DIABETES MELLITUS: AN OVERVIEW

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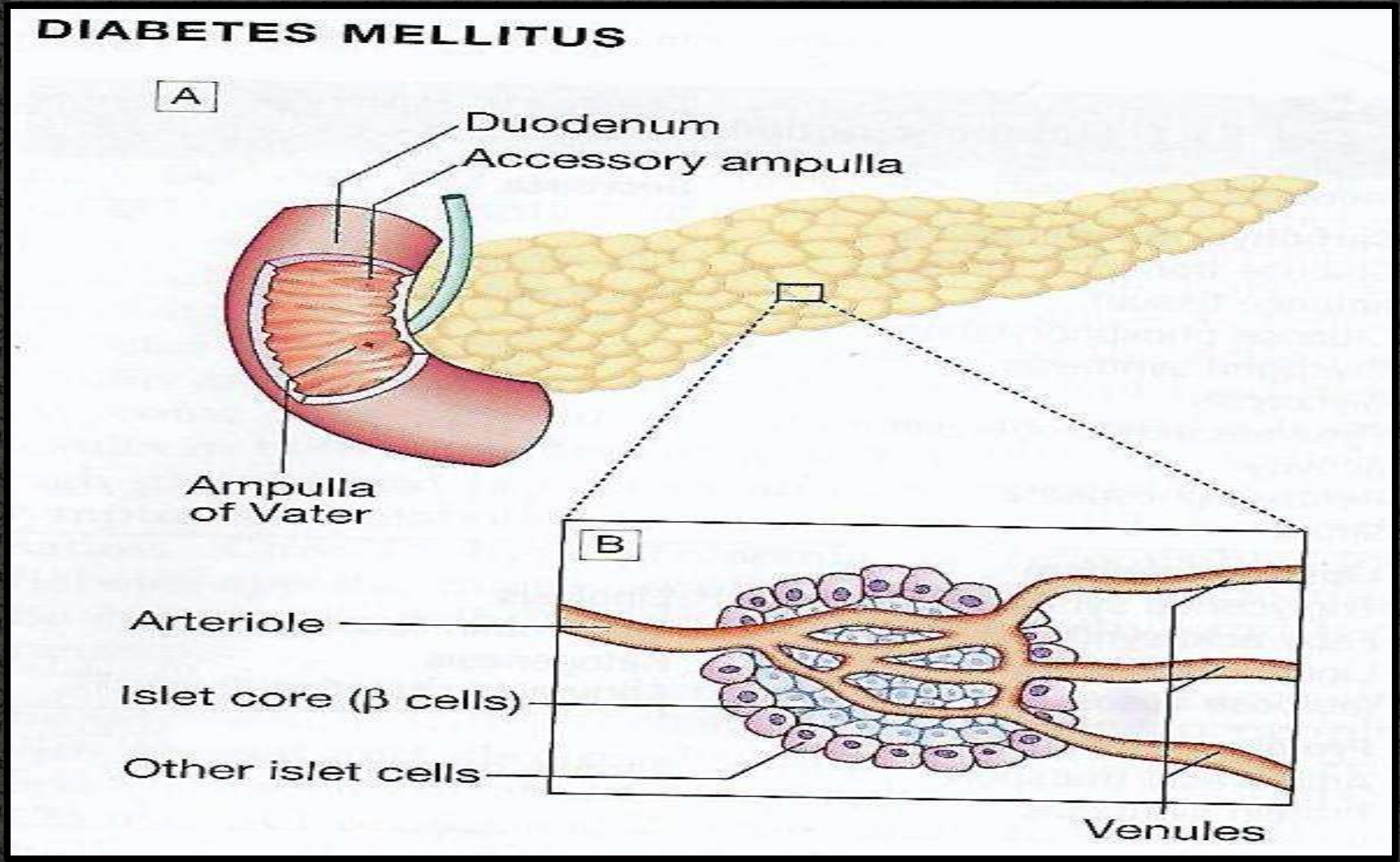
INTRODUCTION:

The number of people with type 1 and 2 diabetes mellitus (T2DM) is increasing rapidly and the latest figures are 387 million people with diabetes globally which is projected to rise to 592 million people in 2035. what is worse is that almost half of the people with diabetes remain undiagnosed. The disease burden due to diabetes is higher in low and middle income countries where four out of five people (80%) now reside. India, one of the largest countries in the Southeast Asian region, has more than 67 million people with diabetes, and this is expected to increase to 101 million by 2035.

DEFINITION: Diabetes Mellitus is a group of metabolic disorder involving carbohydrate, lipid and protein metabolism characterized by chronic hyperglycemia, as a result of defects in insulin secretion from β-cells of pancreas or peripheral action of insulin (insulin resistance) or both.

PENCITIC ISLET (BETA CELL)

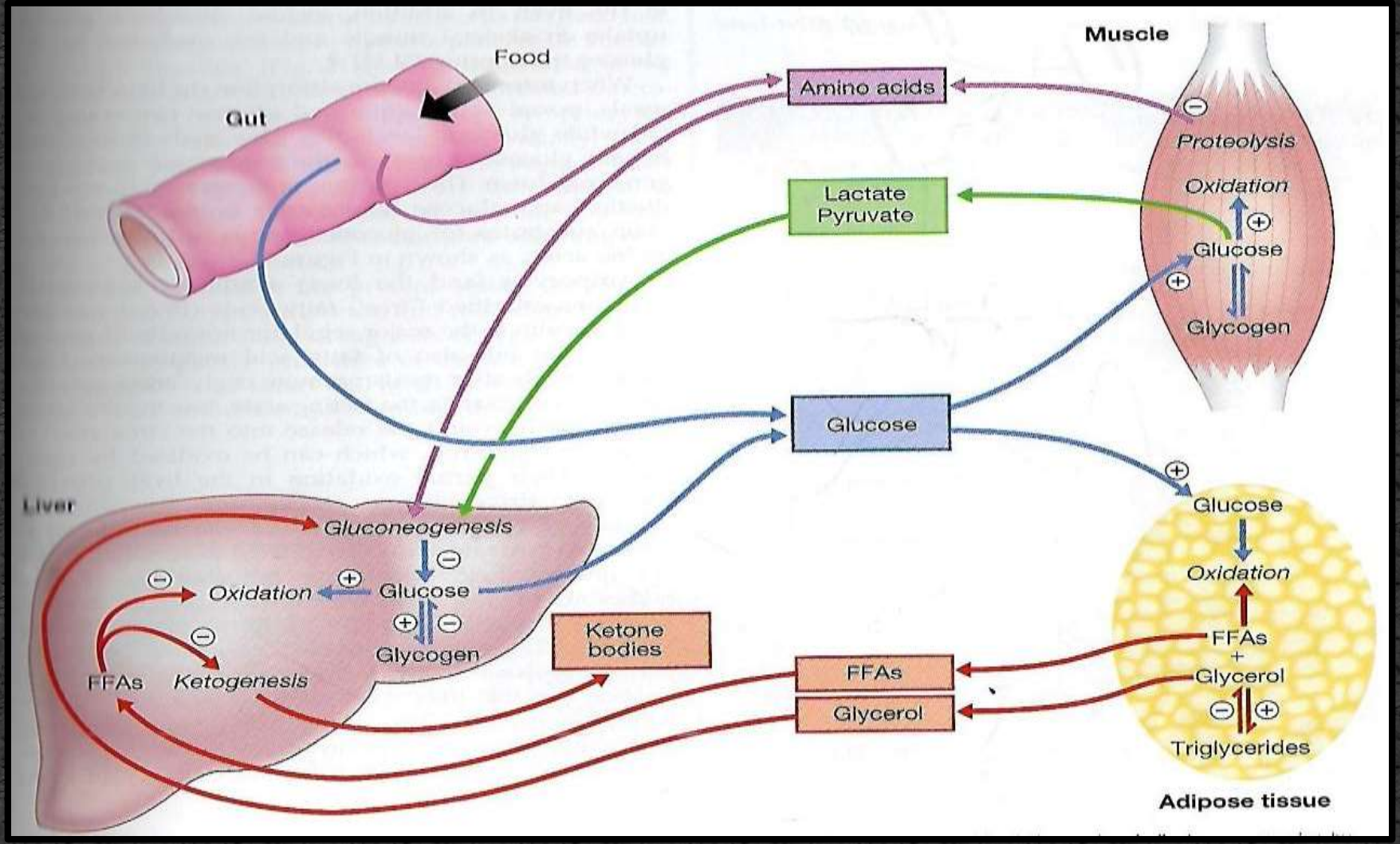


METABOLIC ACTION OF INSULIN

INCREASE	DECREASE
CARBOHYDRATE METABOLISM	
Glucose transport (muscle, adipose tissue)	Gluconeogenesis, Glycogenolysis
Glucose phosphorylation	
Glycogen synthesis	
Glycolysis	
Pyruvate dehydrogenase	
Activity	
Pentose phosphate	
Shunt	

INCREASE	DECREASE
LIPID METABOLISM	
Triglyceride Synthesis	Lipolysis
Fatty acid synthesis (liver)	Lipoprotein lipase (muscle)
Lipoprotein Lipase Activity	Ketogenesis
(Adipose Tissue)	Fatty acid oxidation (liver)
PROTEIN METABOLISM	
Amino acid Transport	Protein Degradation
Protein synthesis	

