Type II Diabetes

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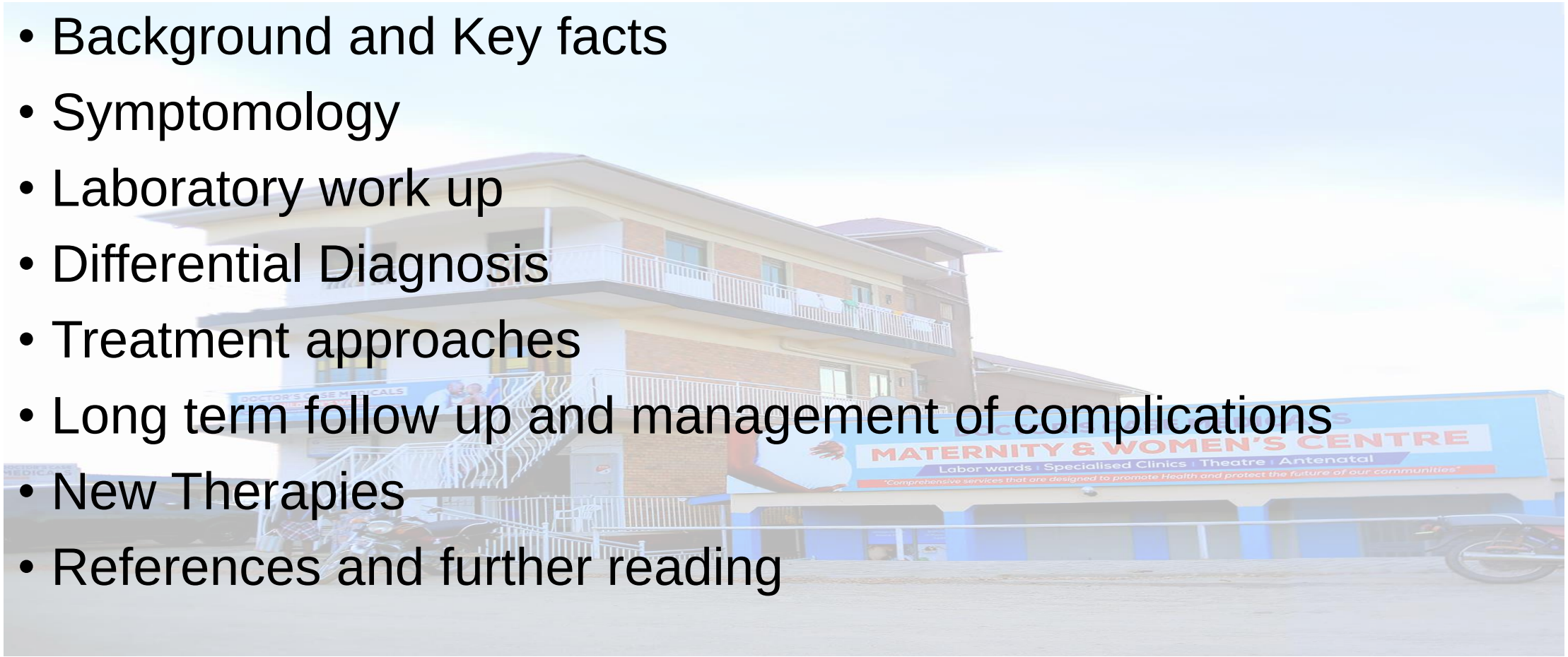
CME SERIES

T2DM-Presentation outline

- Background and Key facts
- Symptomology
- Laboratory work up
- Differential Diagnosis
- Treatment approaches
- Long term follow up and management of complications
- New Therapies
- References and further reading



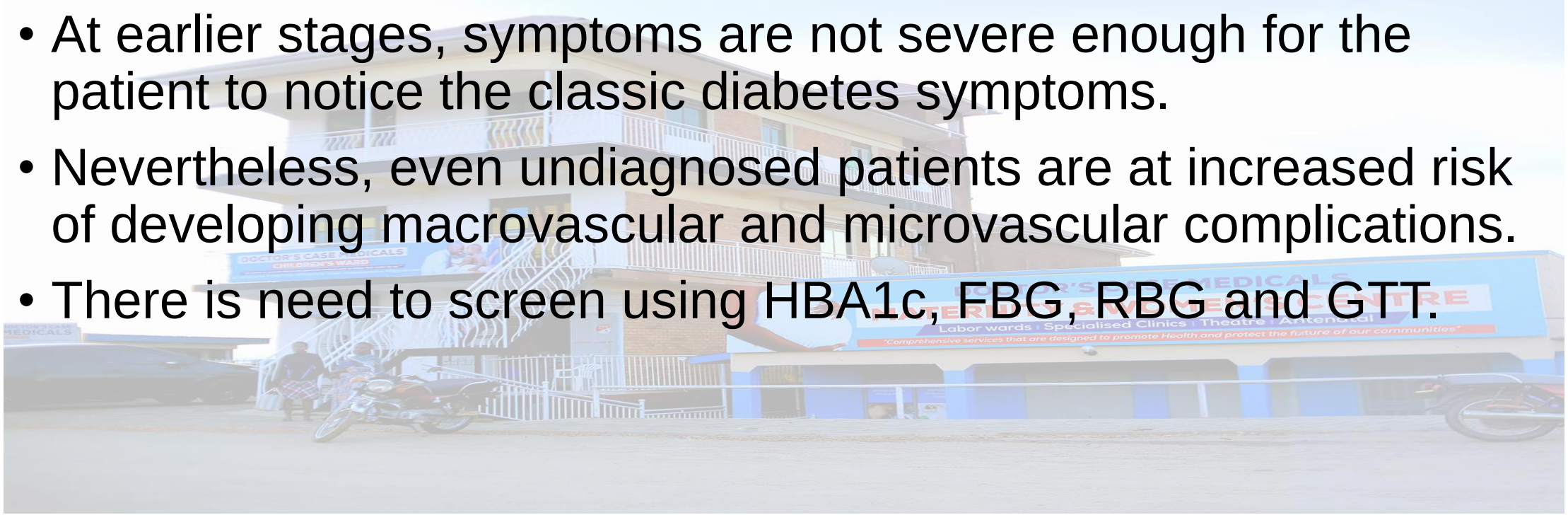
T2DM-overview

Type 2 diabetes, previously referred to as “noninsulin-dependent diabetes” or “adult-onset diabetes,” accounts for 90–95% of all diabetes.

