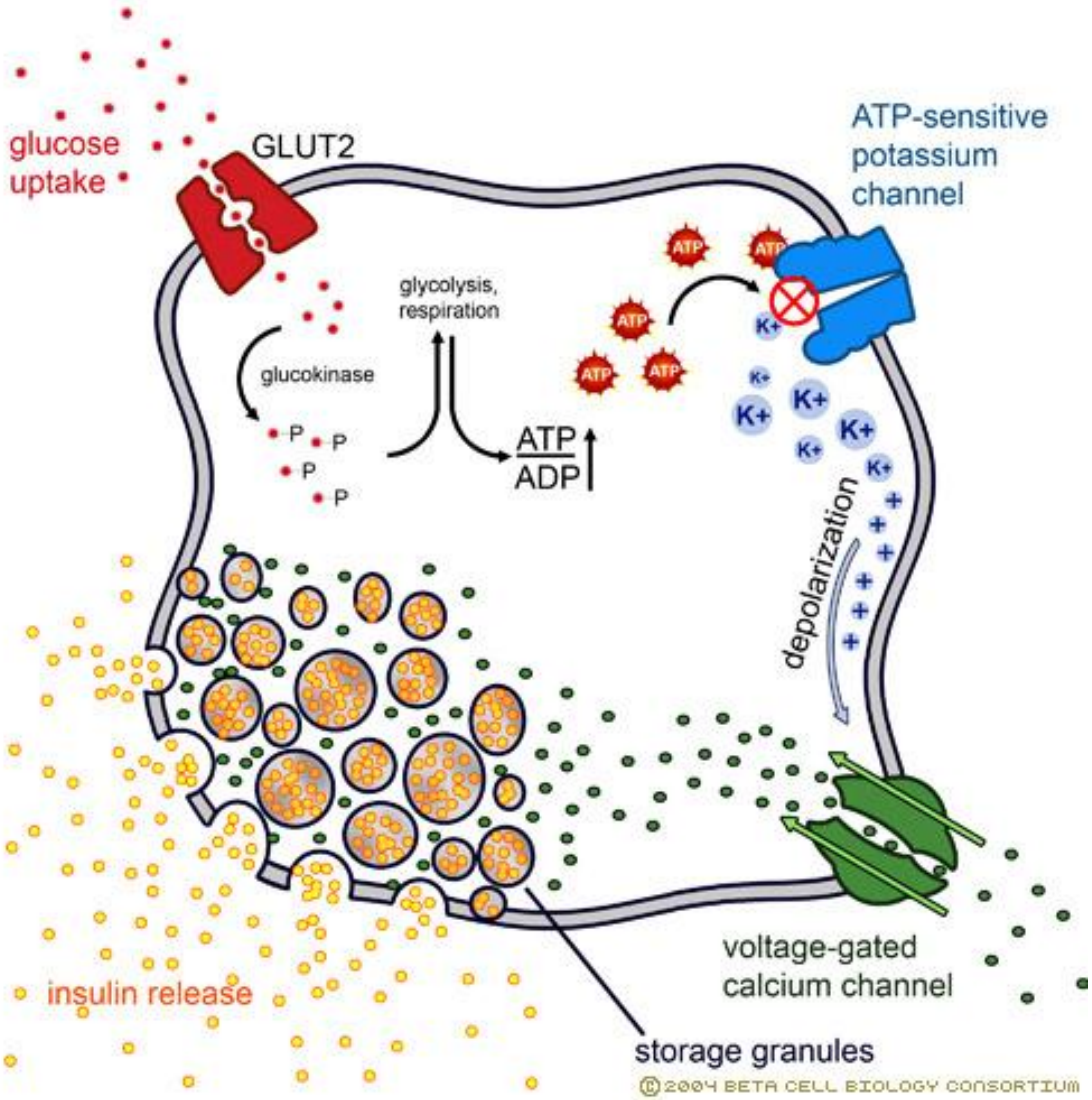
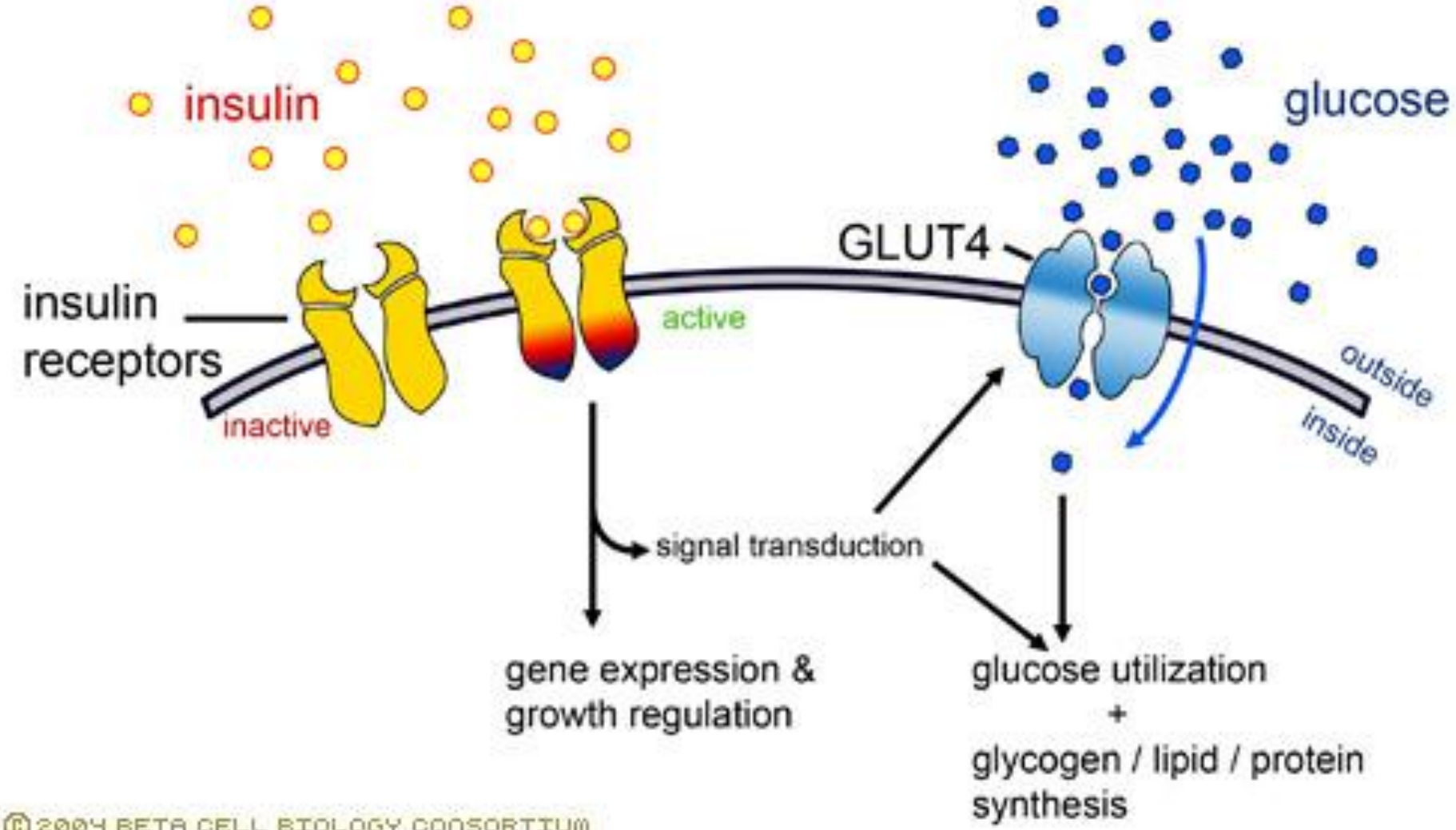
Glucose Metabolism and diabetes Mellitus

