

DIABETES MELLITUS

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DOI: https://dx.doi.org/10.5281/zenodo.10836047



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www.iksadyayinevi.com

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ISBN: 978-625-367-650-6

Cover Design: İbrahim KAYA January / 2024 Ankara / Türkiye Size = 16x24 cm

PREFACE

This book was written to eliminate the lack of resources and course materials in pharmacology courses taught in associate and undergraduate programs. In this book, "Diabetus Mellitus" disease is explained. What is explained here can be used as a resource in associate and undergraduate programs. We hope this book will be a resource for teachers and students.

Assoc. Prof. Dr. İbrahim AKTAŞ

THANKS

We would also like to thank the board of directors and staff of Iksad Publishing House, who encouraged us to write the book and also contributed to the preparation of the book.

Assoc. Prof. Dr. İbrahim AKTAŞ

Ankara-2024

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I. DIABETES MLLITUS

Introduction

Pancreas is the organ that produces internal and external secretions adjacent to the duodenum. External secretion contains enzymes that are important for the digestive system (such as trypsin, lipase, carboxy peptidase, amylase, chemotrypsin and phosphorylase). In the internal secretion, there are hormones that are extremely important for sugar metabolism (such as insulin and glucagon) and local hormones that are relatively less important (somatostatin and pancreatic polypeptide) (Kaya et al., 2013). Diabetes Mellitus (DM) is a metabolic disorder characterized by a chronic increase in blood glucose level, resulting from impaired insulin production or the development of resistance in tissues to the effect of this hormone. Nutrients are broken down in the body to be converted into sugar, which is a source of energy. This resulting sugar passes into the blood and is transferred to the cells via insulin (Gur & Aktas, 2021; Yıldız, 2008). If blood sugar cannot be controlled, acute complications such as ketoacidosis, hyperglycemia or coma occur. The main complications of DM are; heart failure, hypertension, nephropathy, retinopathy, peripheral neuropathy and microvascular deformations. Delayed wound healing, especially as a result of circulatory deformations in the feet, may result in amputation. People with DM can reduce their risk of many of these chronic side effects by controlling their blood pressure and weight and quitting smoking (Gur & Aktas, 2022; Anonim, 2022a). Glucose homeostasis occurs by insulin secretion from pancreatic β cells in response to an increase in glucose concentration in the blood. The increase in insulin secretion inhibits gluconeogenesis in the liver and stimulates glucose entry into target tissues such as liver, muscle and fat. Insulin resistance is defined as the inadequate response of peripheral tissues to insulin. The result of this condition is hyperglycemia, as the body's ability to use and metabolize glucose is reduced blood sugar irregularities can be life-threatening by causing biochemical deteriorations such as diabetic ketoacidosis (DKA). Additionally, by impairing the functioning of the immune system, an increase in infectious diseases may occur (Aktas & Gur, 2021b).

2. Symptoms

Symptoms of diabetes occur in proportion to the patient's blood sugar level.

- Drinking excessive water due to feeling of thirst.
- Frequent urination and urge to urinate, especially at night.
- The need to eat frequently.
- Feeling of weakness and fatigue in the body.
- Refractive errors that develop in a short time, such as nearsightedness.
- Tingling, numbness and cold feeling in hands and feet.
- Wound development on the limbs and skin, especially the feet

3. Diagnostic criteria

It is determined based on blood sugar tests measured at certain times. In the presence of diabetes symptoms, people are diagnosed with diabetes if:

- Fasting blood sugar is over 125 mg/dl.
- Postprandial blood sugar above 200 mg/dl.
- Following the oral glucose tolerance test (OGTT), the 2nd hour blood sugar level is above 200 mg/dl.
- Glycosylated hemoglobin (HbA1c) level above 6.5%

2.1. Drugs administered in hyperglycemia

There are two main types of DM.

1-Non-insulin dependent (Type 2) diabetes (85-90%).

2-Insulin dependent (Type 1) juvenile diabetes (10-15%).

The aim of treatment is to prevent vascular and neurological complications by keeping blood sugar within normal limits. Blood sugar is kept under control by 3 methods.

- Diet therapy
- Insulin administration
- Giving oral antidiabetics (for Type 2 diabetes)

Insulin is a polypeptide hormone secreted from the pancreas. Apart from regulating the blood sugar level in living things, it also plays a role in various metabolic events.

2.2. Drugs used in hypoglycemia

It begins with adrenergic symptoms such as irritability, tremor, tachycardia, confusion and hunger. A measured glucose level <70 mg/dl is defined as hypoglycemia. It should be treated when neuroglycopenic symptoms begin when the blood glucose level drops

to <54 mg/dl. In the treatment of conscious patients with blood glucose <70 mg/dl, 15-20 g of oral glucose is administered. To prevent recurrence of hypoglycemia, the person should have a snack. Those with blood glucose < 54 mg/dl are administered glucagon because they are at risk of serious hypoglycemia. In unconscious patients, vascular access is established and 25g of 50% dextrose is infused (Anonim, 2020a) If hypoglycemia coma that develops during the use of antidiabetics is not treated immediately, cerebral disorder may occur. In cases of mild hypoglycemia where the patient is conscious, recovery occurs 1-2 minutes after ingesting sugar, fruit juice or glucose (20-100 g). In severe hypoglycemia (in case of coma), adequate glycemia can be achieved in a short time by intravenous administration of 30% hypertonic glucose solution. Glucagon, synthesized from the human pancreas, is a hyperglycemic hormone that acts as an insulin antagonist. In cases of hypoglycemia coma caused by insulin or oral hypoglycemic drugs, i.m. or s.c. i.v. It can also be given in 20-40 ml of 20% glucose solution as perfusion (Dökmeci ve Dökmeci, 2016).

3. Clinical pharmacology of insulin and oral antidiabetics

DM; It is a disease characterized by insulin deficiency or resistance accompanied by hyperglycemia and deformations in protein and lipid metabolism. The prevalence of diabetes in society is between 1-2%. In this disease, in addition to glucose, protein and lipid metabolism are also deformed. Due to metabolic deformation, disorders also occur in the peripheral, somatic and autonomic nervous systems over time. Additionally, vascular deformations occur at the level of small vessels such as capillaries and arterioles. The vessels most

affected are the retina (diabetic retinopathy (DR)) and the kidney (diabetic nephropathy (DN)). DM is the most important factor in the development of atherosclerotic cardiovascular disease. Excessive formation of sorbitol within the cell via the aldose reductase enzyme from glucose, whose concentration is increased in body fluids, contributes to neuron deformation (diabetic neuropathy (DNP)) (Gür & Bilgiç, 2023).

4. Glycemia status

It is the increase in glycemia that occurs in the test performed by giving 75 grams (gm) of glucose orally in the morning to people who have been fasting for 10-16 hours (100 gm, 1.75 g/kg for pregnant women and children, respectively). Clinically, a condition called "impaired glucose tolerance" is distinguished between the normal and diabetic state. In pregnant women, the glycemia limits that lead to the diagnosis of gestational diabetes are different. Gestational diabetes (100 g OGTT) 105< 180< 155< 140<. Diabetes diagnosis; Those who show clinical symptoms, whose fasting plasma glucose exceeds 126 mg/dl or whose glucose level exceeds 200 mg/dl at one time of the day are diagnosed without loading. However, the diagnosis must be confirmed by measurements at at least two different times. There is also a situation where fasting plasma glucose is between 110-125 mg/dl, but glucose tolerance is normal; This is called "impaired fasting glucose." There are differences in glucose levels in whole blood, plasma, and serum; That is, glycemia measured in plasma and serum is 10-15% higher than in blood. This is due to the absence in serum or plasma of blood cells that do not contain as much glucose as plasma (Akıcı et al., 2012).

5. Risky patients who need diabetes screening

- Being overweight (body mass index (BMI) ≥ 25 kg/m²) or obese (BMI ≥ 30 kg/m²)
- Type2 DM genetic history
- Being over 45 years old
- Cardiovascular disease
- Lifestyle lacking physical function
- $TG \ge 250 \text{ mg/dl} \text{ or HDL-chole} \le 35 \text{ mg/dl}$
- Deformed fasting glucose and glucose tolerance,
- Polycystic ovarian disease
- Arterial blood pressure \geq 140/90 mmHg and above
- Antipsychotic and medication use for bipolar disorder
- Chronic corticosteroid intake
- Presence of sleep deformation in glucose intolerance (such as obstructive sleep apnea syndrome, frequent waking up at night and inability to sleep) (Anonim, 2020b; Savran et al., 2020).

6. Types of diabetes mellitus

6.1. Type 1 diabetes

It is the absence of insulin, that is, complete insulin deficiency. The majority of people with type 1 diabetes are immune-mediated. In this type, In this type, T-cells destroy beta cells. The idiopathic one develops as a result of virus infection. Type 1 diabetes accounts for 10% of DM. In the treatment of Type 1 DM, synthetic insulin is administered by monitoring the blood sugar level. If insulin is not given, DKA may develop and result in coma. Exercise and diet are important in treating type 1 DM.The blood sugar of people with type 1 diabetes should be close to the normal value of 80–120 mg/dl, 4–6 mmol/l. For hypoglycemia, the most recommended value is 140–150 mg/dl (7-7.5 mmol/l). Patients with blood sugar levels above 400 mg/dl (20 mmol/l) may experience problems that may lead to excessive fluid loss as a result of frequent urination. Above 600 mg/dl (30 mmol/l) they require medical intervention (Akıcı et al., 2012; Aktaş et al., 2020; Anonim, 2022a).

6.2. Type 2 diabetes

It is a disorder characterized by the development of resistance to insulin (decreased sensitivity to its effect) or the decrease or complete disappearance of insulin formation and secretion. Insulin resistance; It is the decrease in the frequency of insulin receptors in the relevant cells or the decrease in insulin function at the postreceptor level. Since type 2 diabetes is closely related to heredity, there is a familial predisposition. In type 2 DM, obesity accounts for approximately 80-85% of the total cases. In this DM, excessive food intake, decreased storage of these nutrients from the blood to the cells, and as a result, beta cell stimulation and hyperinsulinism develop. This situation causes postreceptor insulin resistance by reducing target cell receptor frequency. Reducing food intake by adjusting the diet eliminates the mentioned condition by reducing body weight and increases sensitivity to insulin. Beta-cell dysfunction plays a role in the pathogenesis of nonobese diabetic patients. When glucose increases, insulin secretion from beta cells increases The initial increase due to the stimulation of the glucoreceptors due to this increase disappears (Akıcı et al., 2012; Aktaş &Gür, 2021c; Anonim, 2022a).

6.3. Specific diabetes

- Pancreatic diseases caused by alcoholism or pancreatitis
- Conditions of excessive secretion of diabetogenic hormones (cushing's syndrome, pheochromocytoma, glucagonoma and pancreatic somatostatinoma).
- Treatment with drugs with diabetogenic effects (such as glucocorticoids, oral contraceptives, thiazide diuretics that reduce insulin release, beta-blockers, calcium antagonists and feniton).
- It is rarely observed, such as hereditary diabetes (due to mutations in the insulin gene, insulin receptor gene and glucokinase gene).
- Diabetes accompanying some genetic diseases (down syndrome) (Ak1c1 et al., 2012).