- It consists of an array of metabolic dysfunctions
  - Characterized by hyperglycemia due to
  - Resistance to insulin action
  - Inadequate insulin secretion
  - And excessive or inappropriate glucagon secretion.
- At least initially, and sometime throughout their lifetime, these individuals may not need insulin treatment to survive.

Over view

- Type 2 diabetes frequently goes undiagnosed for many years because hyperglycemia develops gradually.
- At earlier stages, symptoms are not severe enough for the patient to notice the classic diabetes symptoms.
- Nevertheless, even undiagnosed patients are at increased risk of developing macrovascular and microvascular complications.
- There is need to screen using HBA1c, FBG, RBG and GTT.



How it begins – Pathophysiology

- Type 2 diabetes is characterized by a combination of peripheral insulin resistance and inadequate insulin secretion by pancreatic beta cells.

- Insulin resistance, which has been attributed to elevated levels of free fatty acids and pro-inflammatory cytokines in plasma, leads to decreased glucose transport into muscle cells, elevated hepatic glucose production, and increased breakdown of fat.

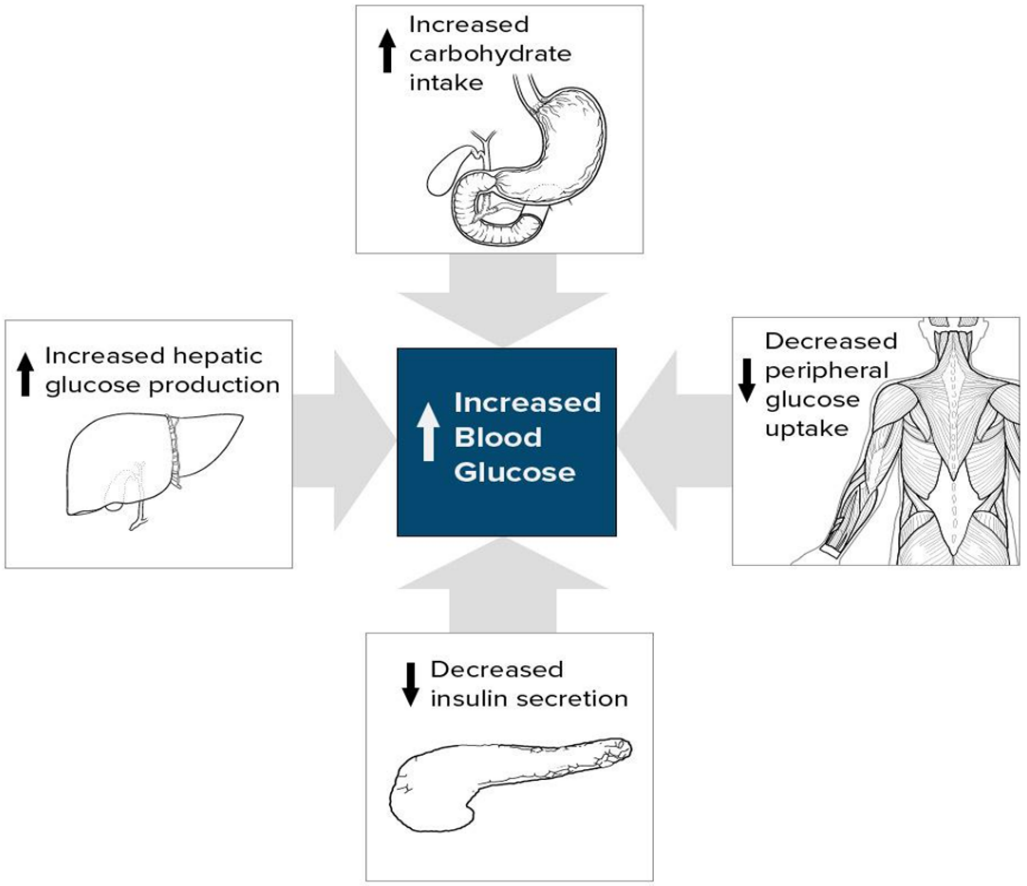
How it begins – Pathophysiology

- A role for excess glucagon: Type 2 diabetes is an islet para-crinopathy in which the reciprocal relationship between the glucagon-secreting alpha cell and the insulin-secreting beta cell is lost, leading to hyperglucagonemia and hence hyperglycemia.
- In normal physiology, Increase in blood glucose increases insulin secretion and reciprocally inhibits secretion of Glucagon. This relationship in lost in diabetic patience and hence there is a constant hepatic release of glycogen.

How it begins –Pathophysiology

- For type 2 diabetes mellitus to occur, both insulin resistance and inadequate insulin secretion must exist.
- overweight individuals have insulin resistance, but diabetes develops only in those who cannot increase insulin secretion to compensate for their insulin resistance.
- Their insulin concentrations may be high, yet inappropriately low for the level of glycaemia.
- In prolonged diabetes, pancreatic atrophy occurs and hence exocrine insulin deficiency occurs.

Dysfunction in T2DM



- Increased Carbohydrate intake
- Decreased Peripheral Glucose Uptake
- Decreased Insulin secretion
- Increased Hepatic Glucose Production

Risk factors

- Family History of Diabetes type II (first-degree relatives)
- Central Adiposity (Big berry)
- Women with History of Gestational diabetes
- Lack of physical activity- sedentary lifestyle
- Patients with Hypertension and Dyslipidemia (Low HDL and High TAGS)
- Medication: Corticosteroids, HIV medication, Thiazides and Atypical Antipsychotics

Clinical Presentation

- Classic symptoms:
  1. Polyuria: Increased frequency of urine
  2. polydipsia: Excessive Thirst
  3. Polyphagia: Excessive appetite
  4. and weight loss
- Blurred vision
- Lower-extremity paresthesia
- Yeast infections (e.g, balanitis in men or Vaginal candidiasis in Women)
- Dizziness and headaches

Diagnostic criteria

- A fasting plasma glucose (FPG) level of 126 mg/dL (7.0 mmol/L) or higher, or
- A 2-hour plasma glucose level of 200 mg/dL (11.1 mmol/L) or higher during a 75-g oral glucose tolerance test (OGTT), or