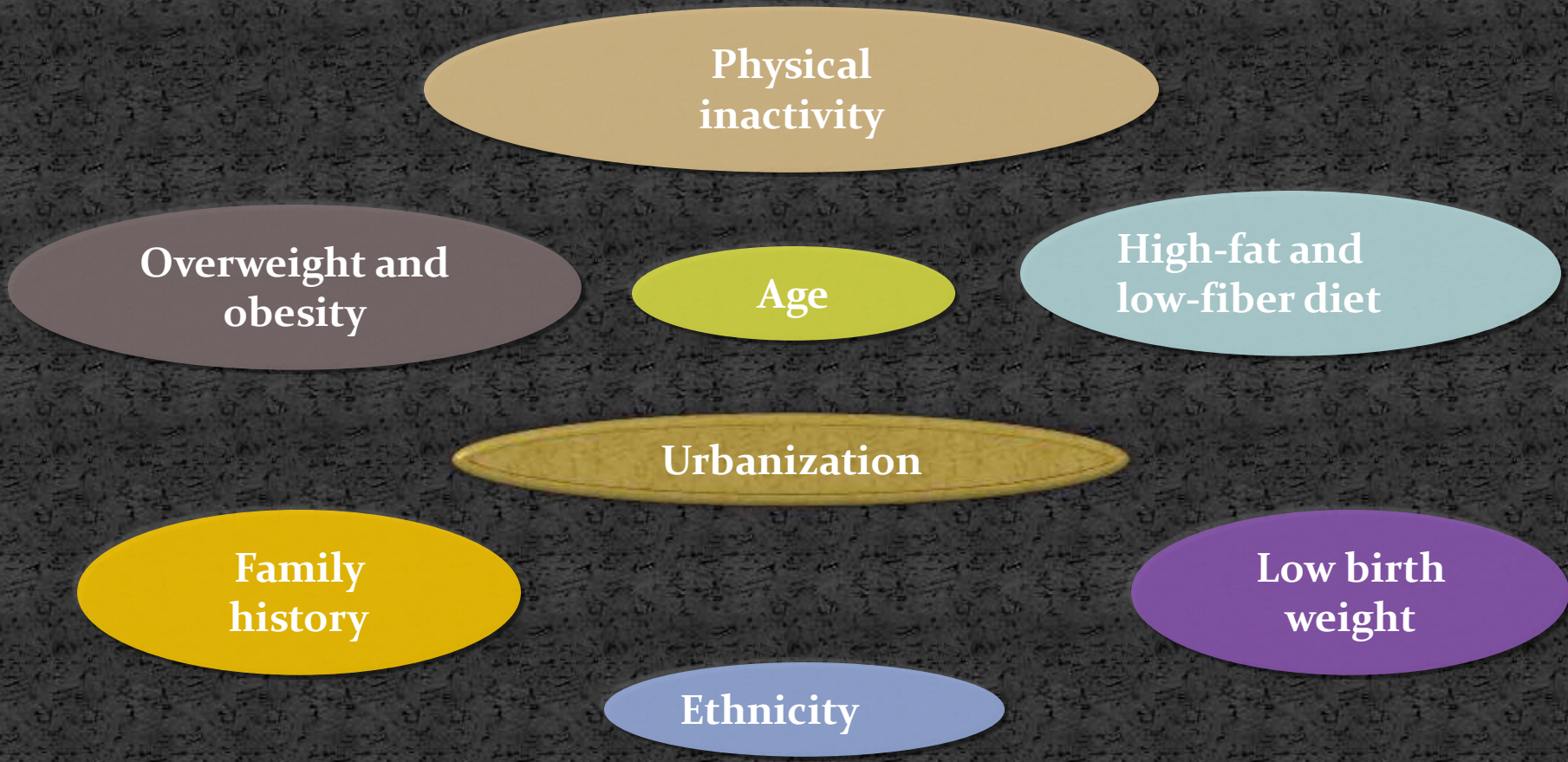
GLUCOSE METABOLISM



REGULATION OF GLUCOSE HOMEOSTASIS

- Glucose homeostasis reflects a balance between hepatic glucose production and peripheral glucose uptake and utilization.
- Insulin is the most important regulator of this metabolic equilibrium, but neural input, metabolic signals, and other hormones (e.g., glucagon) result in integrated control of glucose supply and utilization.
- In the fasting state, low insulin levels increase glucose production by promoting hepatic gluconeogenesis and glycogenolysis and reduce glucose uptake in muscles and fat.
- Postprandially, the glucose load elicits a rise in insulin and fall in glucagon, leading to a reversal of these processes.
- Insulin, an anabolic hormone, promotes the storage of carbohydrate and fat and protein synthesis.
- The major portion of postprandial glucose is used by skeletal muscle, an effect of insulin-stimulated glucose uptake.

RISK FACTORS FOR TYPE 2 DIABETES



Type 2 diabetes, the **metabolic syndrome** and **cardiovascular disease** in Europe

DIAGNOSIS OF DIABETES MELLITUS

DIAGNOSIS OF DIABETES AND PRE-DIABETES

Diabetes is confirmed by either:

- Plasma glucose in random sample or 2 hrs after a 75 g glucose load ≥ 11.1 (200 mg/dL) or
- Fasting plasma glucose ≥ 7.0 mmol/L (126 mg/dL)

In asymptomatic patients, two diagnostic tasts are required to confirm diabetes.

'PRE-DIABETES' IS CLASSIFIED AS:

- Impaired fasting glucose = fasting plasma glucose ≥ 6.0 (108 mg/dL) and < 7.0 mmol/L (126 mg/dL)
- Impaired glucose tolerance = fasting plasma glucose

<7.0 mmol/L (126 mg/dL) and 2-hr glucose after 75 g oral glucose drink 7.8-11.1 mmol/L (140-200 mg/dL)

AETIOLOGICAL CLASSIFICATION OF DIABETES MELLITUS

Type 1 diabetes:

- Immune-mediated
- Idiopathic

Type 2 diabetes:

Other specific types

- Genetic defects of β-cell function
- Genetic defects of insulin action (e.g. leprechaunism, lip dystrophies)
- Pancreatic disease (e.g. pancreatitis, pancreatectomy, neoplastic disease, cystic fibrosis)
- Drug-induced (e.g. corticosteroids, thiazide diuretics, phenytoin)

- Excess endogenous production of hormonal antagonists to insulin,

  e.g:

a. Growth Hormone - Acromegaly
b. Glucocorticoids – Cushing's syndrome
c. Glucagon – Glucagonoma
d. Catecholamine's - Phaeochromocytoma

SYMPTOMS OF HYPERGLYCAEMIA

- Thirst, dry mouth
- Polyuria
- Nocturia
- Tiredness, fatigue, lethargy
- Change in weight (usually weight loss)
- Blurring of vision
- Pruritus vulvae, balanitis (genital candidiasis)
- Nausea
- Headache
- Hyperphagia; predilection for sweet foods
- mood change, irritability, difficulty in concentrating, apathy

INVESTIGATIONS

- ✓ Blood sugars: Fasting, 2 hours postprandial blood sugar(PPBS), Glycosylated Hb should be done.
- ✓ urine for sugar, albumin, microalbuminuria, pus cells for urinary tract infection Liver, renal and lipid profile.
- ✓ X-ray chest for heart enlargement, pulmonary tuberculosis.
- ✓ Plain X-ray abdomen for pancreatic calcification.
- ✓ Electrocardiogram (ECG) and stress test to rule out ischemic heart disease (IHD)

- ✓ 2D echocardiography to rule out diabetic cardiomyopathy.
- ✓ Carotid and vertebral arteries Doppler for cerebrovascular accidents
- ✓ In patients having peripheral artery disease, Doppler study of femoral and popliteal arteries.
- ✓ Ultrasonography (USG) of abdomen and pelvis for nephropathy, renal stones

TYPES OF DIABETES:

1. Type 1 diabetes (absolute insulin deficiency)
2. Type 2 diabetes (Predominantly insulin resistance with relative insulin deficiency)
3. Gestational diabetes mellitus (7% of all Indian pregnancies)

TYPE 1 DIABETES:

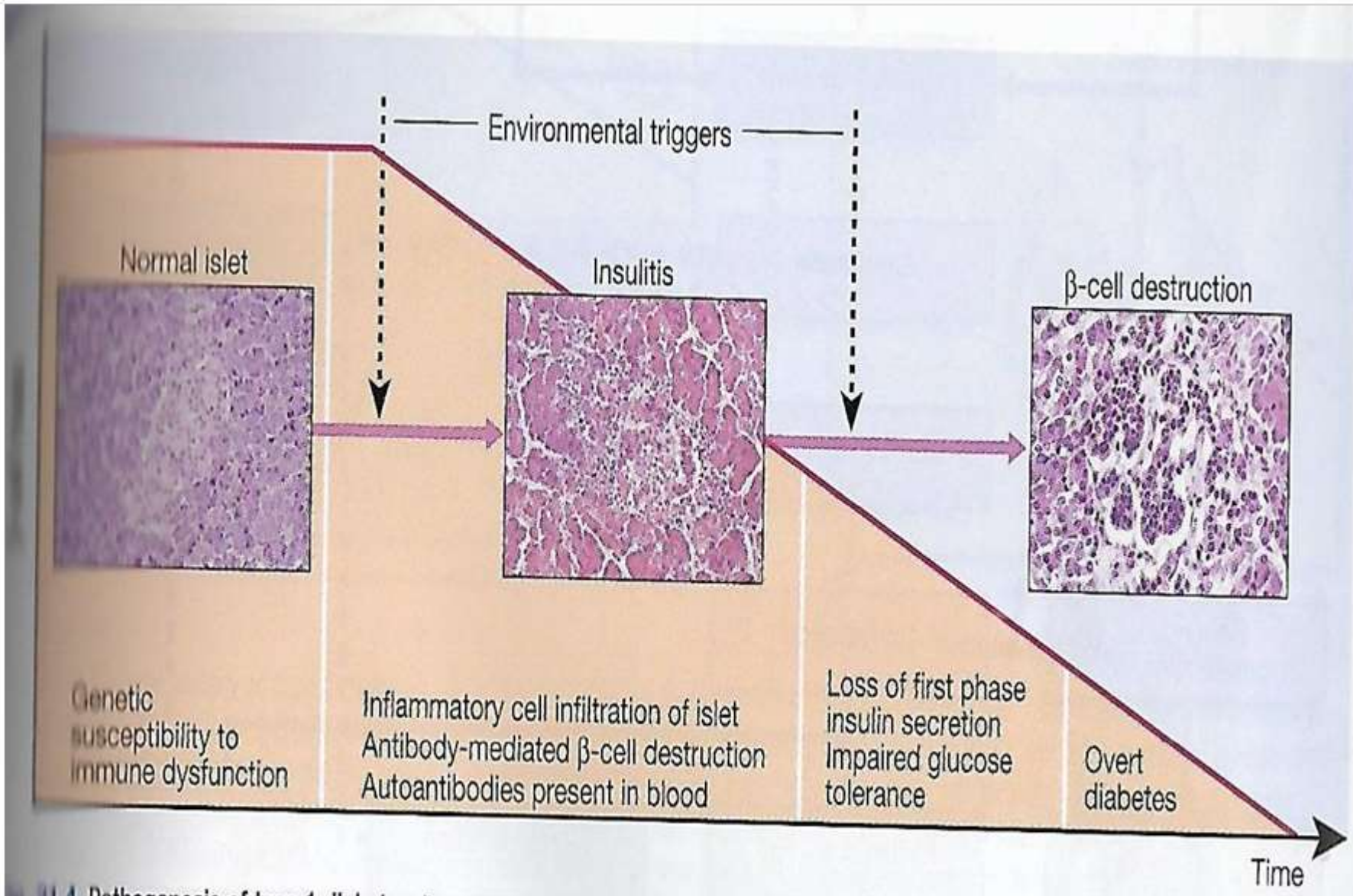
- Was previously called insulin-dependent diabetes mellitus (IDDM) or juvenile-onset diabetes.
- Type 1 diabetes develops when the body's immune system destroys pancreatic beta cells, the only cells in the body that make the hormone insulin that regulates blood glucose.
- This form of diabetes usually strikes children and young adults, although disease onset can occur at any age.
- Type 1 diabetes may account for 5% to 10% of all diagnosed cases of diabetes.
- Risk factors for type 1 diabetes may include autoimmune, genetic, and environmental factors.