Effect of Insulin



Effect of Insulin



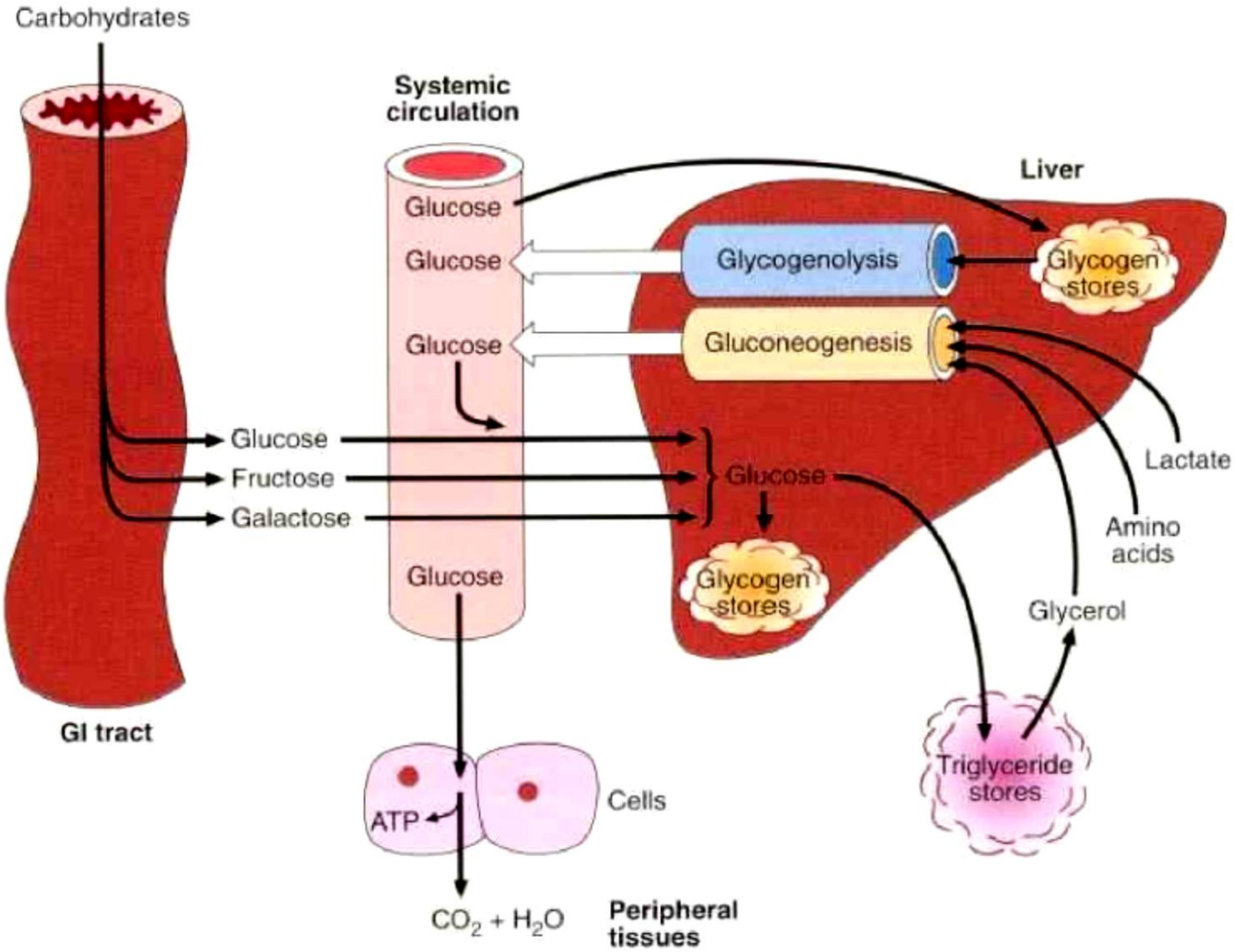
Effect of Insulin

- Carbohydrate
- Facilitates the transport of glucose into muscle and adipose cells
- Facilitates the conversion of glucose to glycogen for storage in the liver and muscle.
- Decreases the breakdown and release of glucose from glycogen by the liver

- Protein
- Stimulates protein synthesis
- Inhibits protein breakdown; diminishes gluconeogenesis

- Fat
- Stimulates lipogenesis- the transport of triglycerides to adipose tissue
- Inhibits lipolysis – prevents excessive production of ketones or ketoacidosis

Effect of Insulin



Introduction

Type 1 diabetes

- Most frequently affects children and adolescents.
- Symptoms include excessive thirst, excessive urination, weight loss and lack of energy.
- Daily insulin injections required for survival.