- A random plasma glucose of 200 mg/dL (11.1 mmol/L) or higher in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis
- HBA1C >6.5%

When to screen a symptomatic patients

- Sustained blood pressure >135/80 mm Hg-All HTN
- Overweight and 1 or more other risk factors for diabetes (e.g, first-degree relative with diabetes, BP >140/90 mm Hg, and HDL < 35 mg/dL and/or triglyceride level >250 mg/dL)
- ADA recommends screening at age 45 years in the absence of the above criteria
- Testing for pre-diabetes and/or type 2 diabetes should be considered in women planning pregnancy with overweight or obesity and/or who have one or more additional risk factor for diabetes

Other screening recommendations

- Risk based Diabetes screening in children should begin after onset of puberty or at 10 years of age whichever is earlier

Prediabetes state- criteria

- FPG 100 mg/dL (5.6 mmol/L) to 125 mg/dL (6.9 mmol/L) (IFG)
- 2-h PG during 75-g OGTT of 140 mg/dL (7.8 mmol/L) to 199 mg/dL (11.0 mmol/L) (IGT)
- A1C: 5.7–6.4% (39–47 mmol/mol)

Note that: Prediabetes is associated with obesity (especially abdominal or visceral obesity), dyslipidemia with high triglycerides and/or low HDL cholesterol, and hypertension.

Management

Goals of treatment:

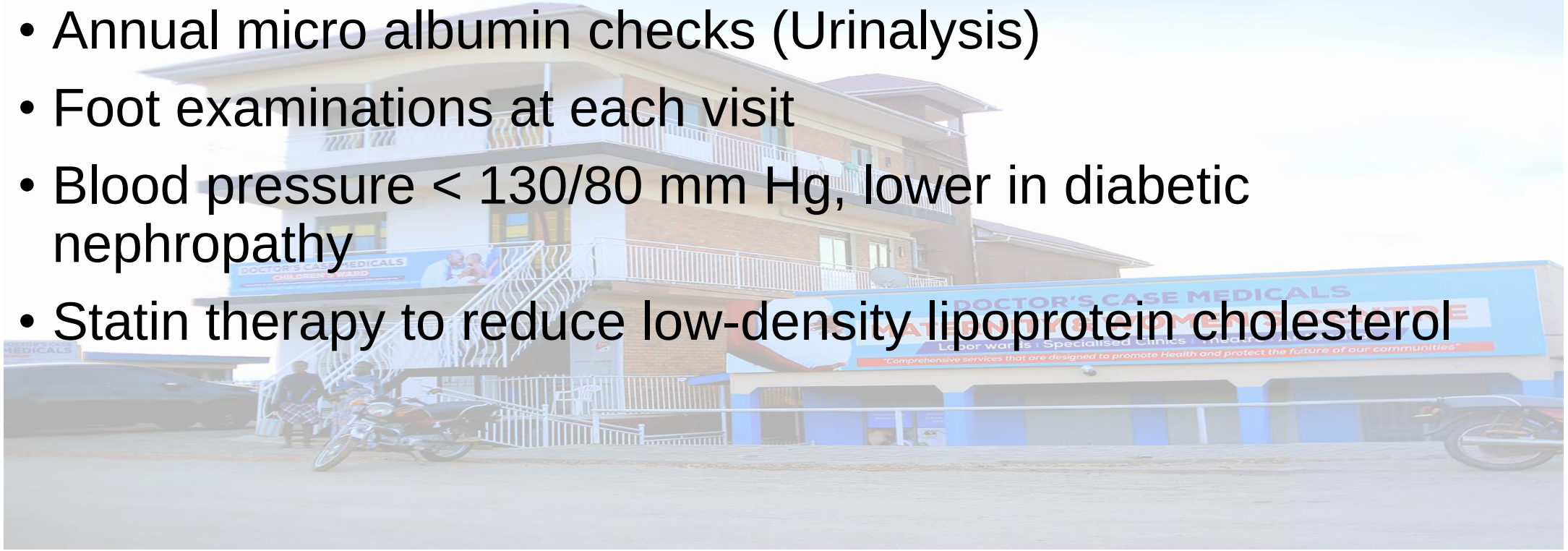
- Microvascular (i.e. eye and kidney disease) risk reduction through control of glycaemia and blood pressure.
- Macrovascular (i.e. coronary, cerebrovascular, peripheral vascular) risk reduction through control of lipids and hypertension, smoking cessation.
- Metabolic and neurologic risk reduction through control of glycaemia

Seven Key points in treatment of Diabetes:

- Individualized glycemic targets and glucose-lowering therapies.
- Diet, exercise, and education as the foundation of the treatment program.
- Use of metformin as the optimal first-line drug unless contraindicated.
- After metformin, the use of 1 or 2 additional oral or injectable agents, with a goal of minimizing adverse effects if possible
- Ultimately, insulin therapy alone or with other agents if needed to maintain blood glucose control
- Where possible, all treatment decisions should involve the patient, with a focus on patient preferences, needs, and values.
- A major focus on comprehensive cardiovascular risk reduction.

Approaches to reduce Diabetic complications

- HbA1c every 3-6 months
- Yearly dilated eye examinations
- Annual micro albumin checks (Urinalysis)
- Foot examinations at each visit
- Blood pressure < 130/80 mm Hg, lower in diabetic nephropathy
- Statin therapy to reduce low-density lipoprotein cholesterol



Complications –Acute

- Hyperosmolar Hyperglycemic state (HHS)
- Diabetic Ketoacidosis
- Hypoglycemia

HHS-Over view

- Life threatening Emergency
- Less common than DKA
- Higher mortality rate of 5-10%
- Hyperosmolar hyperglycemic non-ketotic coma (HHNC); however, the terminology was changed because coma is found in fewer than 20% of patients with HHS.
- Most commonly seen in patients with type 2 DM who have some concomitant illness that leads to reduced fluid intake
- Infection is usually the preceding illness but nonadherence to meds and Glucocorticoids can cause.

HHS-Recognition

- The primary symptom of hyperosmolar hyperglycemic state is altered consciousness varying from confusion or disorientation to coma
- usually as a result of extreme dehydration with or without prerenal azotemia, hyperglycemia, and hyper osmolality.
- In contrast to DKA, focal or generalized seizures and transient hemiplegia may occur
- Elevated blood sugars, Arterial PH>7.3, K+ usually normal but Na+ High or low depending on the level of fluid deficit.