6.4. Gestational diabetes

It occurs during pregnancy. It is observed after the 24th week of pregnancy as metabolic and hormonal changes lead to carbohydrate intolerance. It is high blood sugar that develops with insulin resistance. It is prediabetes that poses a risk for the subsequent development of type 2 diabetes. Due to the hormone secreted from the placenta (human placental lactogen), the pregnant woman's blood sugar increases due to insulin resistance, hyperinsulinemia and mild postprandial hyperglycemia. For this reason, she may be diabetic during pregnancy even though she had no symptoms of diabetes before. Pregnancy hormones make it difficult for the body to break down glucose. They prevent the insulin hormone from fulfilling its task of stabilizing blood sugar. Depression, pregnancy toxicity and the need for a cesarean section increase the risk. For people at risk, the test is performed between the 24th and 28th weeks of pregnancy. Blood sugar testing is performed four times a day. Patients should breastfeed as soon as possible following birth. This condition is effective in the last three months of pregnancy and in 3–9% of pregnant women. This affects 1% of pregnant women under 20 and 13% of those over 44. Postpartum diabetes resolves in 90% of these pregnancies. However, the risk of developing type 2 DM also increases in these people.

6.4.1. Gestational diabetes risk factors in expectant mothers

- Family history of diabetes,
- Being over 25 years of age,
- Physical inactivity,
- Being overweight,
- Having high blood pressure,
- History of heart disease,
- Presence of polycystic ovary syndrome,
- Prediabetes occurrence or history of type 2 diabetes in family members,
- History of gestational diabetes in previous pregnancy,
- Having given birth to a baby weighing more than 4 kilos in previous births,

• Do not give birth to stillbirth.

6.4.2. Gestational diabetes symptoms

- Frequent urination,
- Detection of glucose and acetone in urine,
- Quick thirst,
- Nausea,
- Feeling of fatigue,
- Frequent infections in the urinary tract, vagina and skin,
- Blurred vision,

Pregnant women who are not diagnosed with DM are subjected to an OGTT challenge and observed. Diagnosis is made by meeting two of these criteria:

- Fasting blood sugar is over 92 mg/dl.
- More than 180 mg/dl per hour
- More than 153 mg/dl after one hour
- More than 140 mg/dl after one hour

If the 3-month fasting blood sugar average is over 126 mg/dl, the HbA1c is over 6.5, and the postprandial blood sugar value is over 200 mg/dl, the pregnant woman is diabetic. There is no need to burden these people.

6.4.3. Diabetic ketoacidosis

It is a complication caused by insulin deficiency, which develops when the body breaks down fats and increases blood acids (ketones). Although DKA is observed in pregnant women with type 1 diabetes, those with type 2 diabetes and gestational diabetes are at risk. Situations such as increased insulin resistance during pregnancy, stress and fluid loss caused by vomiting increase the incidence of DKA. In addition, acute illnesses, insulin pump failure, and non-compliance with the insulin regimen are also motivating factors. Since the fetus is fed with the nutrients it receives from the mother through the placenta, the increase in blood sugar of the diabetic mother increases the blood sugar of the fetus. The fetus responds to this situation by increasing insulin secretion. Fetal development accelerates with increasing insulin secretion (the hormone that also increases development) starting from the 24-28 weeks of pregnancy, and the birth weight increases to over 4,000 gm (Bilgic et al., 2020).

6.4.4. Overweight fetus causes birth problems

a. Dystolic birth

- Increase in the incidence of cesarean section,
- Heavy bleeding may be observed at birth,
- During normal birth, tears may develop in the perineum.

b. Risks of gestational diabetes to the fetus and baby

- Birth trauma,
- Excessive weight gain in the baby,
- Increased risk of premature birth,
- Shoulder dislocations,
- Nerve injuries,
- Increased respiratory distress,
- Low blood sugar (hypoglycemia),

- Jaundice,
- Metabolic syndrome,
- Later on, type 2 diabetes,
- Obesity in later childhood
- Heart anomalies,
- Brain and central nervous system anomalies,
- Kidney anomalies,
- Digestive system anomalies,
- Stillbirth

c. Risks of gestational diabetes for the expectant mother

- Birth trauma,
- High blood pressure and preeclampsia during pregnancy,
- Type 2 diabetes,
- Gestational diabetes in subsequent births,
- Metabolic syndrome (Anonim, 2020c).

7. Diet application

The daily diet (nutrient elements) of diabetics should be regulated in terms of total calories. In type 2 diabetics with mild (asymptomatic) hyperglycemia, glycemia can be controlled with exercise and diet, without the need for medication. Diet should not be relaxed in those taking oral antidiabetic and insulin. In type 1 diabetes; Total calories are determined to be sufficient to maintain the patient's ideal weight. In these, meals should be timed according to daily insulin injection times. Delaying a meal, even for a short time, may lead to hypoglycemia. Most people with type 2 diabetes are initially put on a weight loss diet because they are obese. For this purpose, the patient is initially given a diet that is 500-1000 kilocalories (kcal) short of the daily calorie requirement. In this way, the patient is accelerated to lose the predicted weight by losing 0.5-1.0 kg per week. In people with type 2 diabetes, timing the meal during the day or a short delay does not cause much of a problem in terms of hypoglycemia. Daily total energy intake; about 12-20% should be protein, 50-60% should be starch types (polysaccharides) and grain types (carbohydrates), and 30-35% should be fat. As for fat, saturated fat should not exceed 10%. Daily cholesterol intake should also be restricted (<300 mg/day) to prevent atherosclerotic complications.

In diabetics, saccharin sodium (or calcium), sodium cyclamate, aspartame and sucralose (splenda) are used as artificial sweeteners (which have no caloric value and provide sweetness even in small amounts). Aspartame's inactivation at high temperatures may pose a problem. Fructose or sorbitol, which have less sweetening power, can be used for the same purpose. Sorbitol may cause osmotic diarrhea when taken orally. Fructose is a natural monosaccharide and has a low glycemic index. No need for insulin to be used by cells (Akıcı et al., 2012).

8. Treating type 1 diabetes with insülin

Insulin replacement therapy is required. Insulin dose; it is individualized based on diet and daily activity. Sufficient dose insulin treatment can slow down the destruction of beta cells, and after a while, the patient's insulin requirement can be reduced and treatment with lower doses of insulin can be continued. However, after two years, natural insulin production resets and insulin requirements increase

8.1. Insulin dose should be adjusted based on blood glucose8.1.1. Determining and adjusting the insulin dose bymeasuring glycemia

This method is troublesome for patients as it requires blood collection 4 times a day. However, it has become easily applicable with the development of devices that measure glycemia in fingertip capillary blood. The same adjustment system applies to the biphasic insulin analogues biphasic lispro and aspart. Except in emergencies, dosing is changed at least every 2 days. In intensive insulin therapy, where the glucose level is desired to drop to normal in all cases, daily injections are increased to three or even four times. In this case, approximately 25% of the total dose is given as NPH insulin at bedtime. In patients with sudden hypoglycemia (in subcutaneous administration, the rate of absorption is variable), regular insulin is given 4 times a day and long-acting insulin is added to the application at bedtime. The problem in adjusting the insulin dose in type 1 diabetics is the hyperglycemia that occurs early in the morning and before breakfast.

8.1.2. Insulin dosing with urine glucose measurement

In diabetes, glycemia adjustment with urine glucose has no place in these people, as it causes misleading results in those with abnormal bladder function and those whose kidney glucose threshold deviates from the normal. **8.2. Treatment of type 1 diabetes with immunosuppressive drugs.** When administered at the onset of type 1 diabetes, they prolong the lifespan of the residual beta cell. For this purpose, azathioprine is given together with prednisone. High doses of insulin are given to suppress the hyperglycemic effect of prednisone. Insulin prolongs life by putting beta cells into rest. In treatment, intensive insulin should be administered.

9. Treatment of type 2 diabetes with insulin and oral antidiabetics. In obese people with insulinemia (normal and above normal), weight loss through a calorie-restricted diet and exercise can normalize glycemia by increasing sensitivity to insulin. In moderately symptomatic obesity, the use of hypoglycemic (oral antidiabetic) medication is preferred to insulin. If hyperglycemia cannot be adequately corrected with them, insulin is used. It has been observed that administration of the insulin-metformin combination leads to less weight gain. In non-obese type 2 diabetics, glucose stimulation of beta cells is reduced and insulinopenia is present.

9.1. Points to consider in insulin treatment

In treatment, diet and exercise are standardized. Exercise reduces insulin requirements. If the dose of insulin is adjusted while in the hospital, this determined daily dose is increased by 250-300 kcal or the dose of insulin is reduced by 1/3 in a patient who leaves the hospital and starts doing her daily activities.

9.2. Factors that change insulin requirements

a. Stress factors such as infection, trauma (including surgical intervention), excitement and anxiety

These increase adrenocorticotropic hormone (ACTH) secretion and develop acute resistance to insulin. However, when ACTH is injected at a dose that matches the maximum daily secretory capacity of the anterior pituitary, the degree of insulin resistance that develops is low.

- Ketosidosis.
- **Pregnancy:** After the third month, an increasing resistance to insulin develops.
- Lactation
- Menstruation: Increases insulin requirement in some patients,
- Administration of glucocorticoids, adrenaline and other betamimetic sympathomimetics, thyroxine and oral contraceptives. Drugs such as adrenergic neuron blockers, βadrenergic receptor blockers and MAO inhibitors reduce insulin requirement. In those taking these, hypoglycemia may develop if the dose of insulin is not adjusted.

9.3. Chronic complications of diabetes

• Coronary heart disease, stroke and peripheral gangrene occur due to acceleration of atherosclerosis (defects in platelets and clotting factors) in large vessels.

- Somatic and autonomic neuropathies due to neuronal disorder (DN).
- Diabetic dermopathy, foot and leg ulcers and other skin disorders.
- Increase in subcapsular cataract and senile cataract,
- Demineralization of bones, disorders in joint and periarticular structures,
- Increased tendency to certain infections (such as bacteriuria, candidiasis and pyelonephritis).

Occurrence of diabetes-specific infections (such as necrotizing myositis, fasciitis, malignant otitis externa).

The following complications are more common in people with type 1 diabetes: DN, proliferative retinopathy, severe autonomic neuropathy and subcapsular cataract.

9.4. Common complications in type 2 diabetes

Macrovascular angiopathy, macular edema of the eye, acceleration of senile cataract. Primary prophylaxis with strict insulin therapy reduced the risk of retinopathy by 74% and the risk of nephropathy by 35% compared to usual insulin therapy. In secondary prophylaxis, the risk of progression of retinopathy was reduced by 53% and the risk of progression of nephropathy was reduced by 37%. The risk of clinical neuropathy was reduced by 69% and the risk of progression of neuropathy was reduced by 57%.

Other uses: Loss of appetite, such as anorexia nervosa, can be treated by administering a small dose of insulin 1-2 hours before a meal.

10. Treating diabetes-related emergencies

10.1. Diabetes-related emergencies

Because they increase mortality in diabetics, it is important to prevent disease occurrence and meticulous treatment and care when it occurs.