PATHOGENESIS

TYPE 1 DIABETES:

Type 1 DM is the result of interactions of genetic, environmental, and immunologic factors that ultimately lead to the destruction of the pancreatic beta cells and insulin deficiency.

- Age 20 yrs commonly.
- Auto immune destruction of beta-cells genetic predisposition.
- Autoimmunity triggered functions are- infection, environmental stimulus.
- Diabetes develop when 70-80% beta cell loss.



Pathogenesis of type 1 diabetes. Proposed sequence of events in the development of type 1 diabetes. Environmental triggers are described in text.

TYPE 2 DIABETES:

- Was previously called non-insulin-dependent diabetes mellitus (NIDDM) or adult-onset diabetes.
- Type 2 diabetes may account for about 90% to 95% of all diagnosed cases of diabetes.
- It usually begins as insulin resistance, a disorder in which the cells do not use insulin properly. As the need for insulin rises, the pancreas gradually loses its ability to produce insulin.
- Type 2 diabetes is associated with older age, obesity, family history of diabetes, history of gestational diabetes, impaired glucose metabolism, physical inactivity, and race/ethnicity.
- Type 2 diabetes is increasingly being diagnosed in children and adolescents.

TYPE 2 DM:

Type 2 DM is characterized by-

- ✓ **Impaired insulin secretion.**
- ✓ **Insulin resistance.**
- ✓ **Excessive hepatic glucose production.**
- ✓ **Abnormal fat metabolism.**
- ✓ **Genetic susceptibility.**

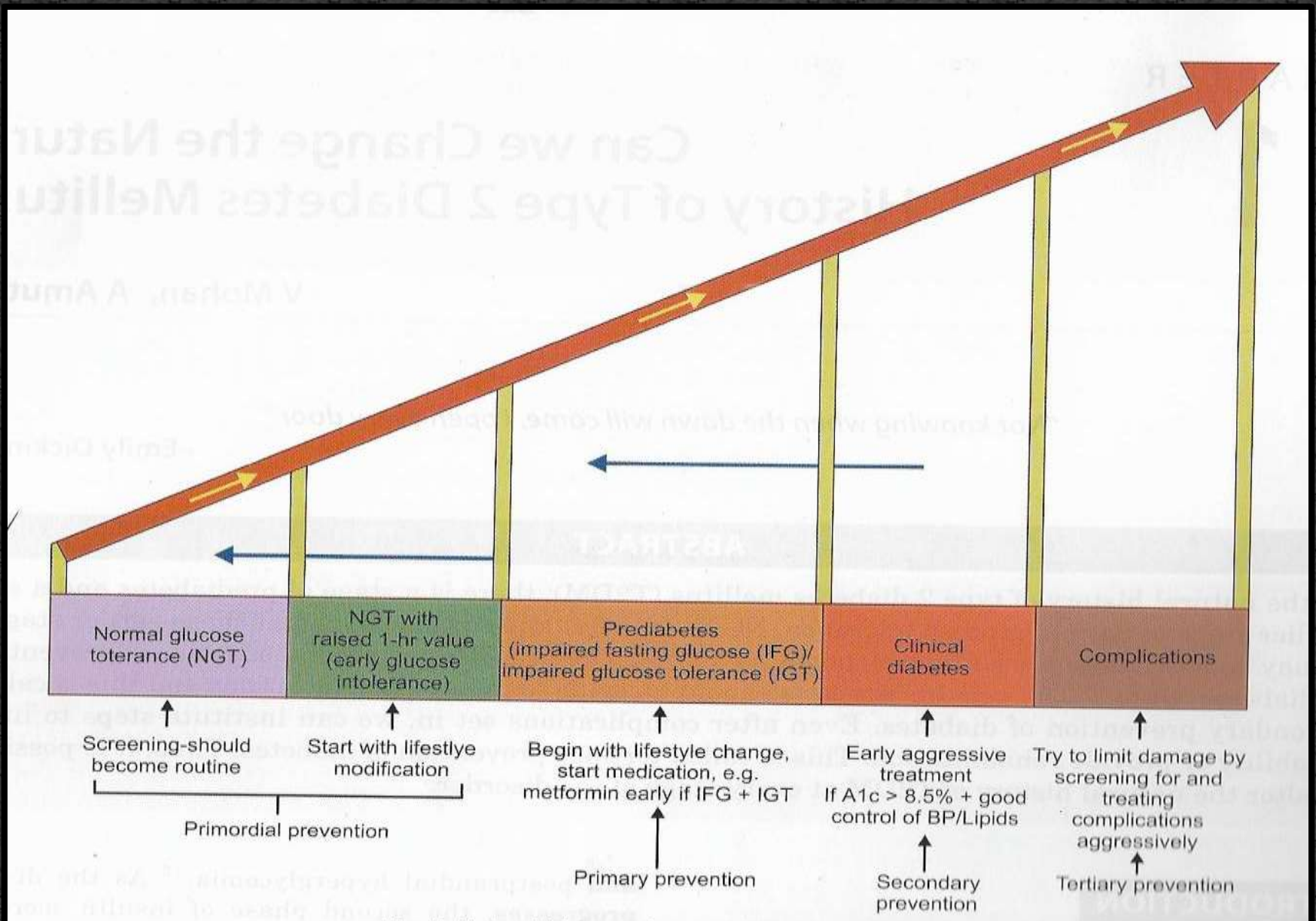


Fig. 1 Natural history of type 2 diabetes mellitus

21.12 Classical features of type 1 and type 2 diabetes

	Type 1	Type 2
Typical age at onset	< 40 yrs	> 50 yrs
Duration of symptoms	Weeks	Months to years
Body weight	Normal or low	Obese
Ketonuria	Yes	No
Rapid death without treatment with insulin	Yes	No
Autoantibodies	Positive in 80–90%	Negative
Diabetic complications at diagnosis	No	25%
Family history of diabetes	Uncommon	Common
Other autoimmune disease	Common	Uncommon

GESTATIONAL DIABETES

- A form of glucose intolerance that is diagnosed in some women during pregnancy.
- Gestational diabetes occurs more frequently among African Americans, Hispanic/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.

OTHER TYPES OF DM:

- Other specific types of diabetes result from specific genetic conditions (such as maturity-onset diabetes of youth), surgery, drugs, malnutrition, infections, and other illnesses.

- Such types of diabetes may account for 1% to 5% of all diagnosed cases of diabetes.

SECONDARY DM:

Secondary causes of Diabetes mellitus include:

- Acromegaly,
- Cushing syndrome,
- Thyrotoxicosis,
- Pheochromocytoma
- Chronic pancreatitis,
- Cancer
- Drug induced hyperglycaemia:
  - Atypical Antipsychotics - Alter receptor binding characteristics, leading to increased insulin resistance.
  - Beta-blockers - Inhibit insulin secretion.
  - Calcium Channel Blockers - Inhibits secretion of insulin by interfering with cytosolic calcium release.
  - Corticosteroids - Cause peripheral insulin resistance and gluconeogensis.
  - Fluoroquinolones - Inhibits insulin secretion by blocking ATP sensitive potassium channels.
  - Niacin - They cause increased insulin resistance due to increased free fatty acid mobilization.
  - Phenothiazines - Inhibit insulin secretion.
  - Protease Inhibitors - Inhibit the conversion of proinsulin to insulin.
  - Thiazide Diuretics - Inhibit insulin secretion due to hypokalemia. They also cause increased insulin resistance due to increased free fatty acid mobilization.

Management of Diabetes Mellitus

GOALS OF DIABETES MANAGEMENT

- Individualization of treatment regimen
- Achievement of metabolic status at normal or as close to normal as possible, especially blood glucose and lipid concentrations
- Achievement and maintenance of normal or reasonable body-weight.
- Adherence to a sound, realistic and appropriate diet and exercise programme.
- Attainment of normal quality of life without symptoms referable to diabetes
- Attainment of utility towards family and society.

TREATMENT GOALS FOR ADULTS WITH DIABETES

INDEX	GOAL
Glycemic control	
HbA1c	<7.0%
Preprandial capillary plasma glucose	4.4-7.2 mmol/L (80-130 mg/dL)
Peak postprandial capillary plasma glucose	<10.0 mmol/L (<180 mg/dL)
Blood pressure	<140/90 mmHg
Lipids	
Low-density lipoprotein	<2.6 mmol/L (100 mg/dL)
High-density lipoprotein	>1 mmol/L (40 mg/dL) in men >1.3 mmol/L (50 mg/dL) in women
Triglycerides	<1.7 mmol/L (150 mg/dL)

MANAGEMENT OF DM

- The major components of the treatment of diabetes are:

A	• **Diet and Exercise**
B	• **Oral hypoglycaemic therapy**
C	• **Insulin Therapy**

A. Diet

- Diet is a basic part of management in every case. Treatment cannot be effective unless adequate attention is given to ensuring appropriate nutrition.

