MEDICAL UNIVERSITY – PLEVEN
FACULTY OF MEDICINE - DISTANCE LEARNING CENTRE
DIVISION OF ENDOCRINOLOGY AND METABOLISM

Lecture №5, №6

DIABETHES MELLITUS

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Physiology

Insulin is produced by beta cells.

Insulin binds to receptors on the cells causing receptors specific to glucose to open allowing glucose in to the cell. It lowers the blood glucose level in the blood.

Three main destinations; muscle, fat and liver. Insulin helps the tissues store glucose as an energy source.

Classification of diabetes

Type 1 diabetes

Type 2 diabetes

Gestational diabetes mellitus.

Other specific types: include a wide variety of relatively uncommon conditions, primarily specific genetically defined forms of diabetes or diabetes associated with other diseases or drug use.

Ethiology

1. Genetic predisposition

Type 1 diabetes is a polygenic disease, meaning many different genes contribute to its onset.

Depending on locus or combination of loci, it can be dominant, recessive, or somewhere in between.

2. Viral infection

The Coxsackie virus family or rubella is implicated, although the evidence is inconclusive.

3. Diet

Autoimmune response is influenced by antibodies against cow ‘s milk proteins.

Pathophysiology

Autoimmune response towards B-cells.

1. Autoimmune attack by autoantibodies against own B-cells or insulin.

2. Absolute insulin deficiency

Signs and symptoms

The classical symptoms of T1DM include: **polyuria,**

polydipsia (increased thirst),

Xerostomia (dry mouth), poliphagya (increased hunger),

fatigue, and weight loss.

Type 1 diabetics are often first diagnosed with **diabetic ketoacidosis**.

Diagnosis

Diabetes is diagnosed on the basis of history (polyuria, polydipsia and unexplained weight loss) PLUS

1. Fasting plasma glucose level at or above **7.0 mmol/L** (126 mg/dL) OR whole blood >= 6.1 mmol/l.
2. Plasma glucose at or above **11.1 mmol/L** (200 mg/dL) two hours after a 75 g oral glucose load as in a OGTT.
3. Symptoms of hyperglycemia and casual plasma glucose at or above **11.1 mmol/L** (200 mg/dL).
4. Glycated haemoglobin (hemoglobin A1C) at or above **6.5%**.

Treatment of diabetes

People with type 1 diabetes **always need to use insulin.**

The goal is lowering blood glucose (BG) to the near normal range, approximately **4.4–7.8 mmol/L.**

The ultimate goal of normalizing BG is to avoid **long-term complications that affect the kidney, the eyes, the nervous system, and the cardiovascular system**.

Insulin treatment

1. Basal–Bolus regimen

There is combining a long-acting agent that is used once or twice daily and provides basal insulin needs and a rapid-acting agent for post-prandial coverage used with meals.

Blood glucose self-monitoring is necessary.

Complication of insulin's treatment

Insulin treatment can lead to low BG (hypoglycemia), i.e. BG less than 3.9 mmol/l.

Diagnosis of the hypoglicaemia

Rapid diagnosis and treatment is essential in any patient with suspected hypoglycemia, regardless of the cause.

The Whipple triad is characteristically present:

1. **documentation of low blood sugar,**
2. **presence of symptoms, and**
3. **reversal of these symptoms when the blood glucose level is restored to normal.**

Physical findings, however, are nonspecific in hypoglycemia and are generally **related to the central and autonomic nervous systems**.

Management
Pharmacotherapy

1. **Glucose solution 40% , administered intravenously until patient's recovering in severe hypoglycemia,**
2. **or glucose as oral supplements (eg, dextrose solution) in mild hypoglycemia.**

2.Glucose-elevating agents (eg, 1 mg dose of glucagon , administered by subcutaneous or intramuscular injection).

The most important of therapy for hypoglycemia is glucose.

Other medications may be administered based on the underlying cause or the accompanying symptoms.

Complications of T1DM

1. **Acute complications**

Hypoglycemic coma,

Ketoacidosis

2. Chronic microvascular complications:

Diabetic nephropathy,

Rethinopathy,

Polyneuropathy

Ketoacidosis

The most common early symptoms of DKA are : polydipsia and polyuria, **smell of acetone** malaise, generalized weakness and

Nausea and vomiting; may be associated with diffuse abdominal pain, decreased appetite, and anorexia

Rapid weight loss in patients newly diagnosed with type 1 diabetes

Management

Treatment of ketoacidosis should aim for the following:

Fluid resuscitation

Reversal of the acidosis and ketosis

Reduction in the plasma glucose concentration to normal

Replenishment of electrolyte and volume losses

Identification the underlying cause

Management Conclusion

Correction of fluid loss with intravenous fluids

Correction of hyperglycemia with rapid acting insulin

Correction of electrolyte disturbances, particularly potassium loss

Correction of acid-base balance

Treatment of concurrent infection, if present

Treatment of T2DM
1. Insulin Sensitizers

1.1.Biguanides (Metformin)

Its primary mechanism of action is suppression of hepatic glucose output, but it also enhances insulin sensitivity of muscle and fat.