- Diabetic coma,
- Necessary emergency surgical interventions in diabetic patients,
- It is acute myocardial infarction.
- Hypoglycemia coma,
- DKA,

Hyperosmolar and hyperglycemic, non-ketotic and lactic acidosis coma.

a. Diabetic ketoacidosis

It is a life-threatening metabolic disorder that acidifies the blood. Although it is seen in people with type 1 diabetes, it can also develop in people with type 2 diabetes. Although sufficient insulin is produced at the beginning of the disease, body cells become insensitive (insulin resistance), and in the later stages and in type 2 diabetics, insulin deficiency develops. It occurs in the absence of insulin in the body (enough to allow blood sugar to enter cells to be used as energy). Instead, the liver breaks down fat (acid ketone bodies) for fuel. Without treatment, diabetic coma may develop. If the missing insulin cannot be maintained, the body uses fat to provide energy to the cells. Fatty acids are broken down into ketonic bodies in the liver. However, when excess ketone bodies form in the blood, the blood becomes acidic and the metabolism is disrupted. The body has a buffer system to keep the pH of the blood between 7.35 and 7.45. If the pH drops below 7.35, the blood becomes "acidic." The body tries to normalize this situation by removing carbon dioxide from the lungs and excreting acidic metabolic products through the kidneys. When the acidic condition cannot be treated, symptoms such as thirst, abdominal pain, fatigue, vomiting can range from diabetic coma (Tutun et al., 2019).

DKA symptoms; it develops before a febrile infection. In this case, frequent urination and strong thirst develop. Additionally, the breath smells like it contains acetone (a sweet, rotten fruit smell). Electrolyte disturbance; it may cause cardiac arrhythmia, brain edema and renal function deformation. In the last stages of ketoacidosis, there is a risk of developing shock and coma. DKA is the leading cause of death in children and teenagers with type 1 diabetes (Bilgic et al., 2018a).

Dehydration of the body; the organism tries to excrete excess ketone bodies and increased blood sugar through urine. A large amount of water is required to keep the sugar dissolved in the urine. Since people with this condition urinate more frequently, the body dries out due to intense fluid loss.

Symptoms of fluid deficiency;

- Folds in the skin
- Muscle spasms in the legs
- Dizziness due to drop in blood pressure
- State of burnout
- Excessive thirst and dry mouth
- As a result of increased water loss, the amount of urine excreted decreases.
- Urine smells sweet and pungent due to lost blood sugar.

Reason for development; The body produces ketone bodies in the liver as a replacement for needed carbohydrates. Ketone bodies develop as an intermediate product of fat metabolism and are present in small amounts in the blood. If there is not enough sugar, the fatty acid is broken down into ketone bodies and released into the blood. This condition develops with alcohol use and starvation. In case of illness or blood sugar level above 240 mg, a ketone test can be performed every 4 - 6 hours with a ketone test kit to control urine.

- Blood sugar level of 300 mg and above
- Breath smelling like fruit
- Vomiting due to inability to reduce food and drinks,
- If you have difficulty breathing

Treatment; circulation and respiration must be assured and internal organs must be protected from deformation. Replacing lost fluid is the most urgent procedure. In addition, sodium replacement, insulin therapy, potassium deficiency and acid-base balance are corrected. Fluid replacement; since it increases urination, it also increases glucose loss, increases the perfusion of the liver and muscles, and ensures the transportation of insulin to target organs, resulting in a significant reduction in hyperglycemia. With good hydration, the patient becomes conscious. In DKA, insulin is used to transport the sugar molecule into the cell. (Akıcı et al., 2012; Çelik, 2020).

Lactic acidosis; increased anion gap is the cause of metabolic acidosis, which develops when plasma lactate concentration exceeds 4-5 mmol/L (normal: 0.5-1.5 mmol/L). When serum lactate increases, the mortality rate also increases, and when lactate reaches 10 mmol/L, the chance of survival is very low. In diabetics; it develops during myocardial infarction (MI), accompanied by shock, sepsis, severe anemia due to excessive bleeding, lung disease and liver failure, or poisoning such as carbon monoxide, alcohol and salicylate (Sargin et al., 2011; Akıcı et al., 2012).

10.2. Insulin therapy in myocardial infarction

Since diabetes is an important risk factor for coronary heart disease, acute myocardial infarction (AMI) is observed 2.5 times more frequently and is more fatal in people with diabetes than in those without diabetes. Due to the stress caused by this situation, antiinsulinic hormone secretion (glucagon, catecholamines and cortisol) increases and further disrupts metabolic homeostasis. Therefore, insulin treatment is required. In patients with mild diabetes who can be controlled with diet, if glycemia is below 10 mmol/L (180 mg/dl), glycemia is monitored and if the patient is taking oral antidiabetics, it is discontinued. If glycemia is above the specified limit, insulin therapy is applied. If the patient can feed, is not in cardiogenic shock and glycemia does not exceed 20 mmol/L (360 mg/dl), s.c. 3 or 4 times a day. Regular insulin is injected. The dose is adjusted to reduce hyperglycemia but not cause hypoglycemia. If one or more of the three conditions listed are not valid, regular insulin is first administered via an infusion pump at a rate of 1 U/hour. Thus, after glycemia is reduced below 10 mmol/L (180 mg/dl), an appropriate GKİ solution (48 U of regular insulin + 40 mmol potassium chloride in 1 liter of 10% glucose solution) is administered i.v. It is given by infusion. Glycemia is measured every 2 hours and the insulin infusion rate is adjusted to maintain glycemia between 6 and 10 mmol/L. Hypokalemia should be avoided as it may worsen the arrhythmogenic state present in AMI. (Akıcı et al., 2012; Aktaş et al., 2024).

II. COMPLICATIONS AND TREATMENT OF DIABETES

1. Diabetic Nephropathy

The longer the duration of DM increases the blood glucose level, the greater the risk of DN. Its pathogenesis is related to oxidative stress, hyperglycemia and developing hypertension. Chronic hyperglycemia; it increases the production of reactive oxygen species (ROS) and triggers oxidative stress, damaging small blood vessels and causing tissue failure. Initially, asymptomatic albuminuria is observed, followed by increasingly severe proteinuria, and over time, hypertension is observed as a result of a decrease in the glomerular filtration rate. Detection of DN during the albuminuria period is important in screening (Aktas & Bayram, 2020; Anonim, 2020b; Aktaş, & Gur, 2021a; Aktaş & Yahyazadeh, 2022).

2. Diabetic neuropathy

It is observed in half of Type 1 and Type 2 DM cases. Reasons; diabetes duration, advanced age, dyslipidemia, hypertension, smoking, being tall and alcohol use. In addition to insulin in the treatment of painful neuropathy, non-narcotic analgesics such as aspirin and paracetamol can be used to relieve pain (Akıcı et al., 2012; Yarsan & Aktaş, 2017; Anonim, 2020b; Aktaş & Sevimli, 2020).

3. Diabetic Retinopathy

It is known as an eye disease for diabetics. It is the damage caused by DM to the retina and is one of the leading causes of blindness. The longer diabetes lasts, the greater the likelihood of developing DR. As blood sugar levels remain high in diabetics, blood glucose reaches higher than normal levels in the tissues and turns into harmful substances in the tissues. Anatomical and functional disorders develop in the tissues, resulting in various disorders. The retina, which is responsible for vision, is one of the areas most affected in diabetes. First, spots form on the retina. Over the course of a few days or a few weeks, a massive blood leak follows, which dulls vision. In extreme cases, he can only receive light from the darkness in his eye. It may take a few days to a few years for the blood to clear, and in some cases the blood may not clear. This type of major bleeding can usually occur more than once during sleep (Anonim, 2021d).

Treatment; lifestyle changes such as diabetes diet, regular exercise, and quitting smoking and alcohol are recommended. Drug treatments and insulin injections (in case of insulin deficiency) can be applied. There is no definitive treatment for diabetes, but the side effects of the disease can be prevented by keeping blood sugar under control. In this way, a normal life can be achieved by improving the quality of life (Anonim, 2021a). The development of DR is the severity and duration of blood glucose, pregnancy, nephropathy, dyslipidemia and high arterial blood pressure. Lipid profile and blood glucose should be kept under control to prevent the development of DR (Anonim, 2020b).

4. Diabetic Foot

As a complication of diabetes, it increases mortality and morbidity by causing amputation and ulcers (Anonim, 2020b).

III. GLUCAGON

It is synthesized and secreted by the alpha cells of the islets of langerhans of the pancreas (Anonim, 2021b). Glucagon-like hormone is secreted in the body from another source. It is called enteroglucagon or glicentin because it is secreted from the small and large intestine mucosa. Pancreatic glucagon concentration in plasma is 100-250 pg/ml. The pancreas contains 5-10 μ g of glucagon per gram of wet weight of this gland.

1. Secretion

Its secretion increases in hypoglycemia. Heavy exercise, glucocorticoids, hunger, sympathetic stimulation and protein-rich foods trigger increased secretion. The increase in glucose in the blood is prevented by secretin, somatostatin and insulin. It increases blood glucose level by increasing glycogen breakdown in the liver and glucose formation from non-carbohydrate substances. It increases the breakdown of fats by activating lipase in fat cells and increases the level of free fatty acids in the blood (Anonim, 2021b). The inhibitory effect of plasma glucose on glucagon secretion is due to its direct effect on alpha cells. It is formed with a lower concentration of glucose than the concentration that increases insulin secretion. Alpha cells of the islets of langerhans have sympathetic innervation, like beta cells. Sympathetic and vagus nerve stimulation increases glucagon secretion. Enteroglucagon secretion is also increased by glucose in food. Glucagon is rapidly inactivated by proteolytic enzymes in the liver, kidneys, plasma and target cells. Half-life in plasma is 3-6 minutes (Akıcı et al., 2012).
2. Physiological function and pharmacological effects

Glucagon and its opposite insulin establish glucose homeostasis. Their secretion is caused by the same factors, and they both regulate glucose, amino acid and fatty acid metabolism in the liver. The metabolism of these substances depends on the molar ratios and relative concentrations of these two hormones in the blood coming from the pancreas to the liver. The ability to keep glycemia at normal levels for days or even weeks during fasting depends on increased glucagon secretion and inhibition of insulin secretion. When measured during fasting in the morning during a normal meal pattern, the insulin/glucagon molar ratio is over 3. After three days of fasting, the ratio drops below 1 and gluconeogenesis reaches its maximum rate. On the other hand, when a carbohydrate-rich meal is eaten, the ratio increases to approximately 70 and the liver's glucose storage reaches its maximum speed. At the moment when the opposite effect of each hormone in the liver is equal and cancel each other (glucose balance is 0), the molar ratio should be between 3 and 70. Accordingly, glucagon is a stronger hormone than insulin in gravimetric activity.

Physiological and pharmacological effects of glucagon;

- It increases insulin secretion by directly affecting beta cells, even at low concentrations.
- It creates hyperglycemia by increasing glycogenolysis in liver cells. It also causes glycogenolysis in the heart cell.
- It increases gluconeogenesis, that is, the production of glucose from amino acids and lactic acid in the liver. This effect also

contributes to increasing glycemia. Keeping glycemia normal during long-term fasting is largely due to this effect.