- **Dietary treatment should aim at:**
  - ensuring weight control
  - providing nutritional requirements
  - allowing good glycaemia control with blood glucose levels as close to normal as possible
  - correcting any associated blood lipid abnormalities

A. Diet (cont.)

The following principles are recommended as dietary guidelines for people with diabetes:

- **Dietary fat should provide *25-35% of total intake of calories but saturated fat intake* should not exceed 10% of total energy. Cholesterol consumption should be restricted and limited to 300 mg or less daily.**
- **Protein intake can range between 10-15% total energy (0.8-1 g/kg of desirable body weight). Requirements increase for children and during pregnancy. Protein should be derived from both animal and vegetable sources.**
- **Carbohydrates provide *50-60% of total caloric content of the diet*. Carbohydrates should be complex and high in fibre.**
- **Excessive salt intake is to be avoided. It should be particularly restricted in people with hypertension and those with nephropathy.**

CALORIE INTAKE BASED ON ACTIVITY

LIFESTYLE	DAILY CALORIE REQUIREMENT
• Sedentary • Moderately active • Strenuous	• 20-25 Kcals/kg of IBW • 26-30 Kcals/Kg of IBW • 31-35 Kcals/Kg of IBW

Obesity is most commonly assessed by a single measure, the Body Mass Index (BMI), which uses a mathematical formula based on a person's height and weight.

$$\text{BMI} = \text{weight (kg)}/\text{height (m}^2\text{)}$$

- Individuals with a BMI
  - between 25 to 29.9 are considered overweight
  - of 30 and above are considered obese.
- The risk of serious health consequences such as type 2 diabetes, coronary heart disease, hypertension, dyslipidaemia, albuminuria and a wide range of other conditions increases with BMI.

Exercise

- Physical activity promotes weight reduction and improves insulin sensitivity, thus lowering blood glucose levels.
- Together with dietary treatment, a programme of regular physical activity and exercise should be considered for each person. Such a programme must be tailored to the individual's health status and fitness.
- People should, however, be educated about the potential risk of hypoglycaemia and how to avoid it.

BENEFITS OF PHYSICAL ACTIVITY

- Decrease insulin resistance/improve insulin sensitivity.
- Decrease overall adiposity.
- Reduce central adiposity.
- Improve blood glucose levels (glucose tolerance).
- Desirable changes in muscle tissue.

PRACTICAL TIPS FOR NUTRITION AND PHYSICAL ACTIVITY

- Calculate calories intake based on weight and activity profile
- Fats-20-25% of total calories
- Increase fiber content (20-30 gm/day)
- Small frequent meals
- Encourage intake of whole grains, beans, fruits, vegetables and nuts
- Stress on portion size/slow eating/monitoring

PHYSICAL ACTIVITY:

Set goal-30-45 mts exercise of moderate intensity every day.

Encourage exercise individual-based and keeping his interest in mind.

May use small gadgets like pedometer.

Start slowly and build up definitely.

OTHERS:

Provide family help and support

Failures be circumvented

Close follow up

GENERAL GUIDELINES FOR USE OF ORAL ANTI-DIABETIC AGENT IN DIABETES

- In elderly non-obese patients, short acting insulin secretagogues can be started but long acting Sulphonylureas are to be avoided. Renal function should be monitored.
- Oral anti-diabetic agent s are not recommended for diabetes in pregnancy
- Oral anti-diabetic agents are usually not the first line therapy in diabetes diagnosed during stress, such as infections. Insulin therapy is recommended for both the above
- Targets for control are applicable for all age groups. However, in patients with co-morbidities, targets are individualized
- When indicated, start with a minimal dose of oral anti-diabetic agent, while reemphasizing diet and physical activity. An appropriate duration of time (2-16 weeks depending on agents used) between increments should be given to allow achievement of steady state blood glucose control

B. ORAL ANTI-DIABETIC AGENTS

- **There are currently four classes of oral anti-diabetic agents:**

i. Biguanides

ii. Insulin Secretagogues – Sulphonylureas

iii. Insulin Secretagogues – Non-sulphonylureas

iv. α-glycosidase inhibitors

v. Thiazolidinediones (TZDs)

B.1 Oral Agent Monotherapy

- If glycaemic control is not achieved (HbA1c > 6.5% and/or; FPG > 7.0 mmol/L or; RPG >11.0mmol/L) with lifestyle modification within 1 –3 months, ORAL ANTI-DIABETIC AGENT should be initiated.

- In the presence of marked hyperglycaemia in newly diagnosed symptomatic type 2 diabetes (HbA1c > 8%, FPG > 11.1 mmol/L, or RPG > 14 mmol/L), oral anti-diabetic agents can be considered at the outset together with lifestyle modification.

B.1 Oral Agent Monotherapy (cont.)

As first line therapy:

- **Obese type 2 patients, consider use of metformin, *acarbose* or TZD.**
- **Non-obese type 2 patients, consider the use of metformin or insulin secretagogues.**
- **Metformin is the drug of choice in overweight/obese patients. TZDs and acarbose are acceptable alternatives in those who are intolerant to metformin.**
- **If monotherapy fails, a combination of TZDs, acarbose and metformin is recommended. If targets are still not achieved, insulin secretagogues may be added.**

B.2 Combination Oral Agents

Combination oral agents is indicated in:

- **Newly diagnosed symptomatic patients with HbA1c >10**
- **Patients who are not reaching targets after 3 months on monotherapy.**

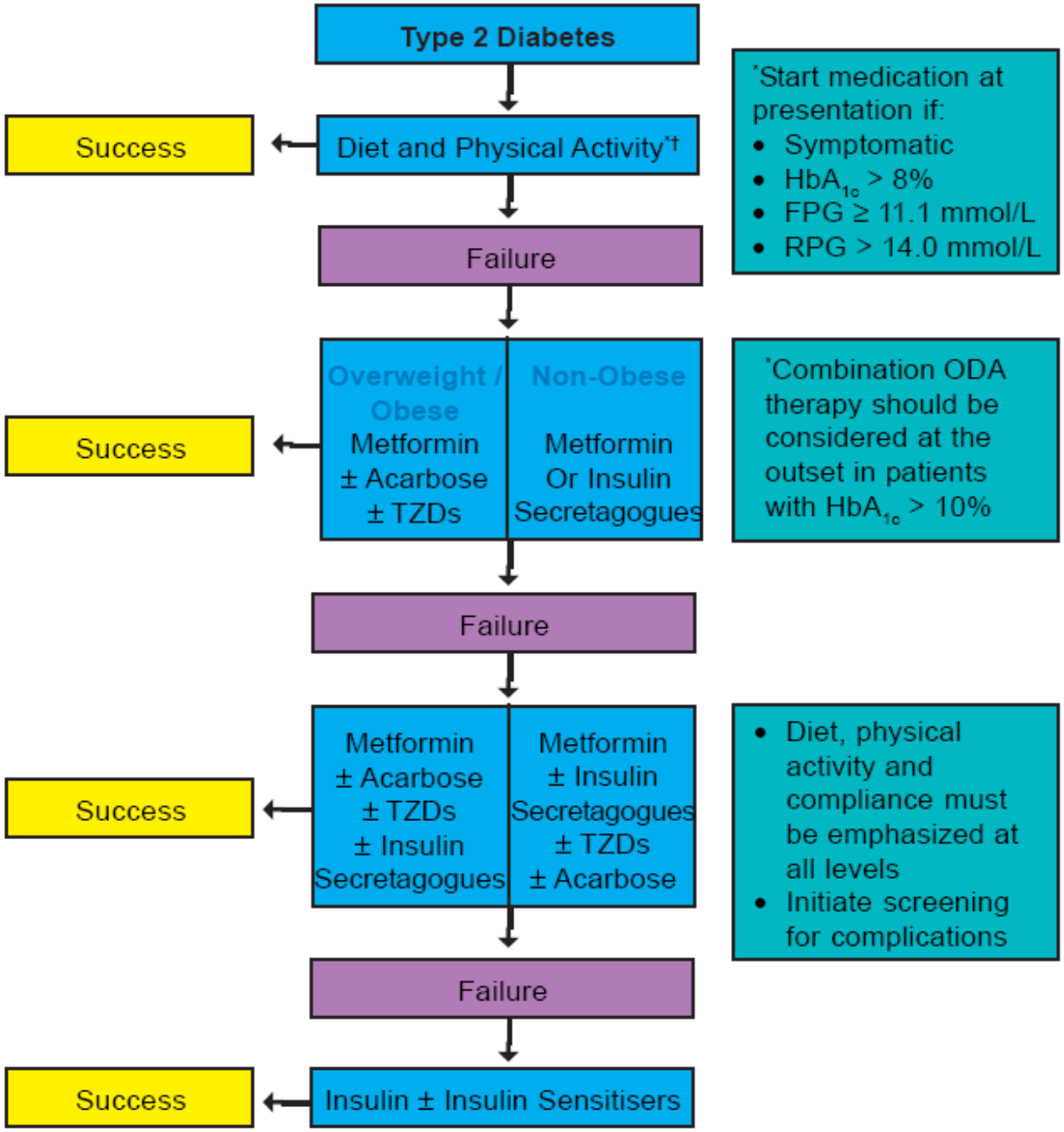
B.3 Combination Oral Agents and Insulin

- **If targets have not been reached after optimal dose of combination therapy for 3 months, consider adding intermediate-acting/long-acting insulin (BIDS).**

- **Combination of insulin+ oral anti-diabetic agents (BIDS) has been shown to improve glycaemic control in those not achieving target despite maximal combination oral anti-diabetic agents.**

- **Combining insulin and the following oral anti-diabetic agents has been shown to be effective in people with type 2 diabetes:**
  - **Biguanide (metformin)**
  - **Insulin secretagogues (sulphonylureas)**
  - **Insulin sensitizers (TZDs)*(the combination of a TZD plus insulin is* not an approved indication)**
  - **α-glucosidase inhibitor (acarbose)**