Type 2 diabetes

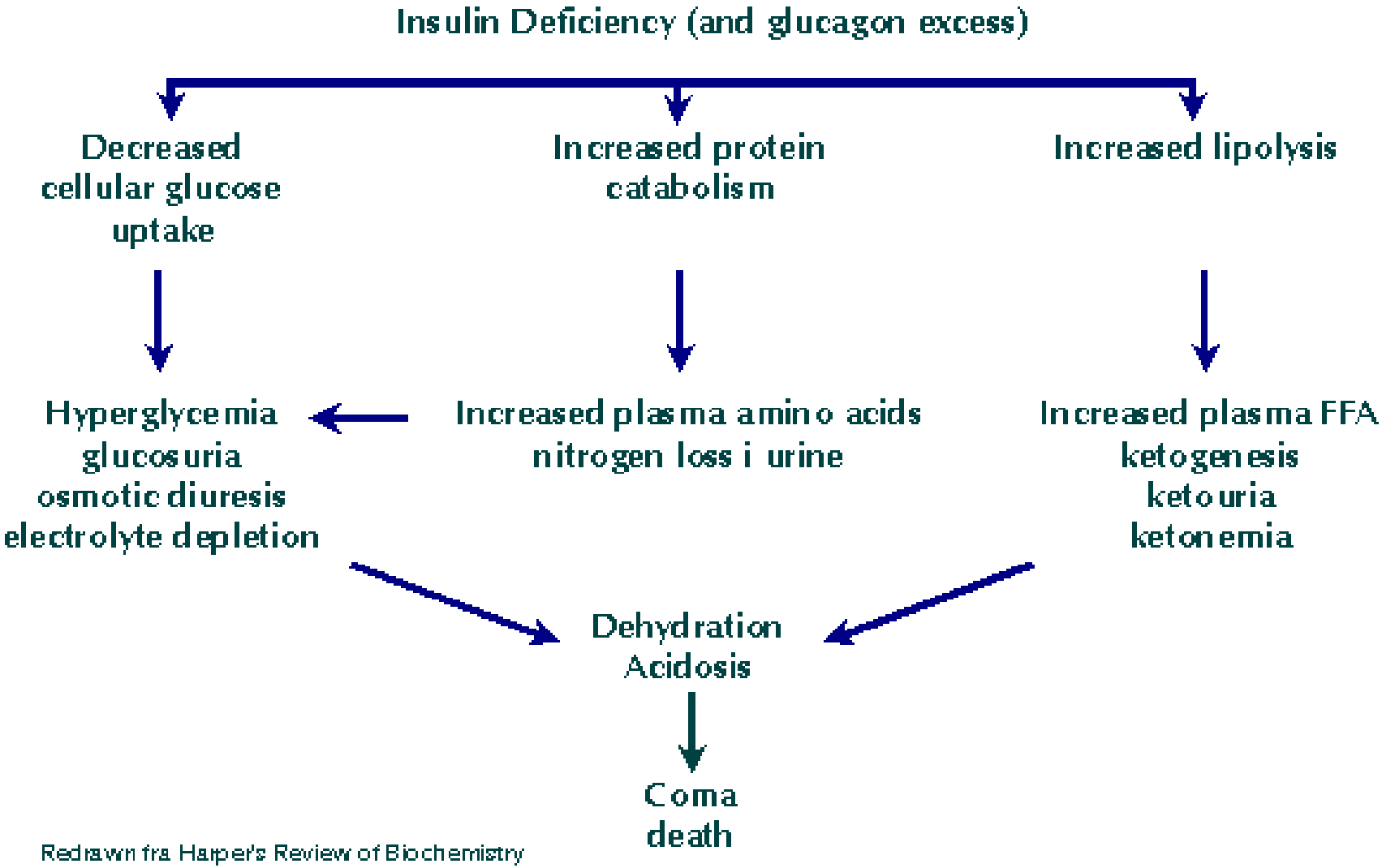
- Occurs mainly in adults.
- Usually people have no early symptoms.
- People may require oral hypoglycaemic drugs and may also need insulin injections.

Diabetes mellitus

- Disease in which the body doesn't produce or properly use insulin, leading to hyperglycemia

Main Features	IDDM	NIDDM
Epidemiology		
Frequency in Northern Europe	0.02–0.4%	1–3%
Predominance	N. European Caucasians	Worldwide Lowest in rural areas of developing countries
Clinical Characteristics		
Age	<30yrs	>40yrs
Weight	Low	Normal or increased
Onset	Rapid	Slow
Ketosis	Common	Under stress
Endogenous insulin	Low/absent	Present
HLA associations	Yes	No
Islet cell antibodies	Yes	No
Pathophysiology		
Aetiology	Autoimmune destruction of pancreatic islet cells	Unclear. Impaired insulin secretion and insulin resistance
Genetic associations	Polygenic	Strong
Environmental factors	Viruses and toxins implicated	Obesity, physical inactivity