- It creates lipolysis in liver cells. Thus, it creates a source of free fatty acids for oxidation. It also regulates the production of ketone bodies from free fatty acids in liver cells. Therefore, glucagon causes the liver cells to shift fatty acids to the production of ketone bodies instead of fat synthesis. It is the most important ketogenic hormone. Insulin blocks this effect of glucagon. If the patient has insulin deficiency, ketogenesis enhanced by glucagon can lead to severe metabolic acidosis.
- It increases the level of free fatty acids in the blood by activating hormone-sensitive lipase in adipose tissue and increasing lipolysis.
- It increases myocardial contraction and creates a positive inotropic effect. Additionally, it has a positive chronotropic effect.
- In high doses, it reduces the external secretion of the pancreas and stomach by preventing the motility and tone of the stomach, bile ducts and intestine. For this reason, it is applied in magnetic resonance and radiological examination of the gastro intestinal tract and bile duct and in the treatment of acute pancreatitis.
- It affects the endocrine glands and increases their secretions, adrenaline, noradrenaline, calcitonin, growth hormone and ACTH. It antagonizes aldosterone, which has the natriuretic

effect of glucagon in humans. This effect of glucagon contributes to fasting natriuresis (Bilgic et al., 2017a).

3. Hypoglycemia coma

If there is no glucose serum, 0.5-1 mg glucagon is injected in the treatment If the glycogen store in the liver is depleted, glucagon becomes ineffective. If there is no improvement in coma within 15 minutes after the injection, i.v. Glucose solution should be given. Due to its ease of administration, glucagon was first administered i.v. is preferred to glucose. Glucagon may become ineffective as liver glycogen stores are depleted within 45 minutes after coma.

4. Beta-blocker drug poisoning and heart diseases

In the treatment of acute intoxication cardiogenic shock caused by beta-blockers, the first 3 mg i.v. If there is no response to atropine, glucagon can be used to antagonize the effects of these drugs. In this indication, glucagon is used in high doses (such as 50-150 mg/kg i.v.). In this case, glucagon should be dissolved in 10 ml of 10% dextrose or physiological solution and given (Aktas & Ozgocmen, 2020).

a. Glucagon test to measure beta cell reserve

C-peptide stimulation test is performed to measure residual beta cell secretory capacity in juvenile type 1 diabetics, slowly progressive type 1 diabetes in adults, and type 2 diabetics. The patient's glycemic control must be ensured before the test, otherwise it may give falsely low results. In the test, the patient's blood is first taken for basal Cpeptide measurement and then 1 mg of glucagons is injected. Blood samples for C-peptide are taken at the 2nd, 4th, 6th, and 10th minutes after the injection. Beta cell capacity is considered adequate when the C-peptide response exceeds 0.6 nmol/P compared to the basal level.

b. Glucagon test to examine hypersecretion of insulin

In cases where this condition is suspected, 1 mg glucagon i.v. should be implemented. It is injected slowly over 30 seconds in the morning on an empty stomach. At the 0th, 2nd, 5th, 10th, 15th, 30th, 45th, 60th, 90th and 120th minutes, blood samples are taken and plasma glucose and insulin levels are measured. If there is excessive insulin secretion in the first five minutes, hyperfunction of beta cells is suspected. If insulin secretion is normal but the rise in glycemia is low, it is possible that other endocrine organs and liver dysfunction may cause hypoglycemia (Gür et al., 2022).

c. Use in radiology and other places

Glucagon, with its relaxant effect, is used to distinguish whether the narrowings seen in radiological and MRI imaging of the upper and lower gastrointestinal and bile ducts are due to spasm or organic lesion. It can also be applied to treat spasms related to the sphincter of oddi, bile duct and acute diverticulitis (Bilgic et al., 2018b).

5. Other antihypoglycemics

a. Diazoxide

It is a thiazide derivative drug. It causes hyperglycemia by increasing glycogen breakdown in the liver. This effect is due to both its direct effect and its inhibition of insulin secretion. It inhibits insulin secretion and hyperpolarizes by opening ATP-sensitive K+ channels in the membrane of beta cells. It increases lipolysis in fat cells. i.v. It creates a strong vasodilator effect when applied. Long-term application causes water and salt retention. It antagonizes the diuretic effect of thiazide-derived drugs. Also used to treat hypertensive crisis. It is used to treat low blood sugar. This includes islet cell tumors that cannot be removed and leucine sensitivity. It can also be used in refractory cases of sulfonylurea toxicity. It works by reducing insulin secretion from the pancreas and increasing glucose release from the liver. It also inhibits insulin secretion by opening the ATP-sensitive potassium channel of pancreatic beta cells. Therefore, it is used against hypoglycemia in diseases such as insulinoma (an insulin-producing tumor) and congenital hyperinsulinism (Akıcı et al., 2012; Anonim, 2022c).

IV. INSULIN

Insulin

Its name is derived from the latin word "insula" meaning "island". It is effective in lowering blood sugar. Insulin (polypeptide structure with a molecular weight of 5.8 kilodaltons) plays a role together with glucagon in the regulation of carbohydrate assimilation of the body (Aktaş & Bilgiç, 2022; Anonim, 2020a). It is produced by ribosomes in the ER of pancreatic β -cells and stored in golgi vesicles. The increase in blood glucose level stimulates β -cells, and the production of mRNAs increases in the stimulated cells and proinsulin is produced. Proinsulin passes from ribosomes to the golgi to form insulin and is stored in vesicles there. The amount of insulin accumulated in the islets of langerhans is at a level that can meet a person's needs for 5 days. Following the increase in blood glucose levels, insulin is secreted from β -cells within 30 seconds and can remain in the blood for 3-4 minutes after entering the blood (Kaya et al., 2013).

1. Secretion

There are 5 types of secretory cells in the pancreas (β -, α , D-, D1 and F cells). 60% of these cells are β -cells. β -cells secrete insulin, α cells secrete glucagon, D-cells secrete somatostatin, and D-1 and F-cells secrete pancreatic poly peptide. There are glucose receptors in the membrane of β -cells. When enough glucose stimulates the receptors, insulin is secreted from these cells. The amount of insulin secreted daily in a human is 2 mg. In case of hunger, this amount can decrease to 1 mg. Receptors on the membrane of β -cells are stimulated by nutrients such as protein and fat, causing insulin secretion. Stimulation of stomach and intestinal hormones, glucagon, beta-adrenergic receptors and cholinergic nerves increases the secretion of pancreatic hormones. Glucocorticoids indirectly promote insulin release by accelerating the breakdown of proteins in the body and increasing the amino acid concentration in the blood. Events that stimulate the central nervous system (CNS) (such as somatostatin, surgery, burns, lack of oxygen in the tissues, temperature drop) reduce insulin release through alpha receptors (Kaya et al., 2013).

1.1. Pattern of insulin release

1.1.1. Nutritional elements: They are effective after being absorbed from the gastrointestinal tract as well as i.v. They also have the same effect with infusion.

a. Carbohydrates: Mannose, glucose and fructose are natural sugars that are effective in insulin release. Fructose gains effectiveness by turning into glucose during absorption from the gastrointestinal tract.

b. Amino acids: Amino acids formed as a result of the digestion of proteins also increase insulin release. In order for some of them to affect secretion, glucose must be present in the environment. The most powerful releasing amino acid is arginine and is active in the presence of glucose. This substance strengthens the insulin-releasing effect of glucose by acting as an oxidizer. Leucine is weakly effective; it increases secretion with its direct effect, independent of glucose. Increasing insulin secretion of absorbed amino acids increases their retention by cells in the body.

c. Fatty acids: As a result of the digestion of fatty foods or i.v. Fatty acids administered via the route increase insulin secretion. On the other hand, the factor that increases insulin release and prevents the development of ketoacidosis in a person who fasts for 8-10 hours is the fatty acids mobilized from the fat tissue. The fact that fatty foods increase insulin secretion is partially mediated by gastric inhibitor polypeptide, which increases the secretion of fatty acids in the intestine. However, these acids also have direct effects on beta cells and i.v. When fatty acid is administered by infusion, insulin levels increase.

1.1.2. Gastrointestinal hormones

It causes food intake, transportation to the gastrointestinal tract, absorption and release of a series of peptide hormones (known as intestinal hormones) from the gastrointestinal mucosa into the bloodstream. These increase the stimulatory effect of glucose on insulin release. In parallel with food intake, the pancreas begins to increase insulin secretion from beta-cells. Following the start of eating, intestinal hormones (known as incretins) begin to be released before glucose is formed and glycemia begins to rise. Other intestinal hormones during food intake and digestion; secretin, gastrin, tokinin, cholecyst, enteroglucagon and vasoactive intestinal polypeptide. Most of them are responsible for regulating digestion in the digestive tract. Vagus stimulation increases insulin secretion from beta cells, both with a direct effect and by increasing intestinal hormone secretion.

1.1.3. Other hormones: These (somatomedins, growth hormone, estrogens, cortisol, somatomamotropin and progesterone) affect insulin

secretion from beta cells by changing the substrate level in plasma. Since cortisol increases protein catabolism, it also accelerates insulin secretion by increasing the amino acid level in plasma.

a. Neural regulation: It plays an important role in regulating insulin secretion and indirectly glycemia during responses to fasting between meals, stress situations and environmental changes. Stimulation of the ventrolateral hypothalamus increases insulin secretion, while stimulation of the ventromedial section stops the secretion.

b. Other factors: Somatostatin is secreted from the delta cells of the islets, and both glucagon and insulin strongly inhibit the secretion of pancreatic polypeptide. The effect of somatostatin on fuel metabolism is to delay the absorption of fats from the intestine. The effect of somatostatin on fuel metabolism is to delay the absorption of fats from the intestine. It also inhibits the secretion of acid, pepsin, saliva, and intrinsic factor of the stomach, external secretions of the pancreas and colon mucosa, and intestinal hormone secretion. It reduces stomach, intestine and gallbladder motility and splanchnic blood flow. It has a cell protective effect on the gastric mucosa. They reduce the secretion of serotonin, dopamine and insulin in the islets of langerhans. Prostaglandins create insulin increasing and decreasing effects. Oral antidiabetics (sulphonylurea), quinine, quinidine and cinchona alkaloids increase insulin secretion in the pancreas (Akıcı et al., 2012).

1.1.4. Mode of action: There are insulin-sensitive receptors in different parts of the body. These consist of 4 subunits, two large and

two small. The larger one is called the α -subunit and the smaller one is called the β -subunit. While the density of insulin receptors is high in the liver and fat tissues, the rate is lower in the red blood cells (Kaya et al., 2013).