Treatment HHS

- I.V 0.9% of Normal Saline. At a rate of 15 to 20 mL/kg/h, for the first few hours. If the corrected sodium is < 135 mEq/L (135 mmol/L), then isotonic saline should be continued at a rate of 250 to 500 mL/h.
- If the corrected sodium is normal or elevated, then 0.45% saline (half normal) should be used.
- Correct Hypokalemia First:
- I.V Insulin only if K+ >3.3mmol/l
- Dextrose should be added once the glucose level reaches 250 to 300 mg/dL (13.9 to 16.7 mmol/L).

Treatment HHS

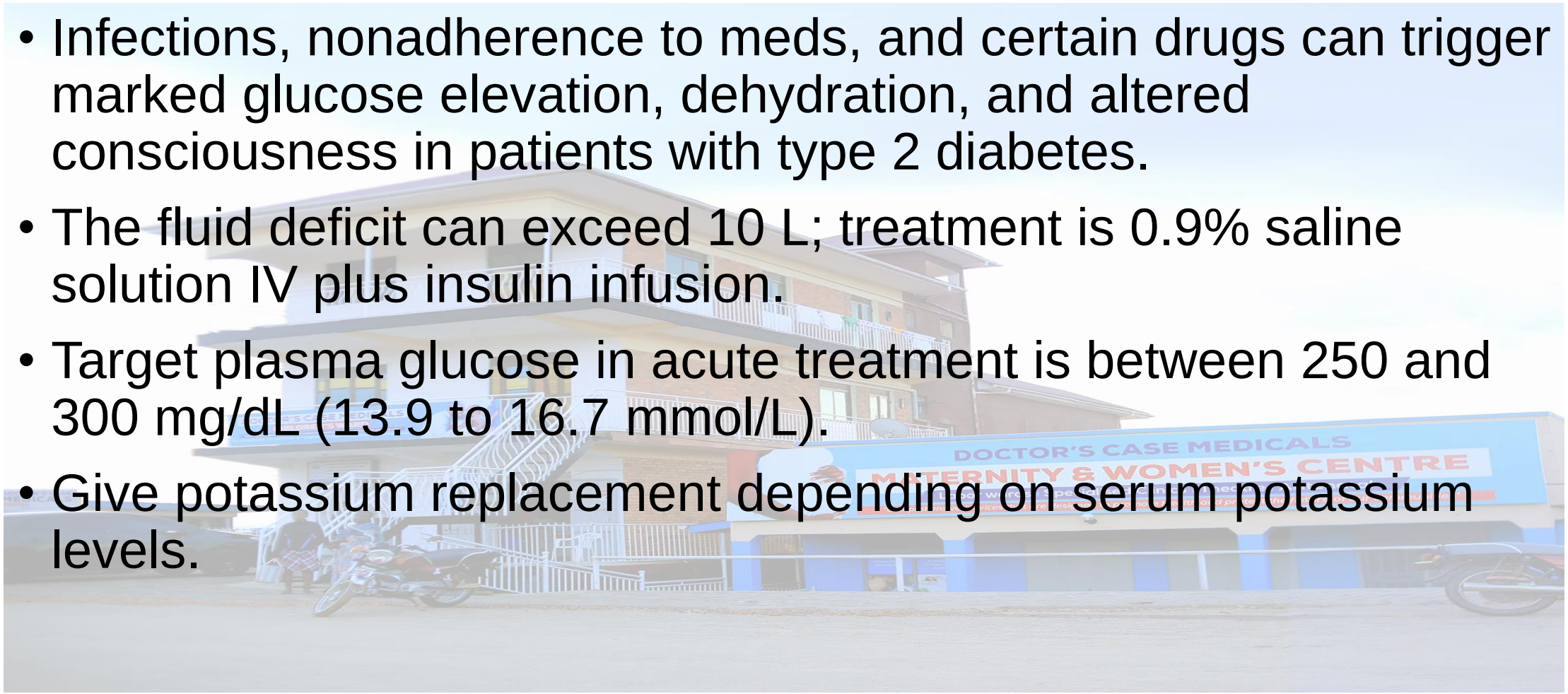
- Insulin is given at 0.1 unit/kg IV bolus followed by a 0.1 unit/kg/h infusion after the first liter of saline.
- Hydration alone can sometimes precipitously decrease plasma glucose, so insulin dose may need to be reduced.
- A too-quick reduction in osmolality can lead to cerebral edema.
- Insulin infusion should be reduced to basal levels (1 to 2 units/h) until rehydration is complete and the patient is able to eat.

