Current Issues in
General Internal Medicine

Editor
Hülya Çiçek

LIVRE DE LYON
2023

Internal Medicine

Current Issues in General Internal Medicine

Editor

Hülya Çiçek

LIVRE DE LYON

Lyon 2023

Current Issues in General Internal Medicine

Editor

Hülya Çiçek

LIVRE DE LYON

Lyon 2023

Current Issues in General Internal Medicine

Editor •. Prof. Dr. Hülya Çiçek • Orcid: 0000-0002-1065-1582
Cover Design • Motion Graphics
Book Layout • Motion Graphics
First Published • March 2023, Lyon

ISBN: 978-2-38236-550-2

Publisher • Livre de Lyon
Address • 37 rue marietton, 69009, Lyon France
website • http://www.livredelyon.com
e-mail • livredelyon@gmail.com

PREFACE

Dear readers,

For societies to survive, they need to progress on the path of science. Continuity of belief and commitment to science is the road to success. We have published this book to contribute to the dissemination of true knowledge with the contributions of our dear friends who have embarked on a long journey in science and working in the fields of internal medicine. In this book, it has been determined that carefully selected different medical sciences topics are discussed and these topics are analyzed together with the past and the future, and the points we have reached in the field of medicine today. The preparation of our book took a long time, it covers very valuable topics that will contribute to science and our readers. I think that the efforts of our department writers, who meticulously write their valuable works by blending up-to-date information with their own academic experiences and literature contributions, are invaluable and I wish them continued success. I would like to thank our writers and publishing team for supporting our book with the hope that it will shed light on the scientists who work devotedly on scientific platforms for humanity.

Prof. Dr. Hülya ÇİÇEK

CONTENTS

CHAPTER I

TYPE 2 DIABETES MELLITUS

AKIF DOĞANTEKIN[1] & NEVZAT GÖZEL[2]

[1]Specialist Medical Doctor, Private Gaziantep Emek Hospital, Internal Medicine Department, E-mail: akifdogantekin@gmail.com, ORCID 0000-0001-6078-540X

[2]Associate Professor, Fırat University, Faculty of Medicine, Department of Internal Medicine, E-mail: drngozel@hotmail.com, ORCID ID: 0000-0001-7326-6860

1. Introduction

Diabetes Mellitus (DM) is now a pandemic health problem that we call an infectious disease. When we add impaired fasting glucose and impaired glucose tolerance to this, it affects approximately 30% of the world's population. Diabetes; is a chronic disease that causes hyperglycemia with insulin deficiency or relative insufficiency. Today, it is a health problem that has increasing importance all over the world due to its frequency and the problems it creates. Its incidence is increasing in the world and in countries. Due to the high prevalence of diabetes, innovative treatments are needed in the treatment of diabetes so that diabetics can lead healthier lives. Diabetes treatment aims to reduce blood sugar to normal levels and to prevent micro and macrovascular complications (1).

Insulin resistance and relatively decreased insulin secretion, which cause the emergence of the disease in type 2 diabetes patients, cause plasma glucose values to remain high during both fasting and postprandial periods. The UKPDS (UK Prospective Diabetes Study), the largest study on type 2 diabetes, clearly demonstrated the importance of glycemic control. Microvascular complications of diabetes in type 2 diabetes should be avoided treatment of hypertension, good glycemic control, and lipid disorders that often accompany type 2 diabetes (2).

2. Diagnostic Criteria for Diabetes

2.1. Fasting Blood Sugar

Two blood glucose measurements measured biochemically on different days after eight-10 hours of fasting are defined as prediabetes, and diabetes if they are between 100-125 mg/d and above 126 mg/dl.

2.2. Measuring Postprandial Blood Sugar

Postprandial blood glucose should be measured 2 hours after taking the first bite. A postprandial blood sugar between 140-200 mg/dL is described as impaired glucose tolerance, and over 200 mg/dL is described as diabetes (3).

2.3. Oral Glucose Tolerance Test (OGTT)

It should be applied to cases with suspected diabetes. After measuring fasting blood glucose, the patient is given 75 grams of sugary liquid to drink and blood glucose is measured again 2 hours later. If the measurement result is below 140 mg/dl, it is normal, if it is between 140-199 mg/dl, prediabetes is diagnosed, and if it is 200 mg/dl and above, diabetes is diagnosed (4,5).

24th-28th of pregnancy. If a postprandial glucose level of ≥140 mg/dl is ≥140 mg/dl 1 hour after drinking 50 g of glucose liquid at a random time during the 1st week of pregnancy, a further test (100 g or 75 g glucose test) should be performed.

2.4. Random Plasma Glucose Measurement

Blood glucose is measured at a random time and if diabetes symptoms accompany it if the measurement result is 200 mg/dl and above, diabetes is diagnosed (6).

2.5. Hemoglobin A1c (HbA1c) Measurement

The making of glycosylated hemoglobin A1c (HbA1c: A1C) as a diabetes diagnosis tool has not been recommended for many years due to problems in its standardization and uncertainty in the diagnostic threshold. In recent years, the making of HbA1c as a diabetes diagnostic test has been accepted as a result of standardization studies and increasing evidence for its prognostic importance all over the world (5,7).

