hours after meals) measurement, is a blood sugar test taken from a non-fasting subject. It is often performed if a patient with hyperglycaemic symptoms like thirst, and polyuria



FASTING

Normal for person without diabetes

70–99 mg/dl (3.9–5.5 mmol/L)

Official ADA recommendation for someone with diabetes

80–130 mg/dl (4.4–7.2 mmol/L)

2 HOURS AFTER MEALS

Normal for person without diabetes

Less than 140 mg/dl (7.8 mmol/L)

Official ADA recommendation for someone with diabetes

Less than 180 mg/dl (10.0 mmol/L)

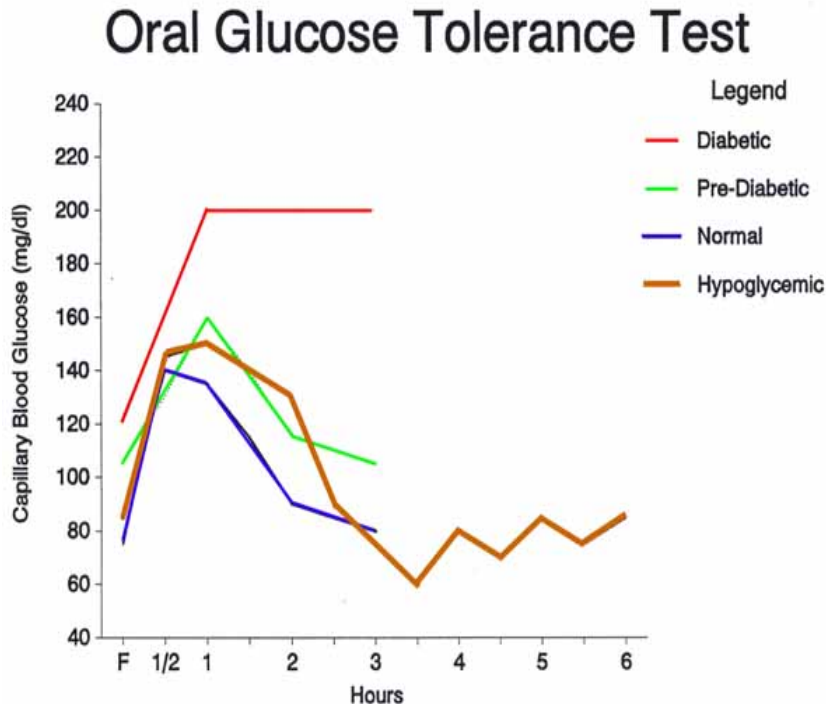
3- Oral Glucose Tolerance Test (OGTT)

Oral glucose tolerance test (OGTT) is a medical test in which a standard dose of glucose is administered orally & then blood sample is taken at set times to see **how quickly the glucose is utilized by the body & cleared off** from blood. **OGTT is used as a confirmatory test to diagnose diabetes & can indicate presence of pre-diabetes (insulin resistance).**

OGTT is advised to individuals at high risk of developing diabetes or those with impaired sugar levels

OGTT is the most sensitive test for detecting **borderline diabetes mellitus**. Glucose tolerance means **ability** of the body to utilize glucose in the circulation.

Interpretation of the Test



A Typical normal curve shows fasting glucose of **around 75** mg/dl. Maximum concentration is reached within 60 min after taking the glucose. Blood level then return to the normal fasting level **in 90-120** min (75-110 mg/dl)

Diabetes is indicated by either of the following:

1- *fasting plasma glucose* above 126 mg/dL

2- *2-hour* reading greater than 200 mg/dL

Criteria for The Diagnosis of DM

Normal		Pre-Diabetes		Diabetes	
Fasting Blood Sugar	2 hrs after glucose load	Fasting Blood Sugar	2 hrs after glucose load	Fasting Blood Sugar	2 hrs after glucose load
< 110	< 140	110 - 125	140 - 199	≥ 126	≥ 200

Why Get Tested for OGTT??