Treatment HHS

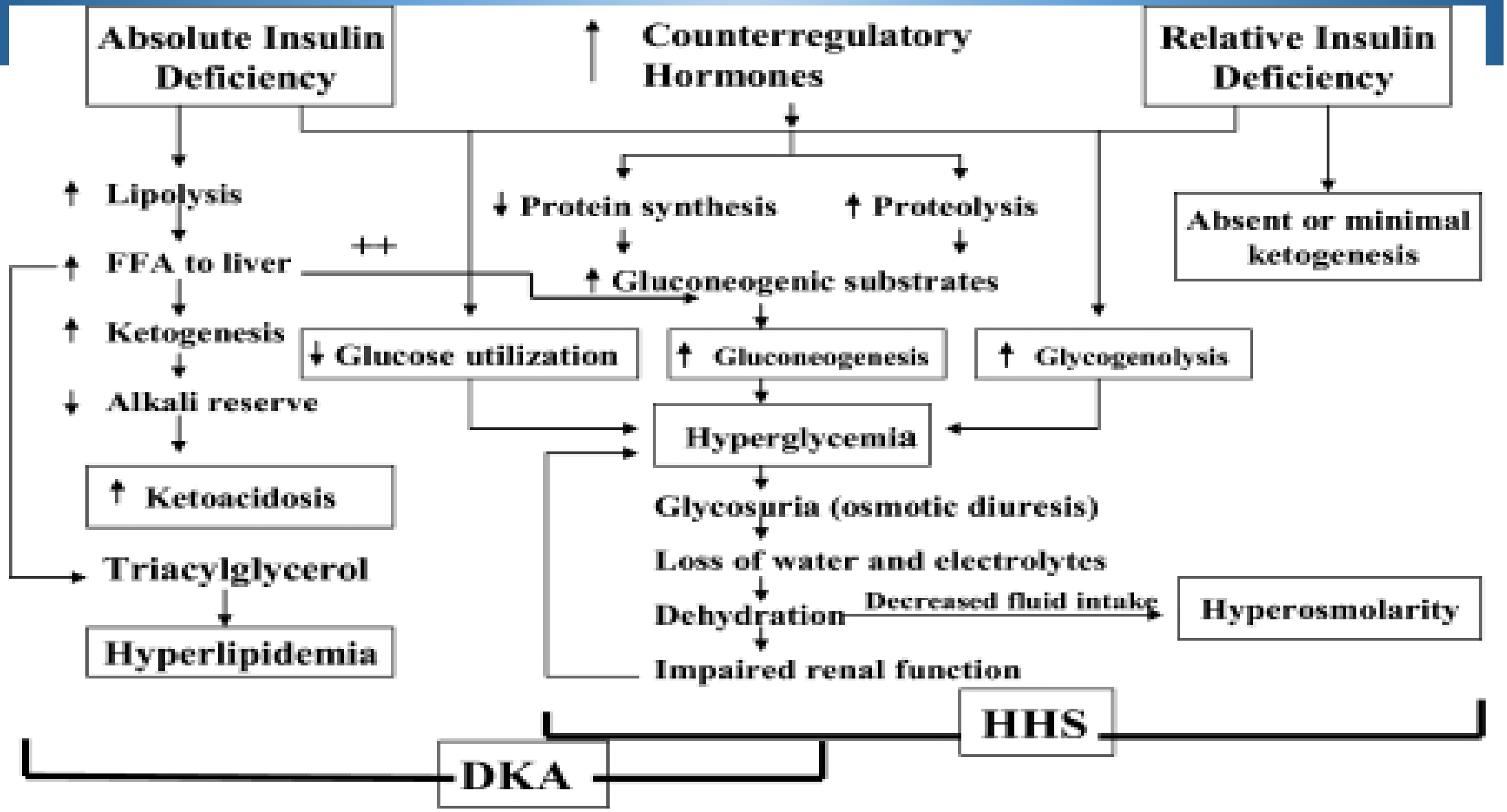
- Potassium replacement is similar to that in diabetic ketoacidosis:
- 40 mEq/h for serum potassium < 3.3 mEq/L (3.3 mmol/L);
- 20 to 30 mEq/h for serum potassium between 3.3 and 4.9 mEq/L (3.3 and 4.9 mmol/L);
- And none for serum potassium ≥ 5 mEq/L (5 mmol/L).
- Target plasma glucose is between 250 and 300 mg/dL (13.9 to 16.7 mmol/L) After recovery from the acute episode, patients are usually switched to adjusted doses of SC insulin

HHS: Key Points

- Infections, nonadherence to meds, and certain drugs can trigger marked glucose elevation, dehydration, and altered consciousness in patients with type 2 diabetes.
- The fluid deficit can exceed 10 L; treatment is 0.9% saline solution IV plus insulin infusion.
- Target plasma glucose in acute treatment is between 250 and 300 mg/dL (13.9 to 16.7 mmol/L).
- Give potassium replacement depending on serum potassium levels.



Diabetic Ketoacidosis



DKA Pathophysiology

- Reduced effective insulin concentrations
- Increases counter regulatory Hormones (catecholamines, cortisol, glucagon, and growth hormone) leads to Hyperglycemia and Ketosis
- Hyperglycemia develops as a result of three processes: increased gluconeogenesis, accelerated glycogenolysis, and impaired glucose utilization by peripheral tissues.

DKA Pathophysiology

- Hyperglycemia is magnified by transient insulin resistance due to the hormone imbalance itself as well as the elevated free fatty acid concentrations.
- The combination of insulin deficiency and increased counter regulatory hormones in DKA also leads to the release of free fatty acids into the circulation from adipose tissue (lipolysis) and to unrestrained hepatic fatty acid oxidation in the liver to ketone bodies (β-hydroxybutyrate and acetoacetate) with resulting ketonemia and metabolic acidosis.

DKA Precipitating Factors

- Infections
- Discontinuation of or Inadequate insulin therapy
- Acute pancreatitis
- Myocardial infarction
- Drugs that affect carbohydrate metabolism, such as corticosteroids, thiazides, sympathomimetic agents, and Pentamidine, may precipitate the development of HHS or DKA

DKA Diagnosis and Labs:

The initial laboratory evaluation of patients include:

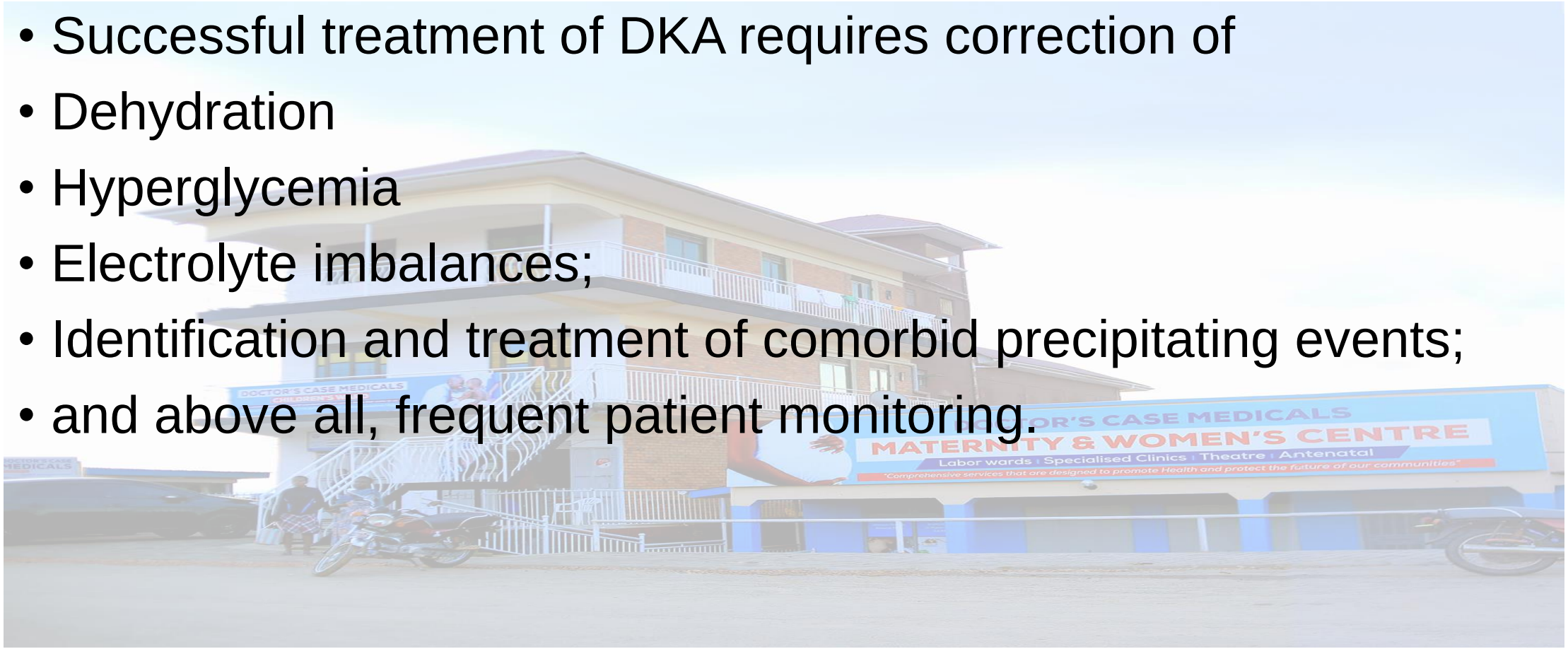
- Plasma glucose
- Blood Urea Nitrogen
- Creatinine
- Electrolytes (with calculated anion gap),
- Osmolality,
- Serum and urinary ketones, and urinalysis, as well as initial arterial blood gases and a complete blood count with a differential