Diabetic Metabolism



Redrawn fra Harper's Review of Biochemistry

Hypoglycemia

- Hypoglycemia involves decreased plasma glucose levels
- The plasma glucose concentration at which glucagon and other glycemic factors are released is between 65 and 70 mg/dL; at about 50 to 55 mg/dL, observable symptoms of hypoglycemia appear all related to the central nervous system.
- The release of epinephrine into the systemic circulation and of norepinephrine at nerve endings of specific neurons act in unison with glucagon to increase plasma glucose.
- Glucagon is released and inhibits insulin.
- Epinephrine is released, increases glucose metabolism and inhibits insulin.
- In addition, cortisol and growth hormone are released and increase glucose metabolism

TABLE 13-8 CAUSES OF HYPOGLYCEMIA

PATIENT APPEARS HEALTHY	
No coexisting disease	Drugs Insulinoma Islet hyperplasia/ nesidioblastosis Factitial hypoglycemia from insulin or sulfonylurea Severe exercise Ketotic hypoglycemia
Compensated coexistent	Drugs/disease
PATIENT APPEARS ILL	
Drugs	
Predisposing illness	
Hospitalized patient	

Laboratory Testing in Diabetes

- Fasting morning venous glucose is the best initial test for diagnosing diabetes.
- An oral glucose tolerance test is reserved for people with equivocal fasting glucose results.
- Patients with impaired glucose tolerance or impaired fasting glucose benefit from lifestyle intervention and annual review.
- HbA_{1C} is the best test of glycaemic control in diabetes.
- Patients with diabetes benefit from aggressive monitoring and management of all cardiovascular risk factors.

People at high risk of diabetes

Unfortunately the risk factors for diabetes, unlike those for cardiovascular disease, have not been quantified.

Factors associated with increased risk for diabetes include:

- Pacific or Indian ethnicity
- Increasing age
- **Metabolic syndrome**
- Impaired glucose tolerance
- Polycystic ovary syndrome
- History of gestational diabetes or having a baby over 4 kg
- Family history of diabetes
- Physical inactivity
- Increased BMI
- Central obesity
- Hypertension
- Adverse lipid profile
- Elevated LFTs
- Patients taking some drugs e.g. prednisone or anti-psychotic drugs (haloperidol, chlorpromazine, and newer atypical anti-psychotics).

People at high risk of diabetes

Three or more of the following risk factors listed below are required for a **diagnosis of metabolic syndrome**.

Risk Factor	Defining Level
Waist circumference*	Men ≥ 100 cm Women ≥ 90 cm
Triglycerides	≥ 150 mg/dL
HDL cholesterol	Men < 40 mg/dL Women < 50 mg/dL
Blood pressure	SBP ≥ 130 or DBP ≥ 85
Fasting glucose	≥ 100 mg/dL

People with the metabolic syndrome are at increased risk of diabetes, cardiovascular disease, sub-fertility and gout despite only moderate elevation in individual risk factors.

*It is likely that people of Indian ethnicity will have features of the metabolic syndrome at lesser waist circumferences than people of European or Pacific ethnicity.

Prevention and identification

Opportunities for prevention

Both impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) refer to metabolic stages intermediate between normal glucose homeostasis and diabetes, in which there is an increased risk of progressing to diabetes.

Who to test

Asymptomatic people without other known risk factors, Men (45 years) and women (55 years)
People with one or more risk factors, Men (35 years) and women (45 years)

Testing for diabetes

- Fasting morning blood glucose is the best initial test.
- Urine glucose should not be used for diagnosis while HbA_{1C} can be used according to the new protocols

People with symptomatic hyperglycaemia

Symptomatic hyperglycaemia may have an acute onset, usually in younger people with type 1 diabetes, or a more insidious onset, usually in older people with type 2 diabetes. The usual symptoms of hyperglycaemia are thirst, polyuria and weight loss but hyperglycaemia can also cause fatigue, lack of energy, blurring of vision or recurrent infections, such as candida.

For people with symptomatic hyperglycaemia,

a single fasting glucose of ***≥ 126 mg/dl***

OR

a random glucose of ***≥ 200 mg/dl***
is diagnostic of diabetes.

Action following fasting venous plasma glucose

Criteria have been recommended by ADA for the diagnosis of diabetes, IGT and IFG.

	Normal		Diabetes
Fasting glucose result	< 110	110-125	≥ 126 mg/dl
Interpretation	Normal result	IFG	Diabetic
Action	Retest in five years or three years for those at risk.	Assess with OGTT. Re-test annually those with IFG or IGT	Two results > 126 on two different days are diagnostic of diabetes. OGTT is not required.