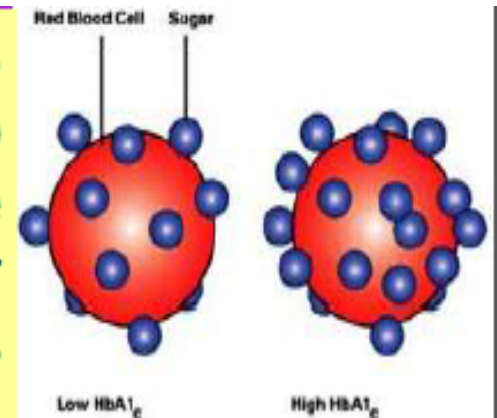
- In asymptomatic persons with **glycosuria**.
- In persons with **symptoms of diabetes** but no glycosuria or hyperglycemia.
- Persons with **family history** but with no symptoms or positive blood findings.
- In persons with or without symptoms of diabetes mellitus showing one **abnormal blood findings**.
- In patients with **neuropathies or retinopathies** of unknown origin.

4- Glycohemoglobin

(Glycated Hemoglobin HbA1c)

Glycated hemoglobin is a form of hemoglobin that is measured primarily to identify the average plasma glucose concentration over prolonged periods of time. It is formed in a non-enzymatic glycation pathway.

In adults, circulating hemoglobin (Hb) consists of 97% Hb A, 2.5% Hb A₂ and 0.5% Hb F. Glycated Hb (Hb A_{1c}) is formed by non-enzymatic condensation of glucose and N-terminal valine of β -chains of Hb & occurs over the life span of the RBC (~120 days). It is expressed as percentage of the total Hb concentration.

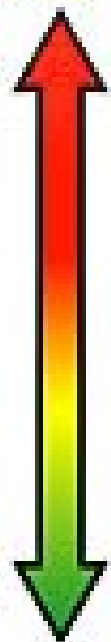


When to Use of Hb A1c Test

- In new patients
- To monitor patient compliance.
- To predict development & progression of microvascular complication.
- For determining the therapeutic options whether to use oral agents or Insulin

In Known diabetics: **Less than 6** indicates good diabetic control
Between 7- 8 indicates fair diabetic control
More than 8: indicates poor diabetic control

Diabetes Control Card



action suggested

good

excellent

HbA_{1c}
test score

MEAN BLOOD GLUCOSE
mg/dL mmol/L

14.0	380	21.1
13.0	350	19.3
12.0	315	17.4
11.0	280	15.6
10.0	250	13.7
9.0	215	11.9
8.0	180	10.0
7.0	150	8.2
6.0	115	6.3
5.0	80	4.7
4.0	50	2.6

Source: ADA 2010 Standards of Care

Glycated Hemoglobin

Falsely high values	Falsely low values
Iron deficiency anemia	Hemolytic anemia
Post splenectomy	Chronic blood loss
Alcohol poisoning	Chronic Renal Failure
Lead toxicity	Pregnancy

5- Serum Fructosamine Estimation

The **fructosamine test** measures **glycated proteins** (predominantly albumin) in the blood instead of glycated hemoglobin.. These proteins circulate in bloodstream for **14 to 21** days, so measuring them gives a picture of the amount of sugar in your blood for that time period.

When is the fructosamine test used?

- 1- After recent *change in medications or insulin*, to monitor *the effectiveness of the new treatments*.
- 2-The test is also used in *gestational diabetes* because changes can happen very quickly during pregnancy. The shorter time span of the test allows the doctor to track blood glucose levels more closely.