Pharmacokinetics: Insulin preparations are generally a. administered parenterally. However, neutral regular insulin is administered only by the i.v. route. Some of it is found free and some of it is found bound to proteins in the blood and lymph circulation. The amount of insulin secreted from the pancreas and passing into the v.porta during fasting is 2 mg. Natural insulin i.v. when given, the plasma half-life is 9 minutes. For short-acting insulin (semilente), this period is 5-7 hours. i.v. a significant part of the administered hormone is retained in the liver and muscles. It is destroyed in the kidneys, especially the liver. Half of the hormone arriving at the liver is exposed to the first pass effect (Kaya et al., 2013; Aktaş, 2016; Aktaş et al., 2019).

b. Effects

- While it increases the production of monosaccharides and oxidation of glucose, it reduces gluconeogenesis, the formation of ketone bodies and the breakdown of glycogen.
- While it increases the synthesis and storage of proteins, it reduces the formation of urea by degradation.
- Increases the synthesis of ATP, DNA and RNA. It increases the breakdown of glucose in tissues, decreases its level in the blood and increases its storage as glycogen in the liver.

- Insulin accelerates the breakdown of sugar and inhibits glycogenesis. People with diabetes have high blood sugar even though they consume very little sugar. The reason for this is carbohydrates synthesized from fats and proteins as a result of gluconeogenesis not being inhibited in the absence of insulin.
- It prevents the breakdown of fats in the body and the formation of ketone bodies. In deficiency, the amount of glucose in the urine is more than the amount taken. Insulin deficiency activates glucagon, increasing the amount of glucose in the blood.
- Gluconeogenesis takes place in the liver. It uses proteins and amino acids released from surrounding tissues. Protein and amino acid loss occurs in the muscles. As the conversion of proteins into glucose accelerates, large amounts of urea and ammonia are formed (Kaya et al., 2013).
- Insulin is an anabolic hormone. It stimulates metabolic reactions aimed at the synthesis and storage of glucose, fats, proteins and nucleic acids.
- It ensures the passage of many endogenous substances through the cell membrane by activating the insulin receptors on the membrane.
- Some of the events that insulin affects are also controlled by glucagon, but in the opposite direction.
- Cortisol, thyroxine, growth hormone, somatomedins and catecholamines also show anti-insulinic activity in some places.

- The degree of insulin action varies with the degree of activity of these anti-insulinic hormones.
- It plays important roles in the intermediary metabolism of liver, striated muscles, myocardium and adipose tissue cells.

c. Regulation of glucose transport and metabolism

Insulin increases glucose utilization in target cells. Insulin increases glucose entry into the target cell. Glucose enters cells through facilitated diffusion. This event is accelerated by insulin,

The number of glucose carrier molecules in the cell membrane is increased,

As a result of activating the phosphorylation of glucose entering the cell, the intracellular free glucose level is reduced. Thus, the "downhill" glucose concentration gradient between the outside and the inside of the cell is increased.

d. Effects on protein metabolism: In insulin deficiency, protein synthesis decreases and protein degradation increases. Insulin, with its permissive effect on the cell membrane, increases the entry of some amino acids (amino acids such as leucine, valine and isoleucine, which are retained while passing through the liver) into the cell. It plays a role in increasing protein synthesis of insulin (anabolic effect).

2. Insulin in cells

Increases mRNA and tRNA synthesis,

• It increases the formation of ATP and activates amino acids by combining with tRNA,

It facilitates the formation of initiation complexes that initiate peptide synthesis in ribosomes and the subsequent incorporation of amino acids into the growing peptide chain. The protein synthesis-enhancing effects of insulin are observed in many cell types, including liver and striated muscle cells. Another important effect of insulin is to prevent protein degradation. In insulin deficiency, amino acids formed as a result of protein breakdown in cells (which are prevented from entering the cells and joining the peptide chain) turn into pyruvate, urea and ammonia as a result of deamination and oxidation in the liver. Urea and ammonia excretion increases in diabetics. In these people, the slowdown in protein synthesis causes delays in wound healing. This condition can be corrected with insulin therapy (Tanbek et al., 2017).

2.1. Antiketogenic effect of insülin

Due to insulin deficiency in diabetics or fasted normal people, the ketogenic effect of glucagon is relieved from the effect of insulin. As a result, the level of ketone bodies in the plasma increases. It becomes evident enough to cause DKA, which is especially common in Type 1 diabetics (Bilgic et al., 2016).

a. There are three causes of ketonemia

In the absence of insulin, as a result of the increased formation of free fatty acids from triglycerides in fat tissue cells, large amounts of free fatty acids pass from these cells into the blood. 2/3-3/4 of these are used directly as fuel by cells. The rest is taken up by liver cells and

converted into ketone bodies. If insulin secretion is sufficient during the anabolic period, very little ketone bodies are produced in the liver. because free fatty acids entering the liver cell are esterified and converted into triglycerides. Thus, the rate-limiting step in fatty acid oxidation is stimulated by disinhibition. As a result, an excess of ketone bodies are formed in the liver from fatty acids. These substances, which enter the bloodstream, are used as energy sources by the central nervous system, skeletal muscle, myocardium and other tissues when glucose use decreases.

b. Other effects: Insulin increases the entry of K+ ions into the cell. This effect is used in the treatment of hyperkalemia. Likewise, it increases the entry of Mg2+ into the cell. It reduces the level of phosphate in the blood due to increased use of phosphate within the cell (phosphate in the extracellular fluid entering the cell). It also has a mitosis-stimulating effect.

2.2. Interaction between insulin and glucagon in controlling intermediate metabolism

In the liver, adipose tissue and striated muscles, enzymes related to carbohydrate, triglyceride and protein production interact inversely with insulin and glucagon. Insulin shows anabolic activity by inhibiting catabolism in terms of carbohydrates, triglycerides and proteins. On the other hand, glucagon inhibits anabolism by showing catabolic activity. While insulin promotes storage, glucagon fuels destruction and burning. In case of adequate nutritional intake, the insulin/glucagon ratio is high and insulin dominates. In the case of starvation, this rate decreases and glucagon becomes dominant.

Usage; the use of proteins in gluconeogenesis results in the presence of excess ammonia and urea in blood and urine. In the blood; increasing the amount of sugar, urea and ammonia increases the feeling of thirst. Due to the breakdown of proteins, muscle weakness, emaciation, delayed healing of wounds and excessive appetite are observed.

Warning; with long-term insulin administration, antibodies develop and their effectiveness gradually decreases, and therefore the dose must be gradually increased. Administration of high doses of hormones may cause coma by excessively lowering blood sugar. May also develop hypersensitivity reactions (Kaya et al., 2013).

2.3. Insulin types, preparations and application (Çakır,2012)

Insulin type; onset of action, peak effect and duration of effect

Short acting; human regular, 30-60 min, 2-4 st, 5-8 st

Fast acting; glulisine insulin (prandial analogue), 15 min, 30-90 min, 3-5 hr

Medium effective; human NPH, 1-3 st, 8 st, 12-16 st

Long acting; basal analogue, 1 st, no peak, 20-26 st

st.

Ready mix human; Regular + NPH, 30-60 min, variable 10-16

Ready-mix analog; lispro + neutral protamine lispro (NPL), 10-15 min, variable 10-16 st.

Ready-mix analog; aspart + neutral protamine aspart (NPA), 10-15 min, variable, 10-16 st.

Some insulin preparations are obtained by extraction and purification from the pancreas of cattle and pigs slaughtered in slaughterhouses. Porcine insulin is preferred because it is less allergenic compared to bovine insulin.

2.4. Classification of preparations according to their source and degree of purification

In sephadex chromatography, molecules. Ion-exchange chromatography method was also added to the purification. Insulin derivatives that could not be removed by sephadex chromatography (despite having molecules the size of insulin) were also removed by this method (ion-exchange chromatography). Thus, highly purified insulin preparations have been prepared and they contain more than 99% insulin. HP insulin preparations are prepared from a single animal species. Because highly purified insulin preparations are stable, they can be stored outside the refrigerator for weeks, provided that they are not exposed to excessive heat or cold.

2.5. Regular and modified insulin preparations and their application

The isoelectric point of insulin is 5.3-5.5. If the pH of its aqueous solution is close to this value (range pH 4.5-7), insulin precipitates.

Insulin is dissolved in acidic or basic environments outside this range. It is quite stable in basic environment. Regular insulin solutions for injection were previously prepared with phosphate buffer at pH = 3. An injection solution of regular insulin that does not precipitate even though its pH is 7 has been made. This is called neutral insulin solution. Neutral regular insulin preparation produces less pain and other local reactions at the injection site than acidic insulin preparation. Also, its effects start a little quicker. Since acidic insulin preparations are not used, they have been replaced by neutral insulin preparations. Regular insulin solution is injected subcutaneously and, when necessary, intravenously. Although they need to be stored in the refrigerator, they do not lose their effectiveness for up to a month at room temperature.

2.6. Injection of insulin

Insulin suspensions are administered subcutaneously in all cases except emergencies. Subcutaneous injection of insulin; it can be done on the arm, in the abdomen, below the navel, on the front of the thigh or anywhere else. The fastest absorption in a person at rest occurs when injected under the skin of the abdomen. In those who exercise (walk and move their legs), subcutaneous absorption in the thigh area is significantly accelerated. Insulin injection should be done with a special insulin injector or insulin injection pen.

2.6.1. Short-acting insulin preparations

Its effect begins 30 minutes after subcutaneous injection (semilente and neutral insulin) and lasts 5-16 hours depending on the type of preparation.

a. Neutral regular insulin: The pH of this insulin is 7. It is applied subcutaneously. i.v. It is the only type of insulin that can be administered. Since it has the same pH as modified insulin preparations (long and medium term), it can be mixed and applied in any ratio. It causes less irritation at the injection site than other regular insulins. The effect of neutral regular insulin on glycemia begins 30-60 minutes after subcutaneous injection. It reaches its peak in 2-4 hours and its duration of effect is 5-8 hours. It can also be given intramuscularly. When given intravenously, its effect wears off within 30 minutes. It is the most appropriate type of insulin for surgical intervention and ketoacidosis treatment.

b. Zinc suspension of semilente insulin: It is an amorphous lente insulin (the solution is cloudy, has a short effect, can be applied by mixing with other lente and regular insulins) preparation.

2.6.2. Long-acting insulin preparations

Its effects have a late onset and last up to approximately 36 hours.

a. Protamine zinc insulin: It contains quite a lot of zinc (about 0.25 mg per 100 U of insulin). The protamine it contains is above what is required to neutralize. Therefore, it contains free protamine. When the mixture with regular insulin is kept waiting, the excess protamine combines with this insulin and does not develop a rapid effect. When it is necessary to give short-term insulin preparations together with protamine zinc insulin, they are injected into separate sites and mixing is done just before injection. The effect of protamine zinc insulin begins 7 hours after injection. If this preparation is administered in a dose that

will eliminate glucosuria for 24 hours, it will develop hypoglycemia after this time. Therefore, it is given at a reduced dose together with a short-acting insulin preparation. It is dangerous if its effect lasts 36 hours or more. Such preparations are not widely used.

b. Ultralente insulin: It is the crystal lente insulin preparation that produces the longest effect. Since it does not contain any non-insulin protein, its allergenicity is less than combined insulins. It can be mixed and applied with semilente and short-acting insulins.

c. Intermediate acting insulin preparations

Its effect begins two hours after application and continues for 18-24 hours. Frequently used modified insulins are in this group.

d. Isophane insulin: It is an insulin preparation prepared with zinc and containing enough protamine to neutralize insulin. Since it does not contain free protamine, it can be mixed with short-acting neutral regular insulin. It is the most commonly used modified insulin.

e. Mixed lente insulin: Contains 30% amorphous semilente and70% ultralente insulin. It does not contain foreign proteins.

f. Mixing insulins: Regular and modified insulin preparations can be mixed in the same injector in certain proportions and injected subcutaneously. As a rule, first regular and then modified insulin is drawn into the syringe (Akıcı et al., 2012).