DKA Diagnostic Lab Findings

Parameter	Mild (RDG >250mg/dl)	Moderate (RDG >250mg/dl)	Severe (RBG >250mg/dl)
Arterial PH	7.25-7.30	7.00 to <7.24	<7.00
Serum HCO3	15-18	10 to 15	<10
Urine Ketones	Positive	Positive	Positive
Serum Ketones	Positive	Positive	Positive
Effective Serum Osmolarity	Variable	Variable	Variable
Anion Gap	>10	>12	>12
Mental Status	Alert	Alert/ Drowsy	Stupor/Coma

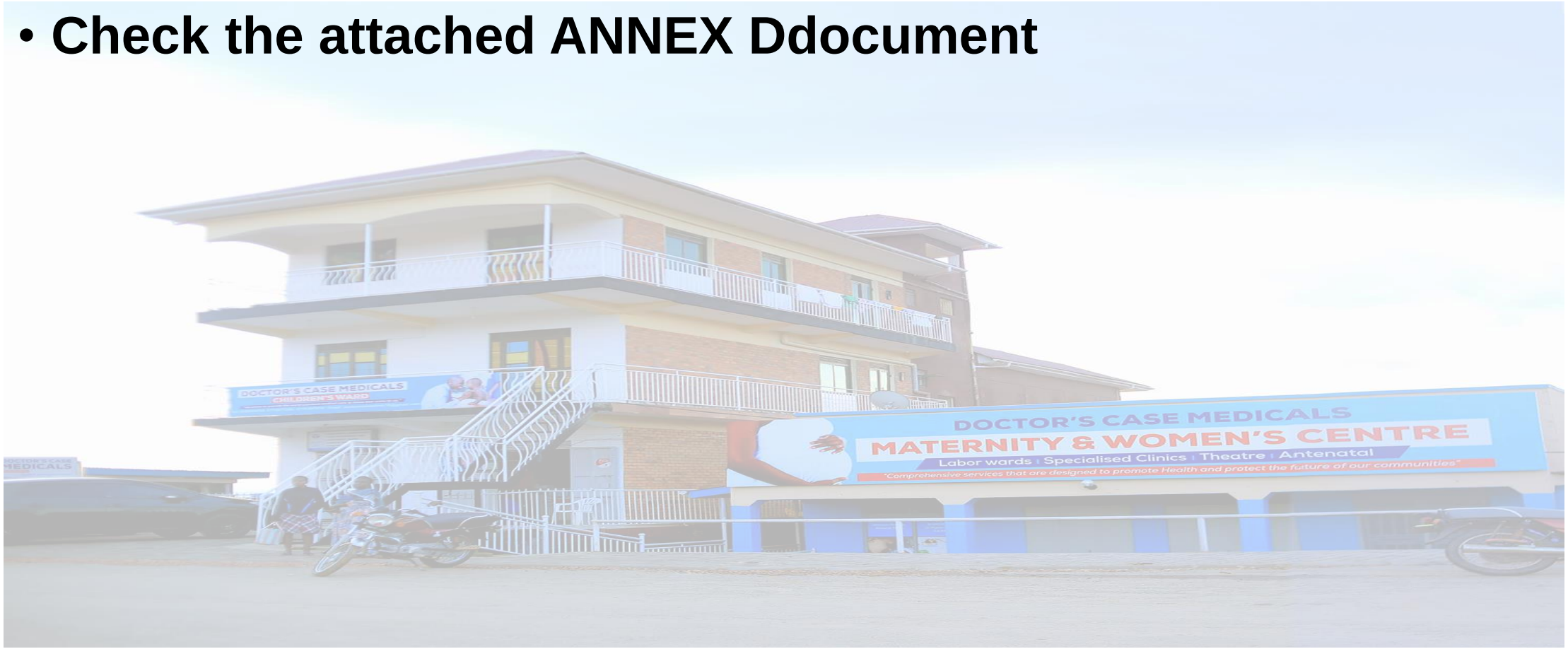
DKA Treatment

- Successful treatment of DKA requires correction of
- Dehydration
- Hyperglycemia
- Electrolyte imbalances;
- Identification and treatment of comorbid precipitating events;
- and above all, frequent patient monitoring.



Protocol For DKA

- **Check the attached ANNEX Ddocument**



Insulin in DM

- Insulin is the primary treatment for all the patients with DM1.
- In T2DM patients, insulin is considered alone or in combination with oral agents when HbA1c is ≥ 7.5% (≥ 58 mmol/mol) after >3months of treatment ; and is essential for treatment in those with HbA1c ≥ 10% (≥ 86 mmol/mol).
- Ensure diet, physical activity, and other antihyperglycemic agents have been optimally used.