- **Insulin dose can be increased until target FPG is achieved.**



Diabetes Management Algorithm

AGENTS USED FOR TREATMENT OF TYPE 1 OR TYPE2 DIABETES

	Mechanism of Action	Examples	HbA1c Reduction(%)	Agent-Specific Advantages	Agent-Specific Disadvantages
ORAL					
Biguanides	↓ Hepatic glucose production	Metformin	1-2	Weight neutral, do not cause hypoglycemia , inexpensive , extensive experience, ↓ CV events	Diarrhea, nausea, lactic acidosis
ά-Glucosidase inhibitors	↓ Gl glucose absorption	Acarbose, miglitol, voglibose	0.5-0.8	Reduce postprandial glycemia	Gl flatulence, liver function tests
Dipeptidyl peptidase IV inhibitors	Prolong endogenous GLP-1 action	Alogliptin, Gemigliptin, linagliptin, saxagliptin, sitagliptin, teneligliptin, vildagliptin	0.5-0.8	Well tolerated, do not cause hypoglycemia	

Insulin secretagogues: Sulfonylureas	↑ Insulin Scretion	Glibornuride, gliclazide, Glimepiride, Glipizide, Gliquidone, Glyburide, Glyclopyramide	1-2	Short onset of action, lower postprandial glucose, inexpensive	Hypoglycemia, weight gain
Insulin secretagogues: Nonsulfonylureas	↑ Insulin Scretion	Nateglinide, repaglinide, mitiglinide	0.5-1.0	Short onset of action, lower post prandial glucose	Hypoglycemia
Sodium-Glucose cotransporter 2 inhibitors	↑ Urinary glucose excretion	Canagliflozin, Dapagliflozin, empagliflozin	0.5-1.0	Insulin secretion and action independent	Urinary and vaginal infections, dehydration, exacebate tendency to hyperkalemia
Thiazolidinediones	↓Insulin resistance, ↑Glucose utlization	Rosiglitazone, Pioglitazone	0.5-1.4	Lower insulin requirements	Peripheral edema, CHF, weight gain, fractures, macular edema

PARENTERAL					
Amylin agonists	Slow gastric emptying ↓ glucagon	pramlintide	0.25-0.5	Reduce postprandial glycemia, weight loss	Injection, nausea, ↑ risk of hypoglycemia with insulin
GLP-1 receptor agonists	↑ insulin, ↓glucagon, slow gastric emptying, satiety	Exenatide, liraglutide, dulaglutide	0.5-1.0	Weight loss, do not cause hypoglycemia	Injection, nausea, ↑ risk of hypoglycemia with insulin secretagogues
insulin	↑ glucose utilization ↓ hepatic glucose production, and other anabolic actions	See text and table 418-4	Not limited	Known safety profile	Injection, weight gain, hypoglycemia

Medical nutrition therapy and physical activity	↓ insulin resistance, ↑ insulin secretion	Low-calorie, low-fat diet, exercise	1-3	Other health benifits	Compliance difficult, long-term success low

C. Insulin Therapy

Short-term use:

- Acute illness, surgery, stress and emergencies
- Pregnancy
- Breast-feeding
- Insulin may be used as initial therapy in type 2 diabetes
- in marked hyperglycaemia
- Severe metabolic decomposition (diabetic ketoacidosis, hyperosmolar nonketotic coma, lactic acidosis, severe hypertriglyceridaemia)

Long-term use:

- If targets have not been reached after optimal dose of combination therapy or BIDS, consider change to multi-dose insulin therapy. When initiating this, insulin secretagogues should be stopped and insulin sensitisers e.g. Metformin or TZDs, can be continued.

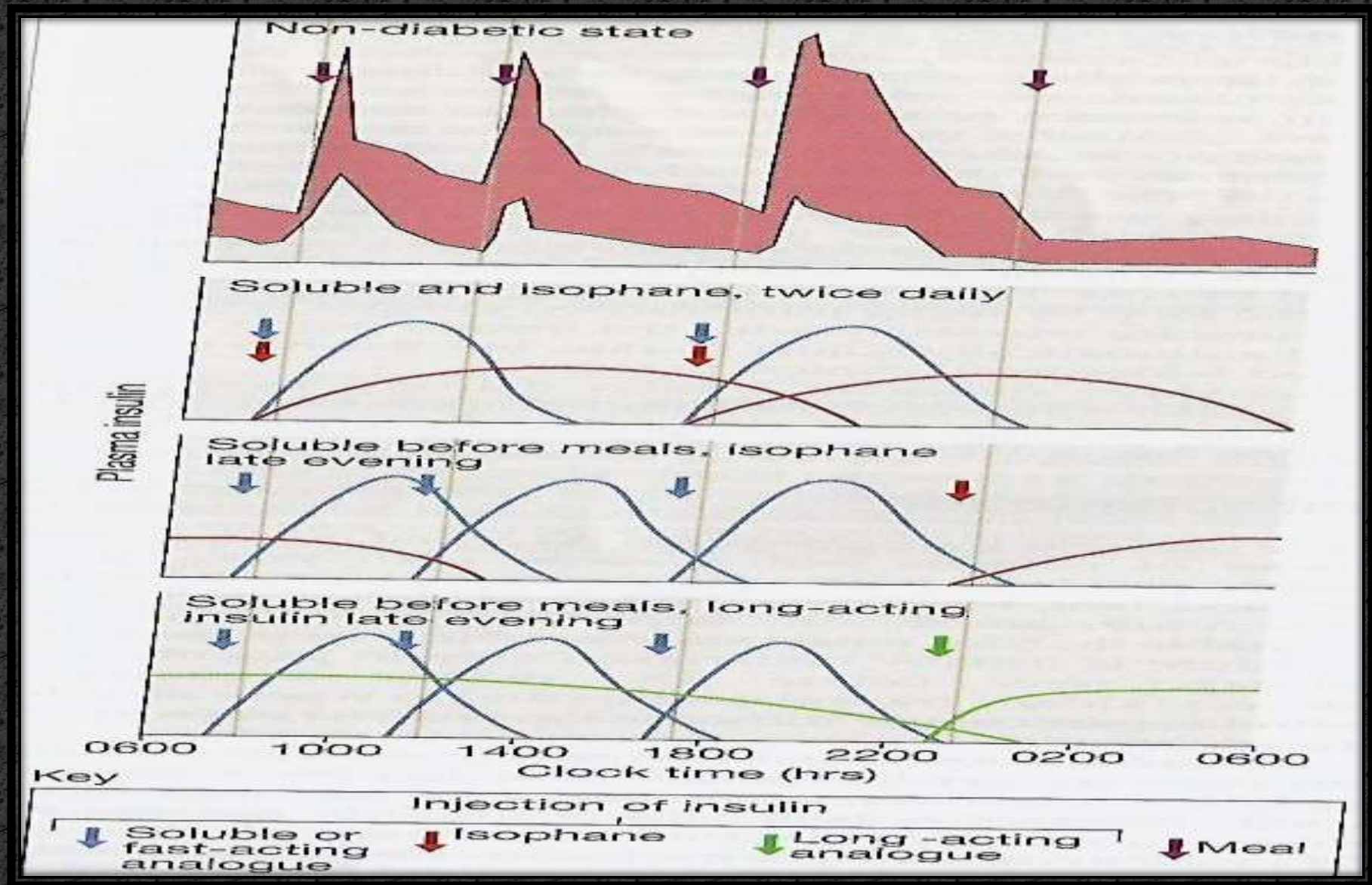
Types of insulin

Insulin type/action (appearance)	Brand names (generic name in brackets)	Basal/bolus	Dosing schedule
Rapid-acting analogue (clear) Onset: 10–15 minutes Peak: 60–90 minutes Duration: 4–5 hours	Humalog® (insulin lispro) NovoRapid® (insulin aspart)	Bolus	Usually taken right before eating or to lower high blood glucose
Short-acting (clear) Onset: 0.5–1 hour Peak: 2–4 hours Duration: 5–8 hours	Humulin®-R Novolin®ge Toronto	Bolus	Taken about 30 minutes before eating, or to lower high blood glucose
Intermediate-acting (cloudy) Onset: 1–3 hours Peak: 5–8 hours Duration: up to 18 hours	Humulin®-N Novolin®ge NPH	Basal	Often taken at bedtime, or twice a day (morning and bedtime)
Extended long-acting analogue (Clear and colourless) Onset: 90 minutes Peak: none Duration: 24 hours	Lantus® (insulin glargine) Levemir® (insulin detemir)	Basal	Usually taken once or twice a day
Premixed (cloudy) A single vial contains a fixed ratio of insulins (the numbers refer to the ratio of rapid- or fast-acting to intermediate-acting insulin in the vial)	Humalog® Mix 25™ Humulin® (20/80, 30/70) Novolin®ge (10/90, 20/80, 30/70, 40/60, 50/50)	Combination of basal and bolus insulins	Depends on the combination

VARIOUS METABOLIC EFFECTS OF INSULIN

Stimulation of the activity of glycol tic enzymes.
Reduce the activity of the enzymes of gluconeogenesis.
Increased synthesis of glycogen.
Increased uptake of glucose by resting skeletal muscles.
Reduction of blood glucose level.
Reduction of lipolysis and stimulation of lipid synthesis.
Prevention of ketogenesis.
Increased transmembrane transport of K+ ions into the cell.
Acceleration of protein synthesis and enhancement of tissue uptake of amino acids

DIFFERENT INSULIN REGIMENS



Insulin regimens

- The majority of patients will require more than one daily injection if good glycaemic control is to be achieved. However, a once-daily injection of an intermediate acting preparation may be effectively used in some patients.
- Twice-daily mixtures of short- and intermediate-acting insulin is a commonly used regimen.
- In some cases, a mixture of short- and intermediate-acting insulin may be given in the morning. Further doses of short-acting insulin are given before lunch and the evening meal and an evening dose of intermediate-acting insulin is given at bedtime.
- Other regimens based on the same principles may be used.
- A regimen of multiple injections of short-acting insulin before the main meals, with an appropriate dose of an intermediate-acting insulin given at bedtime, may be used, particularly when strict glycaemic control is mandatory.