Gestational diabetes mellitus

Gestational diabetes mellitus (GDM) increases the risk of many fetal and maternal complications in pregnancy and the development of type 2 diabetes later in life. Screening is currently recommended for all women between 24 - 28 weeks gestation.

Screening for GDM using 50 gram load

If the one hour blood glucose is ≥ 190 mg/dL, a two hour OGTT is performed.

OGTT for diagnosis of GDM

A fasting glucose ≥ 105 and/or a 2 hour value ≥ 165 mg/dL is diagnostic of GDM.

Interpretation of the glucose tolerance test

A 75 gram oral glucose tolerance test (OGTT) is used to follow up people with equivocal results who may have diabetes, IFG or IGT.

	Fasting mg/dL		2 hours post load mg/dL
Normal	< 110	and	< 140
IFG	110-125	and	< 140
IGT	< 126	and	140-200
Diabetes mellitus	≥ 126	and/or	≥ 200
GDM	≥ 105	and	≥ 165

Target level for HbA_{1C}

- Any sustained reduction of HbA_{1C} is worthwhile because there appears to be a direct relationship between cardiovascular risk and HbA_{1C}.
- The goal is to achieve an HbA_{1C} as low as possible, preferably less than 7.0%, without causing unacceptable hypoglycaemia.
- HbA_{1C} > 7% is a sign of inadequate control for most people.
- HbA_{1C} targets need to be individualised, taking into consideration the patient's age and co-morbidities.

Stable diabetes	Test six monthly
Changes in treatment	Test no more than three monthly

Self monitoring blood glucose (SMBG)

- People who take insulin should regularly self monitor blood glucose (3-4 times daily according to ADA).

- For people with non-insulin treated type 2 diabetes testing is most useful if patients use the results to learn and alter behaviour, or medication.

Methods of glucose measurement

- Glucose oxidase method:
  - β-D-Glucose + H_2O + O_2 $\xrightarrow{GOD}$ D-Gluconate + H_2O_2

    4-AA + Phenol $\xrightarrow[POD]{H_2O_2}$ Quinoneimine + H_2O
- Hexokinase method (more accurate than GO):
  - Glucose + ATP $\xrightarrow{Hexokinase}$ Glucose-6-P +ADP
  - Glucose-6-P +NADP $\xrightarrow{G\text{-}6\text{-}PD}$ NADPH + Phosphogluconate
- Clinitest
  - Reducing substance + Cu^{+2} $\longrightarrow$ CuO

Methods of glucose measurement

- The patient should be on a normal-to high carbohydrate diet and fasting for at least 10 hrs and not more than 16 hrs
- The test should be performed in the morning because of the hormonal diurnal effect on glucose
- The preferred specimen for glucose analysis is fluoride oxalate plasma
- Before and during performance of OGTT, the patient should not exercise, eat, drink (only water), or smoke
- In OGTT, the adult dose of glucose solution is 75 g and children receives 1.75 g/kg of glucose to a maximum dose of 75 g

Measurement of glucosylated hemoglobin

- The specimen required is EDTA whole blood sample
- Method based on structural differences
  - Immunoassay (antibodies against the glycated N-terminal of Hb)
  - Affinity chromatography (separated based on chemical structure using borate to bind glycosylated proeins.
- Methods based on charge differences:
  - Ion exchange Chromatography (positive charge resin bed)
  - Electrophoresis (difference in charge)
  - Isoelectric focusing (method uses isoelectric point for separation)
  - HPLC (ion exchange column)

Ketones

- They increase in case of DM, starvation/fasting, high-fat diet, prolonged vomiting and glycogen storage disease

- Measurement of ketones:
  - Nitroprusside: with acetoacetic acid and alkaline pH gives purple colour
  - Enzymatic: NADH + acetoacetic acid $\xrightarrow{\text{B-HBD}}$ NAD^+ + B-hydroxybutarate

Laboratory tests to prevent and delay complications of diabetes

People with diabetes usually die from macrovascular complications of their diabetes; namely cardiovascular disease. This is influenced by all of the commonly recognised risk factors for cardiovascular disease as well as glycaemic control. Fasting lipid levels are measured three monthly unt stable and then 6 - 12 monthly thereafter.