Types

- Short Acting (Referred to as Regular or Neutral insulin): onset of action of Regular insulin is about 30–60 min, peak effect is in 2–4 h, and duration of action is of 4–8 h
- Rapid acting: Aspart
- **Basal (Long Acting) insulin**: E.g, Neutral protamine Hagedorn (NPH), duration of action can be up to 24 hours.
- **Pre-mixed**: E.g Mixterd has 70/30 of Basal NPH and Regular respectively. Premixed insulin address both PPG and FBG.

Dosing

- In DM1, Doses range from 0.4units/kg/day to 1.0 units/kg/day. For children initial dose is 1.0Units/kg/day.
- DM2, Initial dose of 10Units per day or 0.2 to 0.5 units/kg/day. Adjusted by 10-15% weekly until the HBA1C and BG goals are achieved.
- Total daily dose should be divided into 2/3AM and 1/3Pm.
- Fast acting insulin can be used alone if combined with a GLP1-RA
- Use of metformin and Insulin Mixture, reduces risk of excessive insulin use and over weight.
- Insulin in DM2 can be a primary treatment in patients who are underweight.

Complication-Long term

- Microvascular complications:
  - Retinopathy
  - Nephropathy, and possibly neuropathic disease.
- Macrovascular complications:
  - Coronary artery
  - Peripheral vascular disease.
  - Cerebral vascular Accident.
- Diabetic neuropathy affects autonomic and peripheral nerves.

Long term Monitoring

- Regular outpatient follow-up is key in managing diabetic complications successfully.
- Regular annual urinalysis is recommended for screening for microalbuminuria
- Ensuring optimal glucose control, optimizing blood pressure, and screening for other associated complications of diabetes (e.g, retinopathy, diabetic foot, cardiovascular disease) are also crucial.
- Therefore, Patient must have a harmonized routine monitoring schedule.

Long term Monitoring of DM Patients

Annual

- Urinalysis
- Funduscopic exam
- Renal Function
- Lipid profile (TAGs and HDL, followed by CVS Risk Score)

Half Annual

- HBA1C : Can be done 1-6 months depending of stability. (Target is 6.5-7.5%)

Every Visit

- Blood pressure
- Blood sugar
- Foot examination

New Therapies Available.

Vildagliptin 50mg

- Is a dipeptidyl peptidase-4 (DPP-4) inhibitor.
- The mechanism of DPP-4 inhibitors is to increase **incretin** levels (GLP), which inhibit glucagon release, which in turn increases insulin secretion, decreases gastric emptying, and decreases blood glucose levels.
- Less risk of weight gain and Hypoglycemia
- May cause angioedema if uses with ACEI due to inhibition of substance P.
- Combined with Metformin and marketed as **GalvasMe**t