SIDE-EFFECTS OF INSULIN THERAPY

- Hypoglycemia
- Weight gain
- Peripheral oedema (insulin treatment causes salt and water retention in the short term)
- Insulin antibodies (with animal insulins)
- Local allergy (rare)
- Lipohypertrophy or lipoatrophy at injection sites.

COMPLICATIONS OF DIABETES MELLITUS

ACUTE COMPLICATIONS:

- Diabetic ketoacidosis (DKA)
- Hyperosmolar nonketotic diabetic coma (HONC)
- Hypoglycemic coma (usually due to therapy)
- Lactic acidosis.
- Infections (Boils)

HYPOGLYCAEMIA

Hypoglycemia (blood glucose < 3.5 mmol/L (63 mg/dL)) in diabetes results in most circumstances from insulin therapy, less frequently from use of oral insulin secretagogues such as sulphonylurea drugs, and rarely with other anti-diabetic drugs. When hypoglycemia develops in non-diabetic People, it is called ‘spontaneous’ hypoglycemia.

HYPOGLYCAEMIA IN DIABETES: COMMON CAUSE AND RISK FACTORS

CAUSE OF HYPOGLYCAEMIA:

- Missed, delayed or inadequate meal.
- Unexpected or unusual exercise.
- Alcohol.
- Errors in oral anti-diabetic agents(s) or insulin dose/schedule/administration.
- Poorly designed insulin regimen, particularly if predisposing to nocturnal hyperinsulinaemia.
- Lipohypertrophy at injection sites causing variable insulin absorption.
- Gastroparesis due to autonomic neuropathy causing variable carbohydrate absorption.
- Malabsorption, e.g. coeliac disease.
- Unrecognised other endocrine disorder, e.g. Addison's disease.
- Factitious (deliberately induced).
- Breastfeeding.

ADRENERGIC AND NEUROGLUCOPENIC SYMPTOMS OF HYPOGLYCEMIA

ADRENERGIC SYMPTOMS	NEUROGLUCOPENIC SYMPTOMS
➢ Shakiness	➢ Abnormal mentation, confusion, difficulty in thinking
➢Trembling	➢ Double vision, tube vision
➢ Anxiety	➢ Irritability
➢ Nervousness	➢ Difficulty in speaking, slurred speech
➢ Palpitations	➢ Ataxia
➢ Clamminess	➢ Paresthesia

ADRENERGIC SYMPTOMS	NEUROGLUCOPENIC SYMPTOMS
➢ Sweating	➢ Headaches
➢ Dry mouth	➢ Stupor
➢ Hunger	➢ Seizures
➢ Pallor	➢ Coma
➢ Pupil dilation	➢ Death (if untreated)

RISK FACTORS FOR SEVERE HYPOGLYCAEMIA

- Strict glycaemic control
- Impaired awareness of hypoglycemia.
- Age (very young and elderly)
- Long duration of diabetes
- Sleep
- C-Peptide negativity (indicating complete insulin deficiency)
- History of previous severe hypoglycemia
- Renal impairment
- genetic, e.g. angiotensin-converting enzyme (ACE) genotype.

TREATMENT OF HYPLOGLYCEMA

- To conscious patient – oral glucose 20 gms state.
- Unconscious patient- parental glucose 25 gms.
- Glucagon -1 mg s/c in adults.

DIABETIC KETOACIDOSIS (DKA)

- ✓ DKA is characteristic of Type-1 diabetes
- ✓ DKA result from relation on absolute insulin deficiency.
- ✓ Counter regulation hormones excess.
- ✓ Glucogon, catecholomine, contisal & growth hormone.

THE CARDIVAL BIOCHEMICAL FEATURES ARE:

I. Hyperketonaemia (≥ 3 mmol/L) and ketonuria
II. Hyperglycemia (250-600 mg%)
III. Metabolic acidosis (PH-6.8-7.3)

SIGNS AND SYMPTOMS OF DIABETIC KETOACIDOSIS

- Vomiting
- Increased urination
- Abdominal pain
- Fruity odor to breath
- Dry mouth and tongue
- Drowsiness
- Deep breathing
- Coma
- Decreased skin Turgor
- Prolonged capillary refill time

PRECIPITATING FACTORS FOR DIABETIC KETOACIDOSIS

MOST COMMON

- Infections (urinary tract infection, pneumonia)
- Medication noncompliance
- Inadequate insulin dosing
- New onset diabetes mellitus

LESS COMMON

- Acute pancreatitis
- Trauma
- Pregnancy
- Surgery
- Medications (thiazides, steroids, phenytoin, dopamine)

TREATMENT:

- Insulin
- Fluid & Electrolyte replacement

HYPERGLYCAEMIC HYPEROSMOLAR STATE

Hyperglycemic Hyperosmolar State (HSS) is character by:

- ✓ Severe hyperglycemia > 600 mg/ dl.
- ✓ Hyperosmolylity > 320 mOsm/kg.
- ✓ Dehydration due to osmotic fluid loss.
- ✓ Absence of significant hyperketonaemia (<3 mmol/L)

TREATMENT:

- ➢ Fluid and electrolyte replacement.
- ➢ Insulin parental .

INFECTION:

Infection in diabetes in common because abnormality in cell mediate immunity and phagocyte function associated with hyperglycemia

Common infections are:

- Fungal infection
- Pulmonary tuberculosis
- UTI by- e-coli.
- Furuenculosis
- pneumonia
- Skin and soft tissue infections
- Valvovaginitis.

The Long Term Effects Of Diabetes

The long term effects of diabetes can be divided into

- Macrovascular complications.
- Microvascular complications.

- Macrovascular complications affect the larger blood vessels, such as those supplying blood to the heart, brain and legs. The most common macrovascular fatal complication is coronary artery disease. Strokes are also a common cause of disability and death in people with diabetes.
- Microvascular complications affect the small blood vessels, such as those supplying blood to the eyes and kidneys. The microvascular complications of diabetes are retinopathy, nephropathy and neuropathy.

Type 2 diabetes, the **metabolic syndrome** and **cardiovascular disease** in Europe

COMPLICATIONS OF DIABETES

Despite all the treatments now available, the outcome for patients with diabetes remains disappointing. Long-term complications of diabetes still cause significant morbidity and mortality.

PATHOGENESIS

Numerous clinical studies have implicated endothelial dysfunction as the principal course of macrovascular and microvascular complications seen in both type 1 and type 2 diabetes. Endothelial cells regulate vascular tone by releasing endothelium-derived relaxing factors (EDRF), which include nitric oxide, prostacyclin and endothelium derived hyperpolarizing factor.

COMPLICATIONS OF DIABETES

MICROVASCULAR/NEUROPATHIC:
Retinopathy, cataract
➢ Impaired vision
Nephropathy
➢ Renal failure
Peripheral neuropathy
➢ Sensory loss
➢ Pain
➢ Motor weakness
Automatic neuropathy
➢ Gastrointestinal problems (gastro paresis; altered bowel habit)
➢ Postural hypertension

Foot disease
➢ Ulceration
➢ Arthropathy
MACROVASCULAR:
Coronary circulation
➢ Myocardial ischaemia/infarction
Cerebral circulation
➢ Transient ischaemic attack
➢ Stroke
Peripheral circulation
➢ Claudication
➢ Ischaemia

RISK FACTORS FOR INCREASED MORBIDITY AND MORTALITY IN DIABETES

- Duration of diabetes
- Early age at onset of disease
- High glycated haemoglobin (Hba1c)
- Raised blood pressure
- Proteinuria; microalbuminuria
- Dyslipidaemia
- Obesity

THE MAJOR DIABETIC COMPLICATIONS

Stroke
(cerebrovascular disease)

Heart disease
(cardiovascular disease)

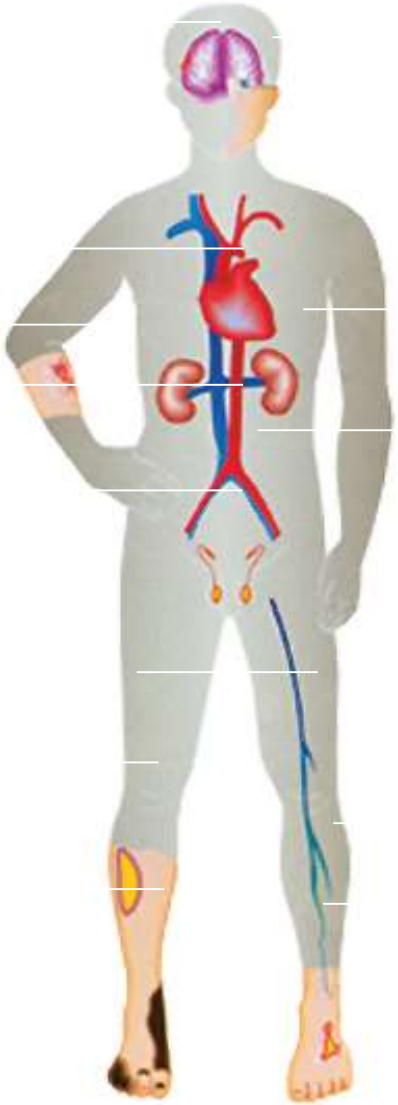
Bacterial and fungal infections of the skin

Severe hardening of the arteries (atherosclerosis)

Sexual dysfunction

Necrobiosis lipidoica

Gangrene



Visual impairment:
diabetic retinopathy, cataract and glaucoma

Kidney disease
(diabetic nephropathy)

Autonomic neuropathy
(including slow emptying of the stomach and diarrhea)

Sensory impairment
(peripheral neuropathy)