6- C - Peptide



Insulin Luminescence assay kit



C-Peptide Luminescence assay kit

1- C-peptide:

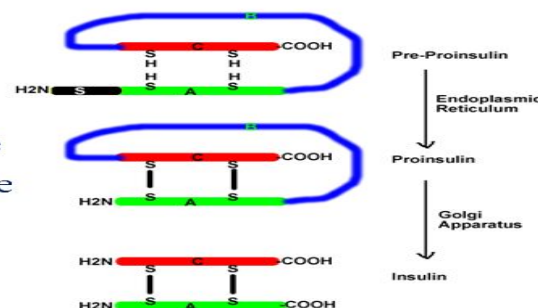
- This test is used to differentiate between type I and II diabetes
type I DM: low level of insulin and C-peptide
type II DM: normal or high level of C-peptide

Advantages of measuring C-peptide than insulin:

- It is better indicator of B-cell function than peripheral insulin.

Normal value:

Fasting 0.51-2.72 ng/ml



C- peptide can assess a person's own insulin secretion even if they receive insulin injections

7- IMMUNOLOGICAL ASSAYS

- Antibodies to insulin, islet cells, or Glutamic acid decarboxylase (GAD) can be estimated to **differentiate between the types** of diabetes mellitus

- They are *absent in type 2* diabetes mellitus.

- **Latent autoimmune diabetes of adults, or LADA**, is a form of slow-onset type 1 diabetes that occurs in middle-aged (usually white) adults. **Thus, It is an autoimmune (type 1 diabetes)**

It can be differentiated from type 2 diabetes by measuring **anti-GAD65** antibodies.

8- URINE ANALYSIS

a) Detection of urinary glucose (Glucosuria)

- First-line **screening** test for diabetes mellitus
- Normally glucose does not appear in urine until the plasma glucose rises above **160-180 mg/dl**.
- In certain individuals due to low renal threshold glucose may be present despite normal blood glucose levels.
- Conversely renal threshold increases with age so many diabetics may not have Glycosuria despite high blood sugar levels.



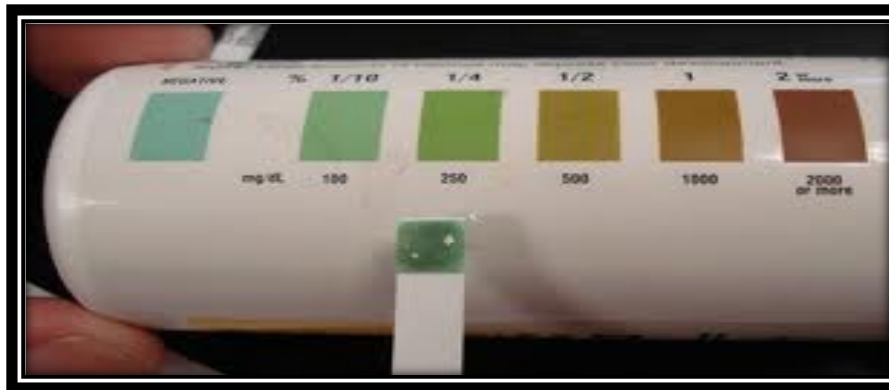
*Positive
Benedict's test*

URINE ANALYSIS

b) Detection of Glucosuria- A specific and convenient method to detect glucosuria is the paper strip impregnated with **glucose oxidase and a chromogen** system (Diastix), which is sensitive to as little as 0.1% glucose in urine.

- **Diastix** can be directly applied to the urinary stream, and differing color responses of the indicator strip reflect glucose concentration.

- **Benedict's** and **Fehling's test** can also detect glucosuria.



*Diastix-
Reagent strips*

URINE ANALYSIS (Contd.)

c) Microalbuminuria

○ May be defined as an albumin excretion rate intermediate between normality (2.5-25 mg/day) and macroalbuminuria (>250mg/day).