3. Side effects of insulin treatment

a. Hypoglycemia

It is the most frequently observed side effect of insulin administration. It is observed more frequently in people with type 1DM than in those with type 2 DM. It develops in patients taking sulforylurea group of oral antidiabetics (when liver and kidney dysfunction is accompanied by elderly patients given long-acting drugs such as chlorpropamide and glibenclamide). Minor symptomatic episodes of hypoglycemia occur approximately every 2 weeks in patients treated with adequate doses of insulin, hypoglycemia coma with loss of consciousness occurs once a year in one in 4 or 5 patients. 3-5% of deaths in insulin-dependent diabetics occur due to hypoglycemia coma. The mortality rate is relatively high in elderly patients hospitalized with sulfonylurea-induced coma. Hypoglycemia in type 1 diabetics; it is caused by an imbalance between the dose of insulin, exercise and nutrition. Delaying a meal, skipping a meal, or exercising more than usual are the most common causes of hypoglycemia in these people. Insulin absorption changes from one day to the next, alcohol habit and liver disease also develop hypoglycemia. Taking beta-blocker medication also increases the incidence and warning signs of hypoglycemia (Bilgic et al., 2017b).

Symptoms vary depending on the rate at which blood glucose levels drop. For these to become evident, glycemia must fall below 50-60 mg/dp. Convulsions occur when glycemia drops below 35 mg/dl. The main clinical symptoms are divided into two: those due to autonomic nervous system stimulation and CNS symptoms due to neuroglycopenia. If the fall occurred quickly, reflex sympathetic hyperactivity symptoms are dominant. As a result of sympathetic nerve stimulation and adrenaline release from the adrenal medulla; tachycardia, sweating, increased blood pressure, tremors, and irritability develop. If glucose decreases slowly, symptoms of not meeting the fuel needs of brain cells dominate the picture (Tastemir Korkmaz et al., 2021).

b. Central nervous system symptoms

Headache, mental confusion, rambling speech, blurred vision and diplopia, amnesia and motor coordination disorder. If hypoglycemia lasts for a long time, organic lesions develop in the brain. If hypoglycemia occurred to the point of causing coma and convulsions and the patient survived; Permanent disorders such as parkinsonism, epilepsy, hemiparesis, ataxia and mental retardation may occur. Before starting treatment of hypoglycemic coma, it must be distinguished from diabetic coma. If there is doubt in the differential diagnosis, the patient should be given i.v. glucose is given. This causes a rapid onset of hypoglycemia coma. Insulin is used in the treatment of diabetic coma. This worsens the situation in hypoglycemia coma. Quick treatment of hypoglycemia before it progresses is important in preventing brain damage. In the treatment of hypoglycemia episode, i.v. 25-50 ml of 50% glucose solution is given by injection. This practice allows to immediately return to normal. consciousness Afterwards. carbohydrate is given orally and continuous i.v. 10% glucose solution

is administered by infusion at a rate of 100-200 ml/hour. This last application becomes important in hypoglycemia due to long-acting insulin and sulfonylureas. In unconscious patients, i.v. If glucose cannot be given, a small amount of honey or syrup can be applied to the oral mucosa. Additionally, 30 ml of these can be dissolved in 500 ml of warm water and given rectally as an enema. The second method is i.v. or i.m. It is an injection of 0.5 mg (0.25 mg in children) glucagon. Glucagon injection corrects hypoglycemia and normalizes consciousness by mobilizing liver glycogen. Since the effect of glucagon is short-lived, oral carbohydrates must be given to maintain improvement. Glucagon injection i.v. It is an easier procedure than glucose injection. For this reason, it is preferred in out-of-hospital treatment, in those with epileptic seizures and in those whose veins cannot be easily accessed. If more than 45 minutes have passed after the coma, glucagon will be ineffective as the glycogen store in the liver will be depleted

c. Posthypoglycemic hyperglycemia

Hypoglycemia that develops as a result of high-dose insulin administration (by increasing the secretion of counter-regulatory hormones) may cause subsequent hyperglycemia. However, hyperketonemia may develop. This occurs in cases of Type 1 diabetes. Hyperglycemia triggered by hypoglycemia can be prevented by additional endogenous insulin release in individuals such as nondiabetics and type 2 diabetics (who have insulin reserves). This improvement does not occur in people with type 1 diabetes (those who do not have insulin reserves in the pancreas) (Cingi & Erol, 1996; Akıcı et et al., 2012)

e. Lipodystrophy

Lipoatrophy is due to local immune reaction. Lymphocyte infiltration occurs in the atrophic area. When insulin is injected into a place continuously, the subcutaneous fat tissue atrophy and a hole forms there. Frequent injections should not be made to the same site and the injection site should be changed alternately. The incidence of this side effect is low with highly purified insulin and recombinant human insulin preparations. In some patients, frequent insulin injection (due to lipohypertrophy) causes lipoma formation. Since no pain is perceived in the area where the lipoma occurs, the patient may prefer to have the injection done there; Injection site should not be made in this place. To prevent this situation, the injection site should be changed sequentially (Bilgic & Armagan, 2020).

f. Weight gain

Due to the anabolic effect of insulin, insulin therapy may cause the patient to gain weight. This is more noticeable if the daily dose is high.

g. Visual impairment

In patients with high glycemia (because there has been no treatment for a long time), when glycemia is lowered by insulin treatment, the osmotic balance in the eye is disrupted. As a result, lens distortion (refraction changes) develops. This condition heals spontaneously in a few weeks (Akıcı et al., 2012).

h. Facial or standing edema

It occurs when high level glycemia is suddenly reduced by insulin and the osmolality of the plasma changes.

i. Carcinogenesis

It is recommended not to use it in breast cancer, and in other cases, it is recommended not to increase very high doses (over 50 units per day).

k. Insulin resistance

It occurs when IgG forms anti-insulin antibodies in the blood during insulin treatment of type 2 diabetics. In patients with long-term insulin therapy, antibodies against insulin form and this antibody binds to insulin and inactivates it. Insulin resistance develops in the patient when the daily insulin requirement exceeds 200 U. In this case, significant levels of anti-insulin antibodies are present in the blood. The daily requirement of 200 U, which determines insulin resistance, is actually a nominal and high value. This value is much higher than the amount secreted by the pancreas in a day. In a person whose pancreas has been removed, 30 U of insulin per day is sufficient to compensate for the deficiency. Thirty days of treatment is sufficient for resistance to develop. Insulin resistance can be treated with a glucocorticoid or an immunosuppressive (cyclophosphamide) drug. These drugs (with their immunosuppressive activity) reduce the binding rate of insulin to antibodies by reducing antibody formation.

l. Dawn phenomenon

It is a temporary hyperglycemia that occurs early in the morning in patients with type 1 and 2 diabetes during insulin treatment. It is the phenomenon in which the sensitivity of tissues to insulin decreases between 5 and 8 in the morning. Posthypoglycemic hyperglycemia that occurs in the morning should not be confused with the dawn phenomenon. In the first case, the insulin dose is reduced, and in the second time it is increased. These two occur frequently and unpredictably and are accompanied by bouts of hyperglycemia and hypoglycemia.

V. NON-INSULIN DRUGS (ORAL ANTIDIABETICS)

Not using insulin orally creates a serious drawback. Incretinmimetic preparations that mimic the effects of incretins (which reduce glucagon secretion and secrete insulin) have come into use.

1.Insulin secretagogues

1.1. Sulfonylurea derivative drugs

Although sulfonylureas can conditionally control glycemia in type 2 diabetes, the primary and secondary failure rate during treatment is high. However, their effect strengths, absorption degrees, metabolism and excretion rates, and accordingly their doses and duration of action are different (Azirak et al., 2022).

a. Pharmacokinetic properties: Oral antidiabetics are given half an hour before meals. Those given once a day are given before breakfast. Sulfonylureas are highly bound to plasma albumin. Except for chlorpropamide, all others are extensively metabolized in the liver.

b. Pharmacological effects and glyceemia-lowering effect mechanism

Sulfonylureas increase insulin secretion from pancreatic beta cells. This increase occurs in basal insulin secretion, glucose loading and meal insulin secretion. Beta cells increase the release of insulin, which is synthesized and stored in vesicles. Sulfonylurea derivatives develop therapeutic effects by increasing insulin secretion from the pancreas at the beginning of treatment. When tolerance to this effect develops (in the later period), they develop antidiabetic activity by increasing the sensitivity of target cells to insulin. When administered to achieve short effect in humans, they prevent glucagon secretion from alpha cells. They also increase somatostatin secretion from the pancreas. The advantage of oral antidiabetics over exogenous insulin therapy is; it increases the portal insulin level, but cannot increase the insulin level in other tissues (as approximately half of the secreted insulin is retained in the first pass through the liver). Insulin injection increases the insulin level in the portal and systemic circulation equally. It facilitates the development of insulin resistance as it creates systemic hyperinsulinemia (Akıcı et al., 2012).

1.2. Medicines

a. Tolbutamide

It is the drug with the shortest duration of action among the sulfonylureas used. In the treatment of type 2 diabetes; it is used together with diet, exercise and other medications. It lowers blood sugar by causing insulin production in the pancreas and helps the body use insulin efficiently. This medication helps lower blood sugar in people whose bodies naturally produce insulin (Anonim, 2021e). It is eliminated in the liver by being metabolized by CYP2C9, a polymorphic enzyme. When given orally, it reaches its peak value in plasma in 3-5 hours. Highly bound to plasma proteins (Akıcı et al., 2012; Kaya et al., 2013).

b. Tolazamid

It is used to treat type 2 diabetes with diet, exercise and other medications. It lowers blood sugar by increasing insulin production in the pancreas. It also helps the body use insulin efficiently. This medication helps lower blood sugar in people who naturally produce insulin (Anonim, 2021e). Its effect begins within 4-6 hours following oral intake and continues for 24 hours. It is given once a day (Akıcı et al., 2012; Kaya et al., 2013).

c. Acetohexamide

It is used in those who cannot control type 2 diabetes with diet. It stimulates the pancreas to secrete insulin and lowers blood sugar. For this medicine to work, the pancreas must produce insulin. It is rapidly metabolized in the liver and converted into hydroxyhexamide. This compound has a stronger blood sugar lowering and uric acid removing effect than the parent compound. The half-life of the drug is approximately 6 hours and the duration of action is 12-16 hours. (Anonim, 2003a; Akıcı et al., 2012; Kaya et al., 2013; Aktaş et al., 2020).