It is important that management should be individualised

Parameter	Optimal value
Total cholesterol	< 4 mmol/L
LDL cholesterol	< 2.5 mmol/L
HDL cholesterol	> 1 mmol/L
TC:HDL ratio	< 4.5
Triglycerides	< 1.7 mmol/L
HbA_{1C}	< 7 %

Diabetic renal disease

The best way of testing for diabetic renal disease is by urinary albumin:creatinine ratio (ACR) and serum creatinine with estimated glomerular filtration rate (eGFR). These tests are performed on everyone with diabetes at diagnosis and repeated at least annually – more frequently if there is proteinuria, microalbuminuria or reduced eGFR.

Albumin:creatinine ratio

- ACR provides an estimate of daily urinary albumin excretion.
- Microalbuminuria cannot be detected on a conventional urinary protein dip stick.
- Microalbuminuria is urinary albumin excretion between 30 and 300 mg/day; above 300mg/day represents proteinuria.
- ACR is best measured in the laboratory using a first morning urine sample where possible when the patient is well.
- An abnormal initial test requires confirmation by testing on two further occasions. If at least one of these tests is positive microalbuminuria has been confirmed.

Renal testing in diabetes

ACR mg/mmol (confirmed)		eGFR mL/min/1 .73^2	Risk	Management
men < 2.5 women < 3.5	and	> 60	2 - 4% per year progress to microalbuminuria.	Annual ACR and eGFR. Good diabetes & BP management.
men ≥ 2.5 women ≥ 3.5	or	< 60	One third progress to overt nephropathy. CVD risk doubled.	Review ACR and eGFR at each visit. Intensive management of glycaemia and CVD risk factors. Use ACE inhibitor and low-dose aspirin. Avoid nephrotoxic drugs. Investigate if suspicious of causes other than diabetes*
> 30	or	< 30	Almost all proceed to end stage renal disease or die prematurely of CVD.	Overt nephropathy Refer specialist

*Non-diabetic renal disease is suspected when there is absence of diabetic retinopathy in a person with renal disease, there are urinary abnormalities such as haematuria or casts, or when there is renal disease without microalbuminuria or proteinuria.

Other tests

Testing of LFTs is recommended for people with diabetes:

- at diagnosis,
- at the start of antidiabetic drug therapy, and
- at any other time indicated by clinical judgement

Other laboratory tests

In patients with type 1 diabetes, intermittent checks for other autoimmune conditions may be useful. This could include testing for thyroid dysfunction or coeliac disease.

CASE STUDY 13-1

An 18-year-old, male high school student who had a 4-year history of diabetes mellitus was brought to the emergency department because of excessive drowsiness, vomiting, and diarrhea. His diabetes had been well controlled with 40 units of NPH insulin daily until several days ago, when he developed excessive thirst and polyuria. For the past 3 days, he has also had headaches, myalgia, and a low-grade fever. Diarrhea and vomiting began 1 day ago.

Questions

1. What is the probable diagnosis of this patient based on the data presented?
2. What laboratory test(s) should be performed to follow this patient and aid in adjusting insulin levels?
3. Why are the urine ketones positive?
4. What methods are used to quantitate urine ketones? Which ketone(s) do they detect?

URINALYSIS RESULTS		CHEMISTRY TEST RESULTS	
Specific gravity	1.012	Sodium	126 mEq/L
pH	5.0	Potassium	6.1 mEq/L
Glucose	4+	Chloride	87 mEq/L
Ketone	Large	Bicarbonate	6 mEq/L
		Plasma glucose	600 mg/dL
		BUN	48 mg/dL
		Creatinine	2.0 mg/dL
		Serum ketones	4+

CASE STUDY 13-2

A 58-year-old, obese man with frequent urination is seen by his primary care physician. The following laboratory work was performed, and the following results were obtained:

CASUAL PLASMA GLUCOSE			225 mg/dL
URINALYSIS RESULTS			
Color and appearance	Pale/clear	Blood	Negative
pH	6.0	Bilirubin	Negative
Specific	1.025	Urobilinogen	Negative
Glucose	2+	Nitrites	Negative
Ketones	Negative	Leukocyte esterase	Negative

Questions

1. What is the probable diagnosis of this patient?
2. What other test(s) should be performed to confirm this? Which is the preferred test?
3. After diagnosis, what test(s) should be performed to monitor his condition?

CASE STUDY 13-3

A 14-year-old, male student was seen by his physician. His chief complaints were fatigue, weight loss, and increases in appetite, thirst, and frequency of urination. For the past 3 to 4 weeks, he had been excessively thirsty and had to urinate every few hours. He began to get up 3 to 4 times a night to urinate. The patient has a family history of diabetes mellitus.