○ The small increase in urinary albumin excretion is not detected by simple albumin stick tests and requires confirmation by **quantization in a 24-hour urine specimen.**

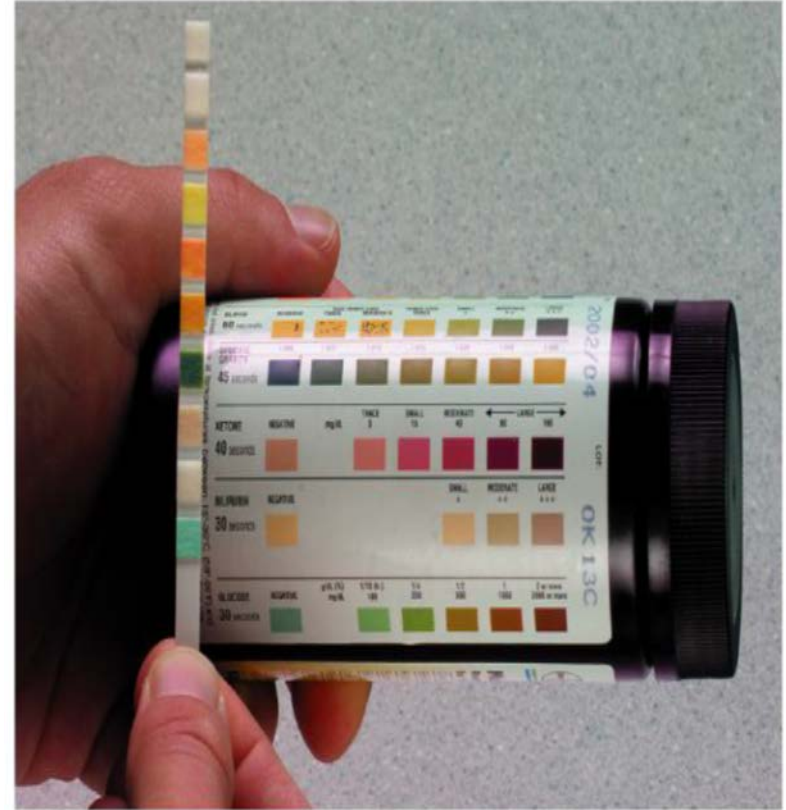


الحماض (الخلال)

يظهر الحماض في حالات
الداء السكري (خصوصا من
النمط الأول)، تناول قوت غني
جدا بالدهن أو فقير بالسكريات،
وكذلك في حالات الجوع الشديد

يتظاهر الحماض بتراكم
الأجسام الكيتونية. تراكم هذه
الأجسام الكيتونية الحمضية
يخفض pH الدم لما دون 7.4

فما هو الحماض وماهي
الأجسام الكيتونية؟



Timberlake, General, Organic, and Biological Chemistry. Copyright © Pearson Education Inc., publishing as Benjamin Cummings

الأجسام الكيتونية Ketone Bodies

تملك متقدرات الكبد القدرة على تحويل acetyl CoA الناتج عن أكسدة الحمض الدسم لأجسام كيتونية
تضم الأجسام الكيتونية المركبات التالية:

Acetoacetate ➤

3-hydroxybutyrate (also called β -hydroxybutyrate) ➤

Acetone ➤

ال ketoacidosis يظهر عندما يكون معدل اصطناع الأجسام الكيتونية أعلى من معدل استخدامها، كما هو عليه الحال في النمط الأول من الداء السكري اللامضبوط

الحماض في الداء السكري:

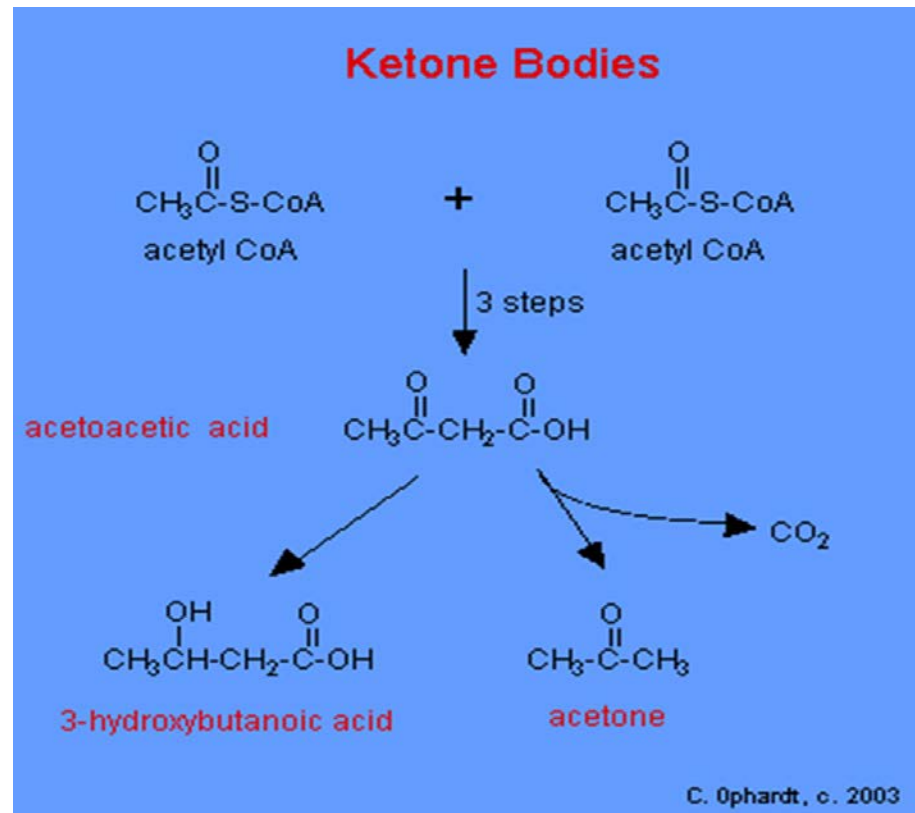
- هناك خلل في أداء ودور الأنسولين
- مستويات الغلوكوز في العضلات، الكبد، والأنسجة الشحمية غير كافية لتوفير الطاقة اللازمة
- بناء عليه: **تقوم خلايا الكبد باصطناع السكر من مصادر لاسكرية**، وبالتالي يتم اللجوء لتحطيم المواد الدسمة إلى acetyl CoA
- ترتفع مستويات ال acetyl CoA
- وبالتالي فإن هذه الزيادة تسبب اصطناع الأجسام الكيتونية التي تتراكم بالدم

Body burns fat for energy instead of carbohydrates = Ketosis

الحماض:

هو الحالة التي ترتفع فيها مستويات **الأجسام الكيتونية** في الدم.

تتشكل الأجسام الكيتونية عند استنفاد مخدرات الغليكوجين في الكبد



تصريف الأجسام الكيتونية وأعراض الحماض

يتعامل الجسم مع زيادة الأجسام الكيتونية بوحدة من ثلاث طرق:

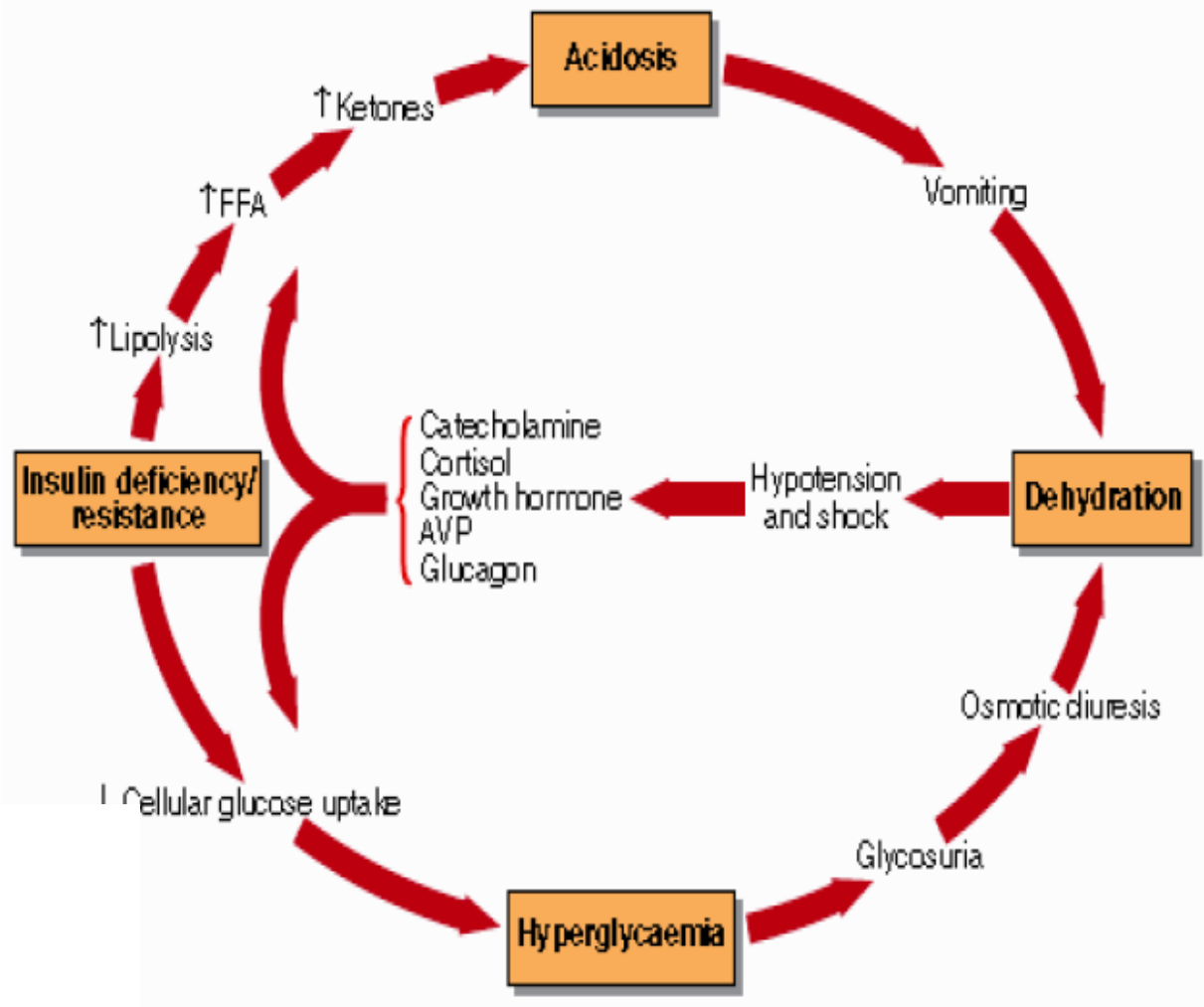
1. تقوم العضلات، الكبد، والدماغ بحرقها من أجل تزويد الخلايا بالطاقة

2. يتم طرحها خارجا عن طريق التنفس الرئوي

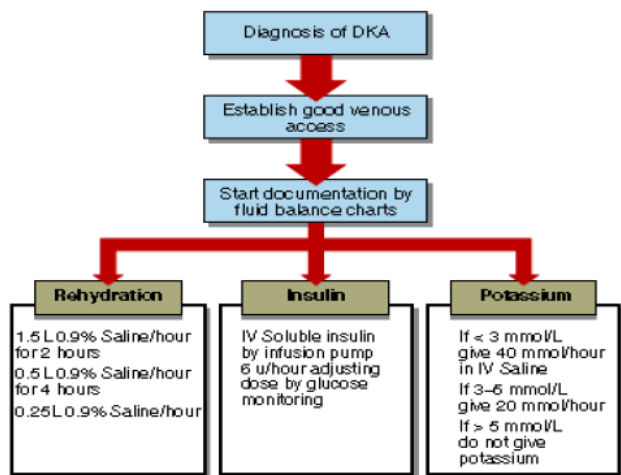
3. تطرح الكيتونات عن طريق الكليتين بالبول