d. Chlorpropamide

It has the longest duration of effect (24-72 hours). Approximately 6-60% of it is excreted unchanged by the kidneys. The reason for its long duration of action is the low rate of hepatic biotransformation and slow excretion from the kidneys. The elimination half-life is about 33 hours. The maximum hypoglycemic effect occurs 10 hours after oral administration. The effect of a single dose lasts up to 60 hours. Since it accumulates in the body, it causes hypoglycemia more frequently and lasts longer than other sulfonylureas. It should not be used in the elderly, those with irregular meal times, or those with liver and kidney failure. The daily dose is 100-500 mg (average 250 mg). It is given once

and half an hour before breakfast. It interacts with antidiuretic hormone and potentiates its effect on the collecting ducts. It may cause water retention and hyponatremia. When given in proper dosage, it reaches the sufficient dose in 3 days. Reaches steady state density in 5-6 days (Akıcı et al., 2012; Kaya et al., 2013; Aktaş & Armağan, 2019).

e. Glyburide

It is used to treat type 2 diabetes. It is recommended to be taken together with diet and exercise. Common side effects are nausea and heartburn. Serious side effects; angioedema and low blood sugar. It is not recommended during pregnancy and can be used during breastfeeding. It works by increasing the release of insulin from the pancreas. It is one of the two long-acting sulfonylureas with the highest hypoglycemic activity. It keeps glycemia under control even with a dose of 2.5 mg per day. It is taken orally. It is absorbed at a rate of 80-85% from the gastrointestinal tract and binds to plasma proteins at a rate of 99%. Its metabolites also show hypoglycemic activity. The halflife of the unmetabolized parent compound in plasma is short (1-2 hours), and the effect of the drug on glycemia lasts for 16-24 hours. This is because this drug accumulates in beta cells and its metabolites are also active. Initially, it is given as a single dose of 2.5 mg in the morning before breakfast. Depending on the response, the dose is gradually increased up to 30 mg (Akici et al., 2012; Anonim, 2021g).

f. Glipizide

It is used together with diet and exercise and other medications to treat type 2 diabetes. It lowers blood sugar by increasing insulin production in the pancreas and helps the body use insulin efficiently. It helps lower blood sugar in those whose bodies produce insulin. The absorption of nutrients is reduced by giving it 30 minutes before a meal. Approximately 90% is metabolized and inactivated in the liver; about 10% is excreted unchanged by the kidneys. It is contraindicated in those with liver and kidney dysfunction as it increases the risk of hypoglycemia. The starting dose is 5 mg, given once a day 30 minutes before breakfast; the dose is increased to 15 mg depending on the response. If a higher dose is required, it is given in two divided doses in the morning and evening. The maximum daily dose is 40 mg (Akıcı et al., 2012; Anonim, 2017a).

g. Glibornuride

It has a medium effect duration. The elimination half-life is about 8 hours. The daily dose is 12.5-75 mg and is given 1 or 2 times. Causes hypoglycemia more frequently than glipizide (Akıcı et al., 2012; Anonim, 2017a).

h. Gliclazide

It is used to treat type 2 diabetes. It shows its effect by increasing insulin release. It is used to control hyperglycemia in patients with type 2 diabetes (not prone to ketosis) who respond to gliclazide. It is also used when diabetes cannot be controlled with diet and exercise and insulin therapy is not appropriate. More than 90% is absorbed from the gastrointestinal tract. The elimination half-life is approximately 8 hours in men and 11 hours in women. The daily dose is 80-320 mg and is taken once or twice a day (Akıcı et al., 2012; Anonim, 2021ı).

i. Sodium glimidine

It is a sulfonylpyrimidine derivative and has a short duration of action. There is no cross-allergy relationship between other sulfonylureas and sodium glimide and it can be used in those who are allergic to them (Akıcı et al., 2012).

k. Glimepiride

It is used orally together with diet and exercise in the treatment of type 2 diabetes. It is a long-acting sulfonylurea and works by increasing the amount of insulin released from the pancreas. Take 1-4 mg once a day before a meal; increased to maximum dose (8 mg) when necessary (Akıcı et al., 2012; Anonim, 2021k).

2. Uses

a. Diabetus mellitus

It can be used in people with type 2 diabetes who cannot be controlled with diet and who do not show a tendency to ketoacidosis. It is recommended as a hypoglycemic drug in patients with fasting blood sugar levels between 160 and 200 mg/dl. In patients with fasting glycemia above 200 mg/dl, treatment is started with insulin. In type 2 diabetics treated with insulin, if 20 units or less of insulin per day is sufficient, insulin can be discontinued and sulfonylureas can be started. If the patient receives 20-40 units of insulin per day, treatment with sulfonylureas can be started. But the dose of insulin should be reduced and discontinued. Suphonylureas cannot replace insulin in patients whose blood sugar can be kept under control with more than 40 units of insulin per day (Bilgic et al., 2023a). **b.** Diabetes insipidus: In the treatment of this disease, chlorpropamide can be used orally at a dose of 0.25-0.5 g per day.

3. Side effects

- Depending on the irritation they cause in the gastrointestinal tract; nausea, vomiting, heartburn, abdominal pain and diarrhea are observed.
- Allergic rashes on the skin.
- They can depress the bone marrow and cause leukopenia, thrombocytopenia and agranulocytosis.
- Since they cause weight gain, they are not recommended for obese patients (weight gain is partly due to the anaboic effect of increased insulin). Metformin can be used instead.
- Sulfonylureas can cause coma due to hypoglycemia.
- Due to their cardiotoxic effects, oral antidiabetics should not be used in heart patients for a long time.
- They are contraindicated in type 1 diabetes, kidney and liver failure, lactation and pregnancy (due to their potential for teratogenic effects). They should not use it during pregnancy (Gür & Bilgiç, 2022).

4. Interactions

• Since sulfonylureas are highly bound to plasma albumin, they interact with drugs that expel them from there. Therefore, aspirin and sulfonamides increase the hypoglycemic side effects of these drugs.

• Since alcohol inhibits gluconeogenesis in the liver and reduces the production and release of glucose into the blood, it potentiates the hypoglycemic effect of sulfonylureas (Bilgic et al., 2022).

a. Meglitinids

It is used to treat type 2 diabetes. Side effects include weight gain and hypoglycemia. They increase intracellular calcium (causing increased pro-insulin secretion). They are taken before a meal (used to suppress post-meal glycemia rise).

b. Repaglinide

Since it is quickly absorbed from the intestine, its effect occurs quickly. It is rapidly broken down into inactive metabolites in the liver. For this reason, the dose should be adjusted in people with reduced kidney function. The elimination half-life is less than 1 hour. It is given as a supplement to patients with mild type 2 diabetes that cannot be controlled with exercise and diet. The dose is 0.5 mg 3 times a day before main meals (30 minutes). It may increase the level of liver enzymes in serum (Bilgic et al., 2023b).

c. Nateglinidine

Its mode of action is the same as repaglinide and it also reduces postprandial glycemia. It is absorbed quickly and almost completely. It has a very short and rapid effect. Its effect begins in 15-30 minutes and the maximum effect occurs in 30-60 minutes. Plasma insulin level returns to its previous level after 3-4 hours. The elimination half-life of the drug is 1.4-1.8 hours. 80% of the ingested dose is excreted in the urine. It is taken as 120 mg 3 times a day, 15-20 minutes before the main meal. If necessary, the dose is increased up to 180 mg. It is generally used together with metformin when it is insufficient (Akıcı et al., 2012; Anonim, 20211).

5. Insulin sensitizers

a. Biguanides

The term "biguanidine" refers to the class of drugs used to treat prediabetes and diabetes (oral antihyperglycemic drugs) (Rang et al., 2003). These drugs contain two guanidine groups combined with each other in their molecules. Phenformin was the first to be found, and it reduces hyperglycemia in diabetics and does not cause hypoglycemia. Metformin, the drug used in this group, is used in combination with sulfonylureas. Its effect is on non-pancreatic structures and reduces insulin levels (Bilgiç & Aktaş, 2022).

There are two opinions regarding the mode of action

- They increase the function of insulin in peripheral tissues at the receptor level. They accelerate anaerobic glycolysis and increase the use of glucose in metabolism. As a result, they accelerate the formation of lactic acid.
- They reduce glucose output from the liver by decreasing gluconeogenesis. This is the result of their potentiation of insulin (Akıcı et al., 2012).

b. Metformin

It is used in T₂DM in the presence of insulin resistance. When taken orally, it is quickly absorbed and eliminated, and its duration of action is short. Less bound to plasma proteins (>5%). It is preferred in obese patients as it does not increase body weight in most cases. It is recommended to start treatment with metformin in newly diabetic patients. In cases where metformin is insufficient, the sulfonylurea derivative can be combined with a glitazone, basal or concentrated insulin, or incretin. In all tolerated cases, metformin is now an indispensable drug alongside other treatments. Initially, 850 mg is taken 1-2 times a day. The daily dose is gradually increased to the maximum dose of 850 mg 3 times. The most common acute side effects (occurring in up to 20% of patients) are diarrhoea, dyspepsia, anorexia, nausea and metallic taste in the mouth. It reduces the absorption of vitamin B12 and folic acid from the intestine. Long-term use develops vitamin B12 deficiency. It should be monitored for renal failure and discontinued in cases of even mild failure (Azirak et al., 2019). In cases that predispose to lactic acidosis (such as breastfeeding women, pregnant women, dehydration, liver and chronic obstructive pulmonary disease, severe heart failure, previous history of lactic acidosis, very low-calorie diet or long-term fasting, alcoholism, shock, sepsis, myocardial infarction) is contraindicated (Akıcı et al., 2012; Taşlıpınar et al., 2017; Anonim, 2020b)

c. Thiazolidinediones

They control glycemic control by reducing insulin resistance. In order for them to be effective, there must be insulin in the environment and resistance must develop against it. These drugs are not effective in the secretion of insulin, but increase sensitivity to insulin in peripheral tissues. They increase glucose utilization in tissues by increasing sensitivity to insulin. To a lesser extent, they prevent hepatic glucose production. They reduce the level of free fatty acids and insulin in serum. By increasing fat storage, they reduce the level of free fatty acids in the blood and their presentation to striated muscle. They are used in type 2 diabetes (accompanied by hyperinsulinemia and insulin resistance). They can be used alone in mild cases that cannot be controlled with diet and exercise. They increase body weight. They can cause water retention and edema in the body. They are contraindicated in patients with heart failure.

d. Rosiglitazon

- It is used in medicine as rosiglitazone maleate.
- It is indicated for type 2 diabetes (non-insulin dependent diabetes).
- In cases where diet and exercise are not sufficient, monotherapy or combination with metformin and sulphonylurea can be used to improve glycemic control in Type 2 diabetics.
- It is combined with insulin in people with Type 2 diabetes where diet, exercise and insulin do not provide adequate glycemic control.
- Treatment of type 2 diabetes should include dietary control.
- Calorie restriction, weight loss, and exercise are mandatory in the proper treatment of diabetics because they increase insulin sensitivity.
- This is important not only for the primary treatment of type 2 diabetes, but also for the continued effectiveness of drug therapy.
- Before treatment, secondary causes of poor glycemic control (infection) should be investigated and treated.
- Can be taken with or without food (Anonim, 2019b).

e. Incretin-mimetics

The release of insulin is secreted after food intake and its release increases with a blood sugar-dependent mechanism. Some incretins also inhibit glucagon release. Additionally, it slows down the absorption of nutrients into the blood by reducing gastric emptying. It is used to treat type 2 diabetes. The three preparations that have been put into practice are; exenatide, vildagliptin and sitagliptin. They find application because they have a low risk of hypoglycemia and cause weight loss (Egan et al., 2002; Akıcı et al., 2012; Anonim, 2021m).