LABORATORY DATA

Fasting plasma glucose	160 mg/dL	
Urinalysis	Specific gravity	1.040
	Glucose	4+
	Ketones	Moderate

Questions

1. Based on the preceding information, can this patient be diagnosed with diabetes?
2. What further tests might be performed to confirm the diagnosis?
3. According to the American Diabetes Association, what criteria are required for the diagnosis of diabetes?
4. Assuming this patient has diabetes, which type would be diagnosed?

CASE STUDY 13-4

A 13-year-old girl collapsed on a playground at school. When her mother was contacted, she mentioned that her daughter had been losing weight and making frequent trips to the bathroom in the night. The emergency squad noticed a fruity breath. On entrance to the emergency department, her vital signs were as follows:

Blood pressure	98/50 mm Hg
Respirations	Rapid
Temperature	99°F

Stat lab results included:

RANDOM URINE		SERUM CHEMISTRIES	
pH	5.5	Glucose	500 mg/dL
Protein	Negative	Ketones	Positive
Glucose	4+	BUN	6 mg/dL
Ketones	Moderate	Creatinine	0.4 mg/dL
Blood	Negative		

Questions

1. Identify this patient's most likely type of diabetes.
2. Based on your identification, circle the common characteristics associated with that type of diabetes in the case study above.
3. What is the cause of the fruity breath?

CASE STUDY 13-5

A 28-year-old woman delivered a 9.5-lb infant. The infant was above the 95th percentile for weight and length. The mother's history was incomplete; she claimed to have had no medical care through her pregnancy. Shortly after birth, the infant became lethargic and flaccid. A whole blood glucose and ionized calcium were performed in the nursery with the following results:

Whole blood glucose	25 mg/dL
Ionized calcium	4.9 mg/dL

Plasma glucose was drawn and analyzed in the main laboratory to confirm the whole blood findings.

Plasma glucose	33 mg/dL

An intravenous glucose solution was started and whole blood glucose was measured hourly.

Questions

1. Give the possible explanation for the infant's large birth weight and size.
2. If the mother was a gestational diabetic, why was her baby hypoglycemic?
3. Why was there a discrepancy between the whole blood glucose concentration and the plasma glucose concentration?
4. If the mother had been monitored during pregnancy, what laboratory tests should have been performed and what criteria would have indicated that she had gestational diabetes?

CASE STUDY 13-6

Laboratory tests were performed on a 50-year-old lean white woman during an annual physical examination. She has no family history of diabetes or any history of elevated glucose levels during pregnancy.

LABORATORY RESULTS	
Fasting blood glucose	90 mg/dL
Cholesterol	140 mg/dL
HDL	40 mg/dL
Triglycerides	90 mg/dL

Questions

1. What is the probable diagnosis of this patient?
2. Describe the proper follow-up for this patient.
3. What is the preferred screening test for diabetes in nonpregnant adults?
4. What are the risk factors that would indicate a potential of this patient's developing diabetes?

CASE STUDY 13-7

For 3 consecutive months, a fasting glucose and glycosylated hemoglobin were performed on a patient. The results are as follows:

	QUARTER 1	QUARTER 2	QUARTER 3
Plasma glucose, fasting	280 mg/dL	85 mg/dL	91 mg/dL (FPG)
Glycosylated hemoglobin	7.8%	15.3%	8.5%

Questions

1. In which quarter was the patient's glucose the best controlled? The least controlled?
2. Do the fasting plasma glucose and glycosylated hemoglobin match? Why or why not?
3. What methods are used to measure glycosylated hemoglobin?
4. What potential conditions might cause erroneous results?

CASE STUDY 13-8

A 25-year-old, healthy, female patient complains of dizziness and shaking 1 hour after eating a large, heavy-carbohydrate meal. The result of a random glucose test performed via fingerstick was 60 mg/dL.

Questions

1. Identify the characteristics of hypoglycemia in this case study.
2. What test(s) should be performed next to determine this young woman's problem?
3. To which category of hypoglycemia would this individual belong?
4. What criteria would be used to diagnose a potential insulinoma?

CASE STUDY 13-9

A nurse caring for patients with diabetes performed a fingerstick glucose test on the Accu-Chek glucose monitor and obtained a value of 200 mg/dL. A plasma sample, collected at the same time by a phlebotomist and performed by the laboratory, resulted in a glucose value of 225 mg/dL.

Questions

1. Are these two results significantly different?
2. Explain.