زيادة الأجسام الكيتونية تترافق مع بعض الأعراض: **نفس ذو رائحة كيتونية**، شعور بالعطش مع جفاف بالفم، صداع خفيف، تكرار عدد مرات التبول مع انطراح هذه الأجسام بالبول، أحيانا شعور بالنشوة بحال استمرار الحماض لفترة طويلة

Severe hyperglycemia,
Increased blood and urine
ketones (Acetone, Acetoacetic
acid, 3-hydroxybutyrate).
Low bicarbonate
Low arterial pH
Low PCO₂ (respiratory
compensation)



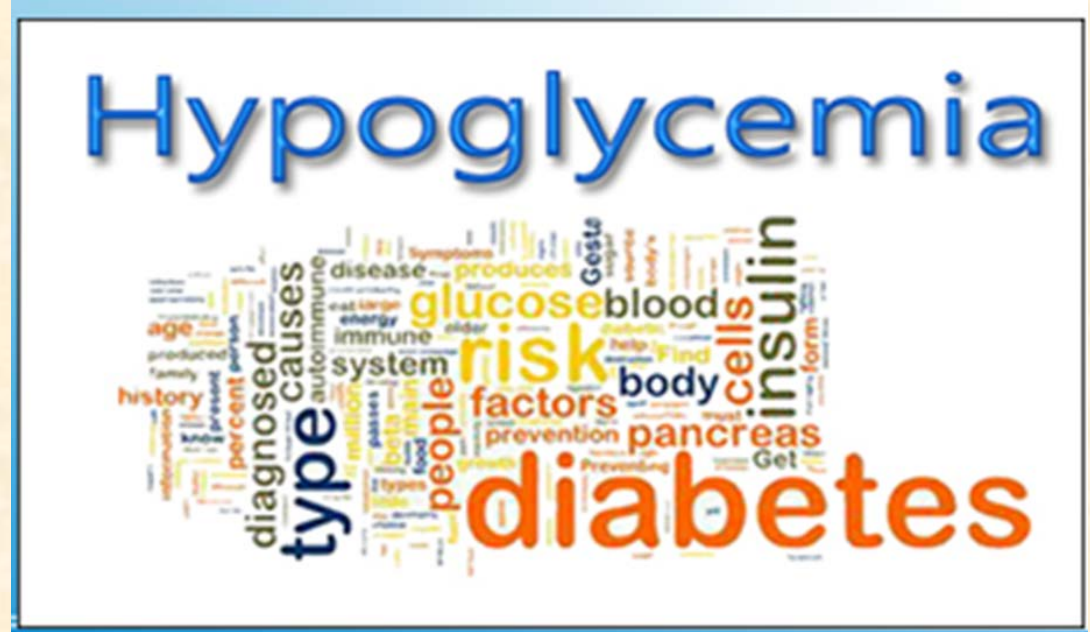
The development of diabetic ketoacidosis.



Hypoglycemia, What is it?

- A person with systematically low levels of blood glucose (sugar) has **hypoglycemia**.

Hypoglycemia is not a disease in itself- it is the result of an underlying issue .



Causes of Hypoglycemia

- It most commonly happens when a person with diabetes has taken too much insulin
- Lack of glucagon (hormone that is secreted from the pancreas that raises blood glucose levels)
- Excessive alcohol consumption: drinking heavily can block liver from releasing stored glucose
- Tumor of pancreas known as an **Insulinoma**

Insulinoma

An **insulinoma** is a rare type of *small pancreatic tumor*. It produces an excess of the hormone insulin. About 90 percent of the time, the tumor is benign.

Because the tumor produces excess insulin, it can lead to **hypoglycemia**. It can cause serious symptoms, such as:

- confusion or forgetfulness
- blurred vision
- Unconsciousness

Most of the time, this tumor needs to be surgically removed.

Mild Symptoms

The typical signs of low sugar levels:

- Trembling/shakiness
- Sweating
- Anxiety
- Irritability
- Pallor (face goes pale)
- Heart palpitations (unregulated pattern)
- Tingling lips