The starting dose is 500 mg per day. The maximum dose is 3000 mg per day.

The major benefits of metformin are that it usually does not lead to hypoglycemia when used as monotherapy.

The use of metformin is contraindicated in patients with a serum creatinine ≥1.5 mg/dL

1. Insulin Sensitizers
1.2Thiazolidinediones

Thiazolidinediones (TZDs) are agonists of peroxisome proliferator-activated receptor gamma (PPARγ) and they primarily enhance sensitivity of muscle and fat, and mildly of the liver, to exogenous and endogenous insulin. **TZD**s lower fasting and postprandial blood glucose levels.

The only TZD medication FDA approved for use in the U.S. is pioglitazone.

2. Insulin Secretagogues

Insulin secretagogues stimulate secretion of insulin from the pancreas, thereby decreasing hepatic glucose production and enhancing glucose uptake by muscles and fat.

Sulfonylureas reduce fasting and postprandial glucose levels.

Insulin Secretagogues

2. 1. Sulfonylureas

The main adverse effects include weight gain and hypoglycemia. Second-generation, sulfonylureas (glipizide and glimepiride) have less risk of hypoglycemia than older ones (glibenclamide) due to a somewhat glucose-dependent mechanism of action.

The benefits include a 25% reduction in microvascular complications with or without insulin.

Insulin Secretagogues

2.2 Glinides

Glinides work in a manner similar to that of the sulfonylureas; however, they have a more-rapid onset of action and a shorter duration of action,.

Glinides are associated with a lower risk of hypoglycemia than are sulfonylureas.

Doses are taken immediately before meals.

3. Incretin based therapies

Exenatide

Exenatide is a synthetic form of exendin-4, a hormone found in the saliva of the Gila monster. Exenatide mimics glucagon-like peptide type-1 (GLP-1). GLP-1 is produced in the small intestine.

It stimulates insulin secretion, and inhibits glucagon secretion and hepatic glucose production in a glucose-dependent manner.

Exenatide

It also delays gastric emptying and suppresses appetite through central pathways.

It primarily decreases **postprandial blood** glucose levels; however, a moderate reduction in fasting blood glucose levels can also be seen.

Due to its delaying effects on gastric emptying, the major side effects are gastrointestinal complaints such as nausea, vomiting, and diarrhea.

Liraglutide

Liraglutide is another GLP-1 analog that is derived from the native human GLP-1 and maintains 97% homology with it.

In a head-to-head study with exenatide liraglutide showed slightly better glycemic control with the same rate of hypoglycemia and slightly more weight loss.

Liraglutide

Liraglutide is taken once a day, at any time of the day; there is no need to take it with meals. Side effects include nausea, vomiting, and diarrhea but only a small percentage of patients stopped therapy due to side effects.

The initial dose is 0.6 mg/day which is increased to 1.2 mg/day after 1 week.

This dose is considered therapeutic but can be increased to 1.8 mg/day after another week if glycemic goals are not achieved.

4. Dipeptidyl Peptidase 4 Inhibitors

Dipeptidyl peptidase 4 (DPP 4) is a cell membrane protein that rapidly degrades GLP-1 and glucose-dependent insulinotropic polypeptide (GIP).

Suppression of DPP 4 leads to higher levels of insulin secretion and suppression of glucagon secretion in a glucose-dependent manner.

Dipeptidyl Peptidase 4 Inhibitors

DPP 4 inhibitors act primarily on **postprandial blood glucose levels**, but reductions in fasting glycemia are also seen.

Benefits include that it is weight neutral and does not cause hypoglycemia when used as monotherapy or in combination with metformin or TZDs.

Insulin

Patients with T2DM often require insulin, which can be combined with oral hypoglycemic agents.

Regimens include:

only basal

twice-daily premixed insulin,

basal – bolus insulin therapy.

ADA recommendation -

Monotherapy

Initiate monotherapy when HbA_{1c} levels are 6% to 7%

Options include:

Metformin

Thiazolidinediones

Secretagogues

Dipeptidyl-peptidase 4 inhibitors

Alpha-glucosidase inhibitors

SGLT2 inhibitors

Monitor and titrate medication for 2 to 3 months

Consider combination therapy if glycemic goals are met at the end of 2 to 3 months, if HbA_{1c} **levels are more than 7%**

Chronic Complications of Diabetes Mellitus

Chronic complications can be divided into **vascular and nonvascular** complications.

The vascular complications of DM are further subdivided into **micro vascular** (retinopathy, neuropathy, and nephropathy) and **macro vascular** complications (coronary artery disease, peripheral arterial disease, cerebrovascular disease).

Chronic Complications of Diabetes Mellitus

The **microvascular** complications (retinopathy, neuropathy, and nephropathy) are typical for T1DM

The **macrovascular** complications coronary artery disease, peripheral arterial disease, cerebrovascular disease are more typical for T2DM .