Ulceration

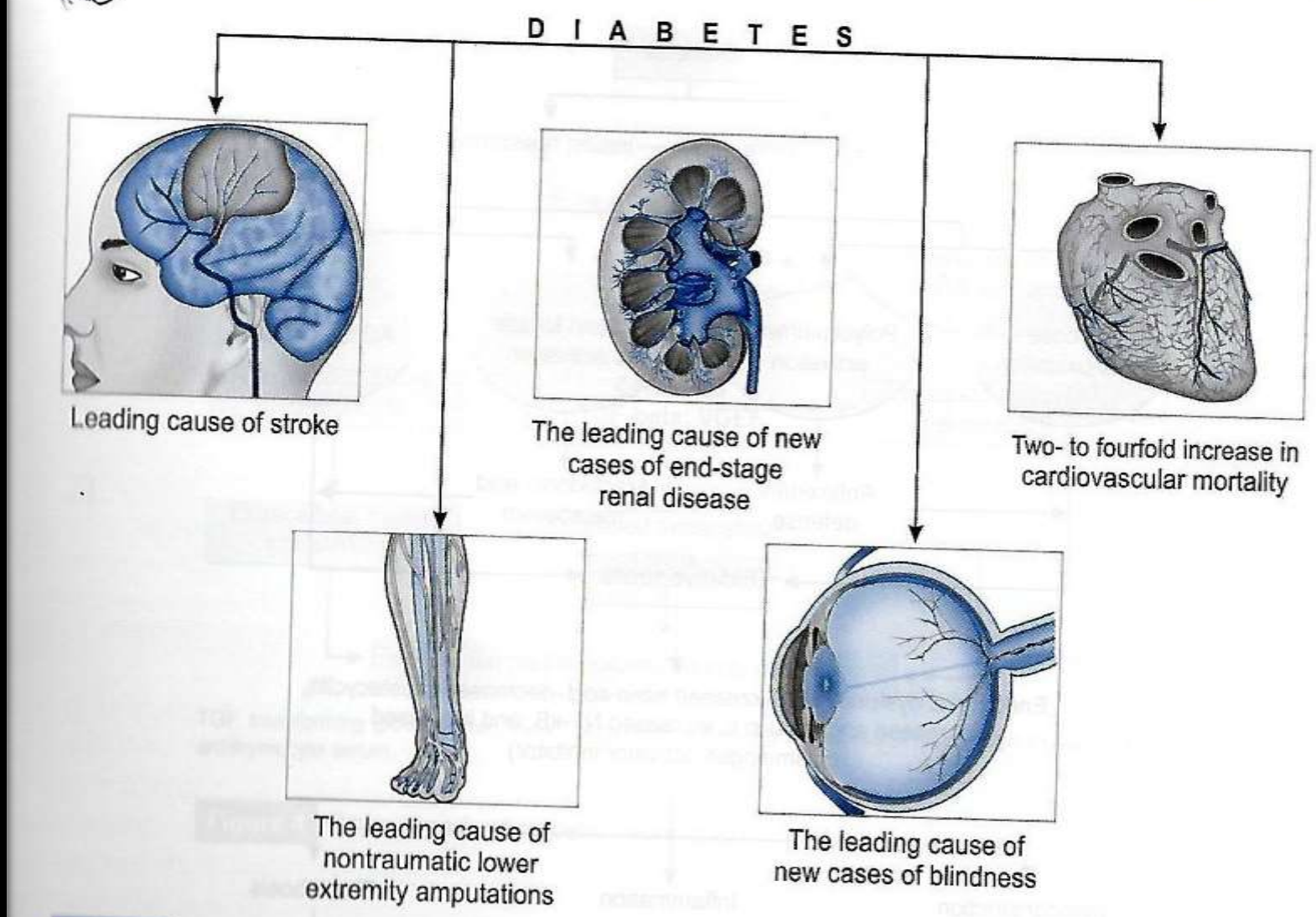


Figure 1 Chronic complications of diabetes.[5]

PREVENTING DIABETES COMPLICATIONS

Glycaemic control:

The evidence that improved glycaemic control decreases the risk of developing microvascular complications of diabetes was established by the Diabetes control and Complications Trial (DCCT) in type 1 diabetes, and the UK prospective Diabetes Study (UKPDS) in type 2 diabetes. The DCCT was a large study that lasted 9 years.

CONTROL OF OTHER RISK FACTORS

Randomized controlled trials have shown that aggressive management of blood pressure minimizes the microvascular and macrovascular complications of diabetes. Angiotension-converting enzyme (ACE) inhibitors are valueable in improving outcome in heart disease and in treating diabetic nephropathy. The management of dyslipidaemia with a stain limits macrovascular disease in people with diabetes. This often results in the necessary use of multiple medications, which exacerbates the problem of adherence to therapy by patients; it is not unusual for a patient to be taking two or more diabetes therapies, two or more blood pressure drugs and a stain.

SELF-CARE

- Patients should be educated to practice self-care. This allows the patient to assume responsibility and control of his / her own diabetes management. Self-care should include:

  - Blood glucose monitoring
  - Body weight monitoring
  - Foot-care
  - Personal hygiene
  - Healthy lifestyle/diet or physical activity
  - Identify targets for control
  - Stopping smoking

Prevention or delay of diabetes: Life style modification

- Research studies have found that lifestyle changes can prevent or delay the onset of type 2 diabetes among high-risk adults.
- These studies included people with IGT and other high-risk characteristics for developing diabetes.
- Lifestyle interventions included diet and moderate-intensity physical activity (such as walking for 2 1/2 hours each week).
- In the Diabetes Prevention Program, a large prevention study of people at high risk for diabetes, the development of diabetes was reduced 58% over 3 years.

Prevention or delay of diabetes: Medications

- Studies have shown that medications have been successful in preventing diabetes in some population groups.
- In the Diabetes Prevention Program, people treated with the drug metformin reduced their risk of developing diabetes by 31% over 3 years.
- Treatment with metformin was most effective among younger, heavier people (those 25-40 years of age who were 50 to 80 pounds overweight) and less effective among older people and people who were not as overweight.
- Similarly, in the STOP-NIDDM Trial, treatment of people with IGT with the drug acarbose reduced the risk of developing diabetes by 25% over 3 years.
- Other medication studies are ongoing. In addition to preventing progression from IGT to diabetes, both lifestyle changes and medication have also been shown to increase the probability of reverting from IGT to normal glucose tolerance.