6. Glucagon-like peptide-1 (glp-1) agonists

a. Exenatide

They are used to treat type 2 diabetes. It is used together with diet, exercise and other antidiabetic drugs. It is given by subcutaneous injection one hour before the first and last meal of the day. It works by increasing insulin release. It reduces excessive glucagon release. It is used in combination with metformin and sulphonylurea in cases where metformin and sulphonylurea are insufficient in the treatment of type 2 diabetes. As side effects, severe hemorrhagic and necrotizing pancreatitis have been observed (Akıcı et al., 2012; Anonim, 2022b).

b. Liraglutide

It is similar to glucagon, which is a member of the family of hormones that lower blood glucose levels. It is a glucagon-like peptide-1 (GLP-1) analogue that binds to the same receptor as GLP-1 and provides long-term effects. They increase endogenous insulin secretion. They are combined with metformin and other oral antidiabetic drugs (Akıcı et al., 2012; Anonim, 2021n).

7. Dipeptidyl peptidase-4 (dpp-4) inhibitors

a. Sitagliptin

It is a new agent in the treatment of type 2 diabetes. It stimulates insulin secretion with glucose-dependent insulinotropic polypeptide and GLP-1. It increases islet cell neogenesis and reduces beta cell apoptosis. It also induces satiety (Ahrén, 2009).

b. Vildagliptin

It is an oral anti-hyperglycemic agent of the dipeptidyl peptidase-4 inhibitor class of drugs. It increases insulin secretion from beta cells and suppresses glucagon release by alpha cells. It reduces hyperglycemia in type 2 DM. It is also used in combination with thiazolidinediones (Mentlein et al., 1993; Ahrén et al., 2004; Akıcı et al., 2012).

c. Saxagliptin

It is used together with exercise and diet to reduce blood sugar in people with Type 2 DM. It is applied after meals (increases the amount of insulin) in cases of high blood sugar. It can be combined with metformin and other oral antidiabetics (Akıcı et al., 2012; Anonim, 2019a).

8. Other antidiabetic drugs

a. Glucosidase inhibitors

It is used in the treatment of type 2 diabetes. Alpha-glucosidase breaks down large carbohydrate molecules to release glucose. It inhibits the enzyme glycoside hydrolase, which is necessary for the digestion of carbohydrates. It especially inhibits alpha amylase enzymes and brush border enzymes. Alpha amylase enzyme breaks down complex starches into oligosaccharides in the small intestine lumen. Alpha-glucosidase enzyme converts oligosaccharides into other monosaccharides and glucose in the small intestines. Failure to secrete these enzymes greatly reduces the digestion of carbohydrates. As a result, the amount of glucose entering the circulation (carbohydrates taken with food cannot be reduced to glucose) decreases. Applying this to people with DM causes the blood glucose level to decrease in the short term and the HbA1c level to decrease slightly in the long term. It is used together with these preparations to increase the functions of metformin, insulin and sulphonylureas administered to diabetics. As a result, undigested carbohydrates remain in the intestinal lumen and are excreted with feces. When taken at the beginning of meals, they reduce postprandial

blood glucose elevations by approximately 30% to 50% (Anonim, 2021o).

b. Aldose reductase inhibitors

Under the influence of this enzyme, the intracellular sorbitol level increases in diabetic patients as a result of excessive sorbitol formation from glucose. Glucose entry into the cell via the polyol pathway increases. Increased glucose disrupts the permeability of the membrane. As a result, the functions of peripheral nerve cells, kidney and retina are impaired. The mentioned peraperates prevent the conversion of glucose to sorbitol. These drugs were developed to prevent diabetic neuropathy, retinopathy, and nephropathy (because of the importance of transformation in these diseases) (Akıcı et al., 2012).

VI. NUTRITION and DIABETES

Diabetics (in order to have a balanced and adequate diet) should take the recommended amounts of all nutrients and energy.

1. Energy

Ideal body weight and maintaining it are of great importance in controlling diabetes. Energy balance ensures the maintenance of body weight. 80% of people with type 2 diabetes are obese. Weight loss by reducing energy intake positively affects metabolic control. It is important for diabetics to determine their energy needs and meet their required energy through diet for ideal body weight (Yıldız, 2008).

1.1. Carbohydrates

It is a source of energy in daily nutrition and must be taken. Types of carbohydrates in foods; pulp, starch and sugars. In diabetics who receive intensive insulin therapy, the amount of pre-meal insulin is adapted according to the carbohydrate content of the meal. In this way, the amount of carbohydrates taken per day does not affect glycemic control. Foods recommended as carbohydrate sources for diabetics; legumes, whole grains, whole grain bread, fruits, vegetables, milk and dairy products (Yıldız, 2008).

a. Effects of dietary fiber on the body

- It reduces the need for insulin,
- Increases blood sugar slowly,
- It creates weight control by creating a feeling of fullness.

- Prevents constipation by regulating the functioning of the intestine
- Prevents the increase of fats in the blood (Yıldız, 2008).

b. To increase the fiber content in the diet

- Whole wheat bread should be preferred to white bread,
- Bulgur should be preferred over rice,
- Fruits should be preferred to fruit juice,
- Fruits with shells should be washed and consumed without peeling them.
- 5 or more portions of fruits and vegetables should be consumed daily.
- Salad should be added to meals,
- Legumes should be taken frequently (Yıldız, 2008).

1.2. Proteins

It is responsible for the development and growth of the body and the repair of worn-out tissues. DM does not affect the body's protein needs. It should be taken in recommended proportions. However, if kidney deformations occur due to DM, protein intake should be reduced (Yıldız, 2008).

1.3. Oils

They are nutrients containing high energy. Excess cholesterol and fat taken with food can cause cardiovascular disease and obesity.

Amount of fat removed

- It consists of invisible fats in the structure of foods and visible fats added to foods from outside.
- The type and amount of fats are important in the development of cardiovascular diseases.
- Fats are grouped according to the type of fatty acid they contain.
- **Saturated fats:** A large proportion of the fats in solid fats, butter, lard, tallow, milk, meat and cheese (Y1ld1z, 2008).
- Polyunsaturated fats: Hazelnut oil and olive oil,
- **n-6 series:** Cotton, sunflower, soybean and corn oil.
- n-3 series: Fish oil
- To maintain health, the types of fat used in the diet should be in a certain balance.
- For this
- Red meat consumption should be stopped and chicken and fish meat should be preferred,
- 1-2 meals of fish should be consumed weekly.
- Extra oil should not be added to meat dishes.
- Solid fat should be left out in meals and replaced with oil, and the amount of fat should be minimized whenever possible.
- Eggs should be consumed 2 times a week,
- Organ meats and cholesterol (since they have high saturated fat content) should not be consumed.

- Meat products such as bacon, sausage, sausage and salami should not be consumed.
- Solid fats, lard, butter and tallow should not be consumed.
- Meals should be baked, boiled, and grilled instead of roasting and frying (Yıldız, 2008).

1.4. Minerals and vitamins

Diabetic patients with a balanced diet can meet their daily mineral and vitamin needs through diet (Bilgiç & Aktaş, 2022).

Meal time and number; consuming the foods recommended in the diet on time and in recommended amounts prevents hyper and hypoglycemia.

2. Diet products and artificial sweeteners

- Contains energy: Mannitol, fructose, xylitol and sorbitol.
- Those that do not contain energy: Acesulfame-K, saccharin, aspartame and cyclamate.
- It is recommended to have 3 main meals and 2-3 snacks. (Yıldız, 2008).
- Artificial sweeteners containing energy may increase blood sugar if taken in excess of a certain amount. Therefore, foods containing sweeteners should not be consumed without consulting a dietitian.
- Diet products are not products that can be consumed without restrictions. Although many diet products have low

carbohydrate content, they have high fat content. (Yıldız, 2008).

a. Nutrition recommendations

- Care should be taken to have a balanced and adequate diet,
- Appropriate body weight should be established and maintained,
- Meals should not be skipped,
- The timing and dosage of medication or insulin must be observed,
- Recommended physical activities such as walking should be done,
- Smoking should not be used (Yıldız, 2008).

b. Skin care

- A soapy bath should be taken daily or 2-3 times a week with warm water whose pH is suitable for skin health (pH 5.5). Irritating scrubs should not be used in the bathroom.
- Waxing and razor should not be used to remove body hair as they may cause injury. Hair removal creams should be preferred instead.
- When using cutting tools, care should be taken to avoid cuts or scratches on the skin. If there is a scratch or injury, it should be washed with warm soapy water and covered with sterile-gauze.
- The skin should not be exposed to sunlight, products with high protection properties should be applied (Anonim, 2020b).

c. Oral-dental health

- Teeth should be cleaned with a soft toothbrush at least 2 times a day and for not less than 3 minutes. Toothbrush should be renewed every 3 months.
- The spaces between the teeth should be cleaned once a day by using appropriate dental floss.
- After blood sugar is measured, a dental check-up should be performed. This process should be repeated every 6 months. If insulin is administered, it should be administered at the right time and dose before dental treatment (Anonim, 2020b).

d. Foot care

- Feet should be checked daily, and the back of the foot, sole of the foot and between the toes should be observed.
- Feet should be washed and dried every day. The spaces between the fingers should be kept dry as fungal infections can easily develop when wet. The temperature of the water in which the feet will be washed should not be too hot as it can easily cause burns on the skin. Feet should be kept moist with a moisturizing cream. However, the cream should not be applied between the fingers. Callus tapes and callus medicine should not be applied to calluses on the feet, and calluses should never be cut. Pumice stones should not be applied to the feet (Iraz et al., 2015).
- Nails should be cut with straight edges after bathing and should not cut deeply and injure.

- If your feet are cold, have heat sources; it should not be contacted with radiators, stoves and heaters. Instead, booties or thick socks should be worn.
- The soil should not be touched without slippers or shoes. Appropriate slippers should be worn when walking on the beach. The sole of the shoe worn must prevent foreign matter from sinking in.
- As for socks, woolen or cotton socks should be preferred instead of synthetic ones, with no seams on the toes, not boring at the ankles, and light colored ones if possible. These should also be changed daily (Anonim, 2020b).

e. Sex life

- Genital hygiene; people should be warned about washing from front to back when urinating, not touching the front areas with the hand touching the anus, drying with toilet paper, using cotton underwear, changing underwear daily, using disposable pads during menstruation, and changing pads for 3-4 hours.
- People with Type 1 and Type 2 DM should apply a good birth control program if pregnancy is not desired (Anonim, 2020b).

g. Smoking and alcohol use

- Smoking is prohibited because it increases the damage to large and small vessels.
- Drinking alcohol is prohibited. Alcohol use prevents blood sugar control. It causes high blood lipids and hypoglycemia. It

may trigger health problems such as acute cardiovascular diseases, fatty liver and coma (Anonim, (2020b).

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