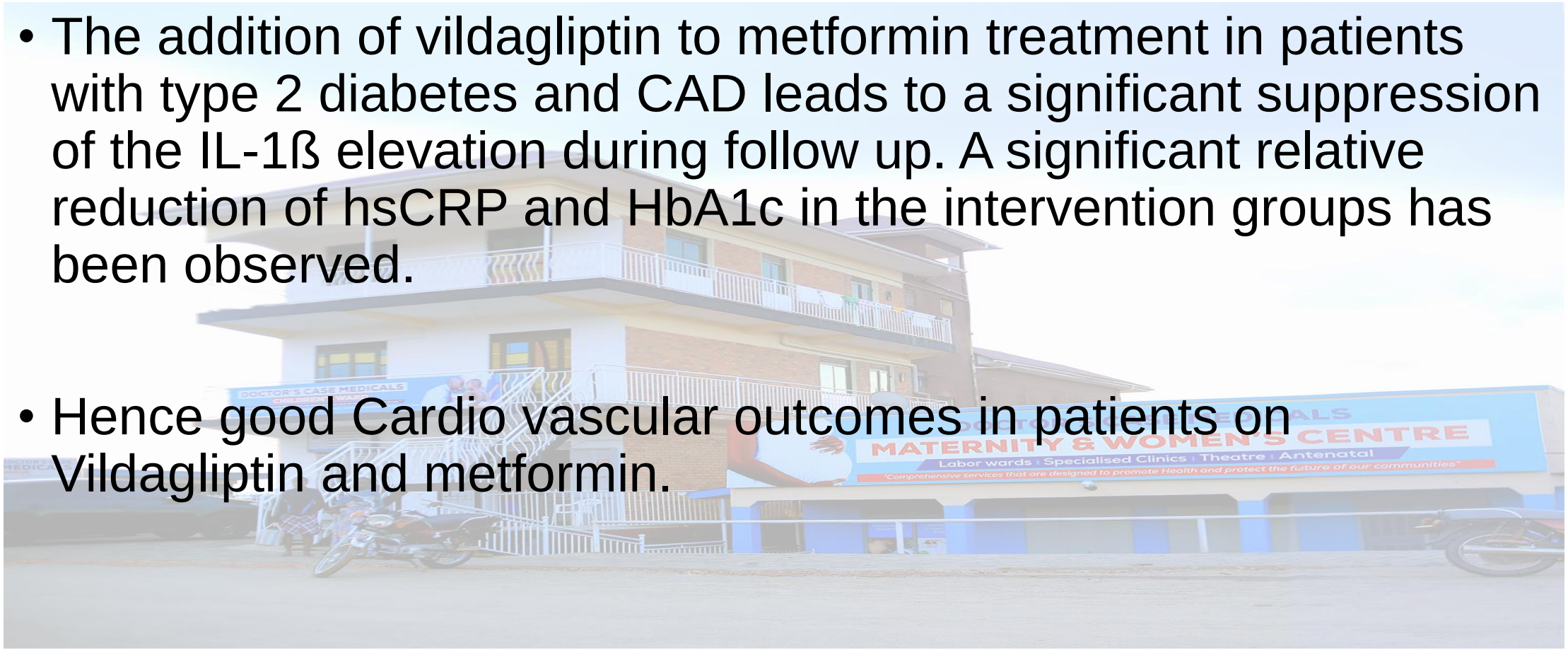
New therapies

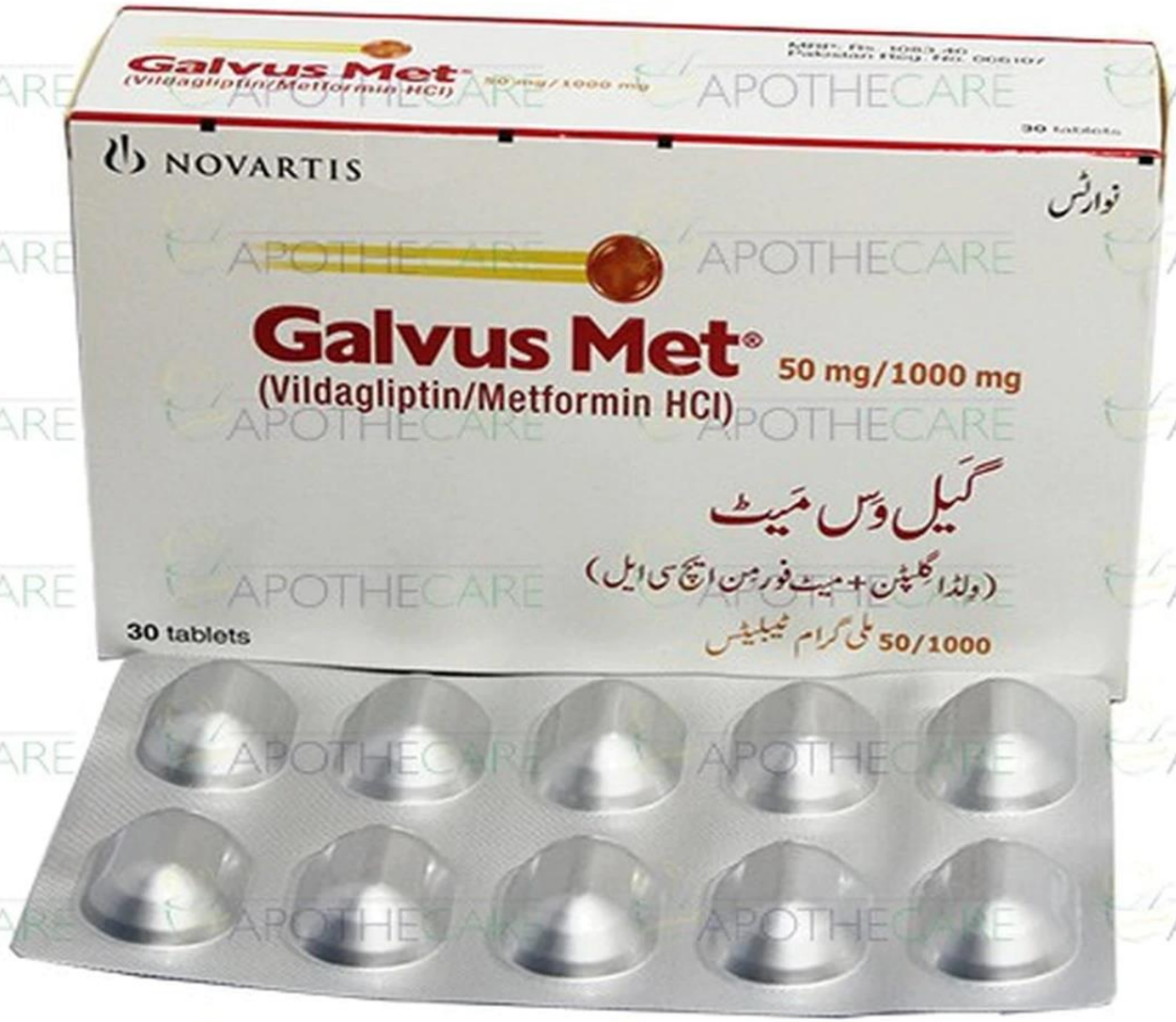
- Saxagliptin/metformin: Is marketed as Kombiglyze XR.
- Available as 2.5/1000mg or 5/1000mg

New Therapies Available.

- The addition of vildagliptin to metformin treatment in patients with type 2 diabetes and CAD leads to a significant suppression of the IL-1ß elevation during follow up. A significant relative reduction of hsCRP and HbA1c in the intervention groups has been observed.

- Hence good Cardio vascular outcomes in patients on Vildagliptin and metformin.




Galvus Met
(Vildagliptin/Metformin HCl)
50 mg/1000 mg
30 tablets
NOVARTIS
نوارٹس
Galvus Met®
50 mg/1000 mg
(Vildagliptin/Metformin HCl)
گیل وس میٹ
(ولڈا گلپٹن + میٹ فورمن ایچ سی ایل)
50/1000 ملی گرام ٹیبلیٹس
30 tablets

New Therapies

Dapagliflozin 5 or 10mg: SGLT2 inhibitor

- Dapagliflozin is an orally administered, potent and selective inhibitor of SGLT2 that significantly reduces blood glucose levels and improves glycaemic variability.
- Sodium-glucose co-transporter 2 (SGLT2) is a glucose transporter expressed in the proximal renal tubules and is mainly responsible for glucose reabsorption from urine.

- Accordingly, inhibitors of SGLT2 have been developed to enhance urinary glucose excretion

New Therapies

- Dapagliflozin is approved for the treatment of T2DM and has been shown to improve glycaemic control, stabilize insulin dosages and reduce body weight with low rates of hypoglycaemia.
- Because its activity is independed of insulin, Dapagliflozin has been used in T1DM successfully to prevent episodes fo DKA and achieving good glycemic control.
- In the Japanese DEPICT-5 study of 151 patients on 5mg of dapagliflozin for 52 weeks, results showed long-term safety and tolerability of dapagliflozin added to insulin with improved general clinical outcome.

AstraZeneca

Summery

- Diabetes develops over time, sometimes with obvious warning
- DM treatment must be individualized
- Maintenance insulin 0.5-1IU/Kg/day and for hyperglycemia 1IU/kg/day
- Long term clinical outcomes depend on monitoring, detection, prevention and treatment of Complications.
- Its important to detect and treat DKA and HHS correctly to reduce mortality.
- New therapies are changing the way diabetes is managed.


DOCTOR'S CASE MEDICALS
MATERNITY & WOMEN'S CENTRE
Labor wards | Specialised Clinics | Theatre | Antenatal
"Comprehensive services that are designed to promote Health and protect the future of our communities"

Thank you

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