Fig. 9.4 Acanthosis nigricans in nape of neck

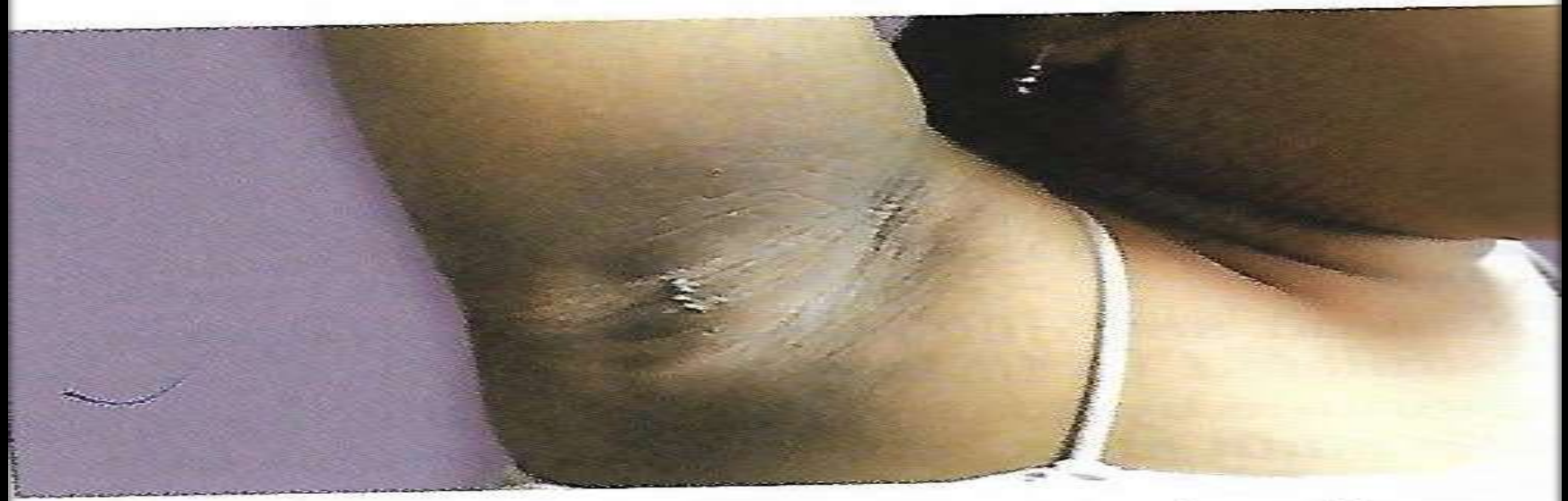


Fig. 9.5 Acanthosis nigricans in axilla

Fig. 9.6 Diabetic foot showing ulcers and gangrene

Fig. 9.7 Fungal infection of nails in DM

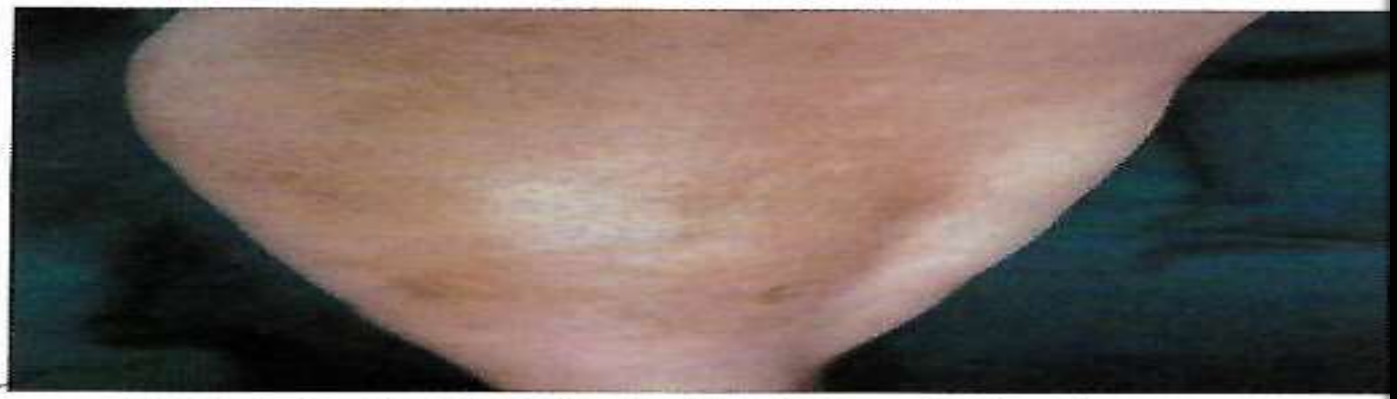


Fig. 9.8 Necrobiosis lipoidica diabeticorum

Figure 1 Neuropathic Plantar Ulcer

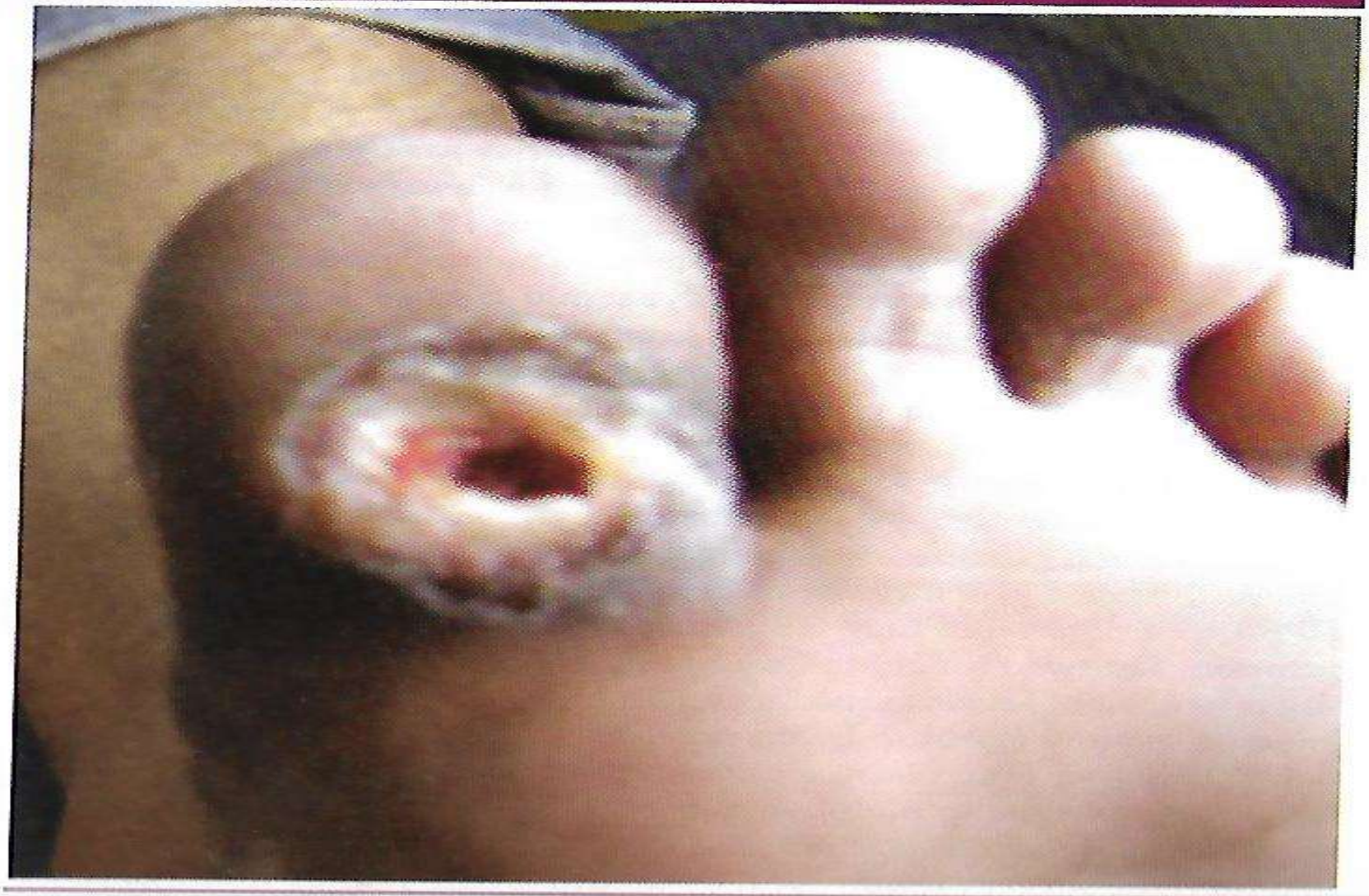
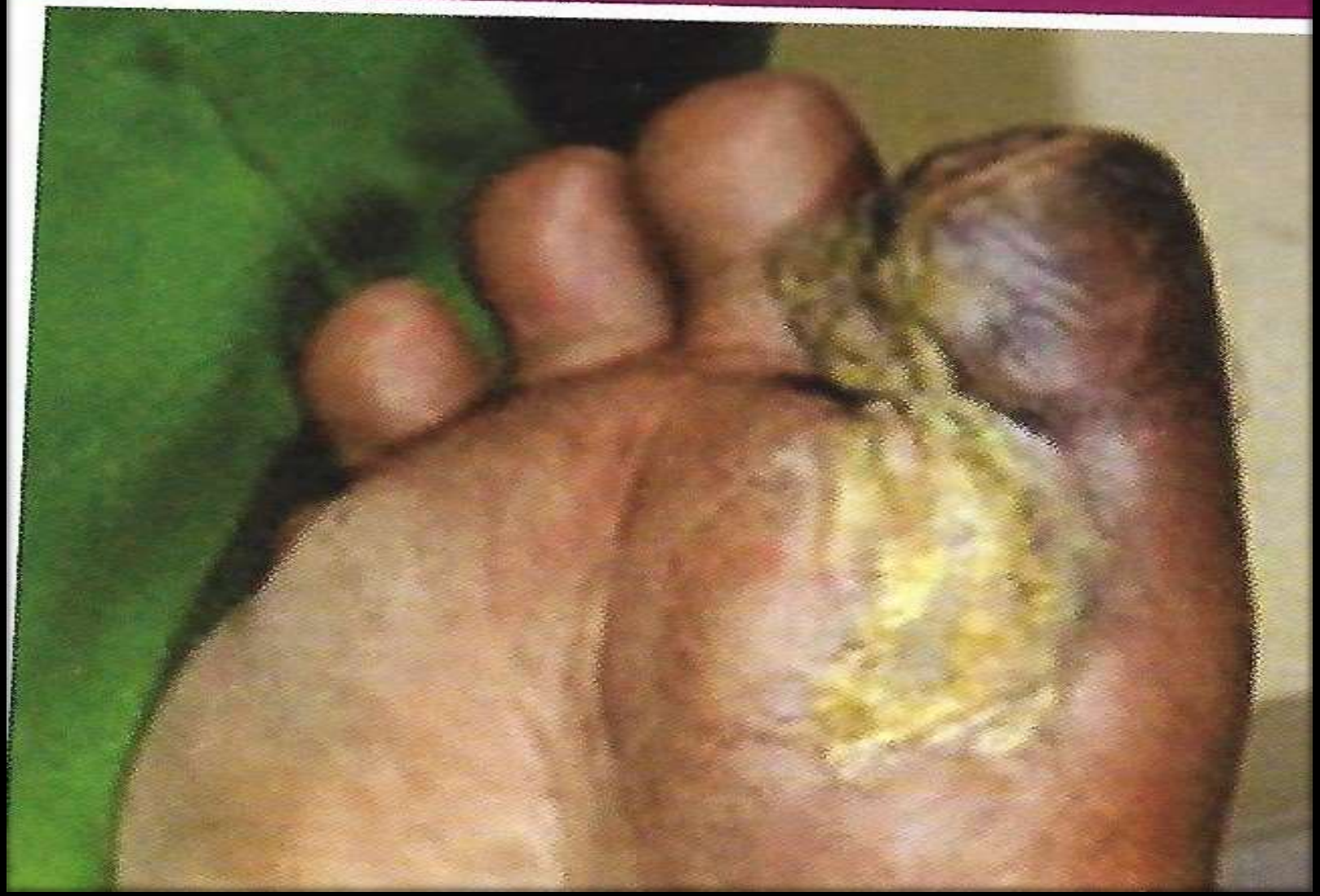


Figure 2 Neuroischaemic Foot



HOW TO REVIEW A PATIENT IN THE DIABETES CLINIC

LIFESTYLE ISSUES:

- ✓ GENERAL HEALTH
- ✓ WORK OR SCHOOL
- ✓ SMOCKING
- ✓ ALCOHOL INTAKE
- ✓ STRESS OR DEPRESSION
- ✓ SEXUAL HEALTH
- ✓ EXERCISE

BODY WEIGHT AND BMI-SHOULD BE MAINTAIN

BLOOD PRESSURE:

- ✓ Individualized target of 130-140/70-80 mmHg, depending on risk factors and presence of nephropathy.

URINALYSIS:

- ✓ Analyse fasting specimen for glucose, ketones, albumin (both macro- and micro-albuminuria)

BIOCHEMISTRY:

- ✓ Renal, liver and thyroid function
- ✓ Lipid profile and estimated 10-yr cardiovascular risk to guide need for lipid-lowering therapy.

GLYCAEMIC CONTROL:

- ✓ Glycated haemoglobin (HBA); individualized target between 48 and 58 mmol/mol (6.5 and 7.5%)
- ✓ Inspection of home blood glucose monitoring record (if carried out by patient)

HYPOGLYCAEMIC EPISODES:

- ✓ Number and cause of severe (requiring assistance for treatment) events and frequency of mild (self-treated) episodes and biochemical hypoglycemia.
- ✓ Awareness of hypoglycemia.
- ✓ Driving advice

TAKE HOME MESSAGE

- ✓ PREVENTION IS BETTER THAN CURE SO -MAINTAIN BODY WEIGHT AND DO REGULAR PHYSICAL EXERCISE.
- ✓ BE ADHRENT TO DIABETIC TREATMENT AND FOLLOW UP THOSE WHO ARE DIABETIC TO PREVENT DIABETIC COMPLICATION.

THANKS