Glycosylated hemoglobin (HbA1c) is glycosylated by binding to hemoglobin, the sugar in the bloodstream. Glycosylated hemoglobin remains

glycosylated for 120 days. As blood sugar increases, HbA1c also increases. HbA1c in the last 3 months, how did the blood sugar level It allows us to understand. The diagnosis of DM is made by measuring 6.5% or more of these values (8).

Age, ethnicity, and pregnancy may influence HbA1c results. The American Diabetes Association (ADA) emphasizes that healthcare professionals should wise up to this situation, make the right type of HbA1c test, and evaluate alternative diagnostic tests (fasting plasma glucose test or oral glucose tolerance test) when it's incompatibility with hemoglobin. HbA1c) and blood sugar levels (9).

It is recommended to measure glycosylated hemoglobin at the earliest every 3 months in patients with type 1 diabetes and type 2 diabetes using insulin or with uncontrolled sugar, and at the earliest every 6 months in patients with controlled type 2 diabetes (5,10).

Even though type 1 and type 2 diabetes are called by the same name, they are heterogeneous diseases and their clinical manifestations and progressions are different. Classification is essential in determining treatment. However, it may not be possible to classify every patient as type 1 or type 2 diabetes at the time of diagnosis. The approach that types 2 diabetes is seen in adults and type 1 diabetes in children is an old perspective. Type 2 diabetes may present with diabetic ketoacidosis. Children with type 1 diabetes can present with polyuria and polydipsia.

Classification:

1) Type 1 Diabetes: It develops autoimmune pancreatic β cells injury.

2) Type 2 Diabetes: The main trigger is insulin resistance and decrease insulin secretion from β cells day by day.

3) Gestational Diabetes: Diabetes who was healthy before pregnancy, diagnosed in the 2nd or 3rd trimester of pregnancy

4) Specific types due to other causes: Pancreatic diseases or tumors, drug- and chemical-induced diabetes (11).

3. Physiopathology

Metabolic disorder in Type 2 Diabetes Mellitus develops because of two disorders: 1- Insulin resistance in liver and muscle tissue, and 2- Decreased insulin production in the pancreas. Insulin resistance occurs with environmental reasons and genetic problems. The most important environmental causes are obesity and inactivity.

A person with insulin resistance, normal glucose tolerance in the early stages of Type 2 Diabetes adapts by secreting large amounts of insulin. Although the liver is also resistant to the influence of insulin, hyperinsulinemia is sufficient to prevent glucose secretion from the liver during fasting in people whose blood sugar begins to rise. Thus, the fasting sugar level is kept at normal levels (12).

Hyperinsulinemia is a buffer response of beta cells to overcome insulin resistance. Insulin has different effects on muscle and liver; such as the amount of insulin required to suppress glucose secretion from the liver is approximately 1/3 of the amount of insulin required to ensure glucose absorption into the muscle tissue. Over time, the liver's insulin resistance rises, causing a small increase in fasting blood sugar. The fasting glucose level of these people deteriorates and rises to 110-125 mg/dl. As a result, insulin secretion from the pancreas decreases and glucose secretion from the liver increases during sleep hours, and fasting blood sugar rises above 125 mg/dl. This set of pathophysiological disorders explains why postprandial hyperglycemia occurs many years before fasting hyperglycemia (13).

4. Treatment Approach

When the identification of type 2 diabetes is first made, the first thing to do is to create a medical nutrition therapy and exercise program and inform the patient about the disease. In addition, in the treatment of type 2 diabetes, medication or insulin therapy is required to control sugar. Medical treatment can only be effective in the long term with lifestyle changes. Existing metabolic problems in a patient with type 2 diabetes mellitus must be resolved. Since β-cell damage levels follow a progressive course, treatment interventions should be followed and developed. HbA1c levels must be reduced to 7% and below it to prevent reduced microvascular complications. Achieving the ideal weight and performing a regular sports program that reduces insulin resistance are the things that should be done before the person develops type 2 diabetes mellitus. Weight reduction and exercise are known to slow the onset of type 2 diabetes (2).

Antidiabetic drugs to make glycemic control in type 2 DM :

- Those that increase insulin discharging (sulfonylureas, glinides)
- Those that increase insulin sensitivity (biguanides, thiazolidinediones)
- Those that inhibit glucose absorption; alpha-glucosidase enzyme inhibitors (acarbose)

- Incretin-based therapies; dipeptidyl peptidase-4 (DPP-4) inhibitors, Glucagon-like peptide-1(GLP-1) analogues
- SGLT(Sodium Glucose Transporter) inhibitors (dapagliflozin, kanagliflozin, and empagliflozin)
- Amylin analogs (pramlintide)

4.1. Sulfonylureas

They increase insulin secretion by binding to sulfonylurea (SUR) receptors on the β cells of the pancreas. Thus, while insulin secretion decreases liver glucose output, it further increases glucose usage in peripheral tissues.

Sulfonylureas can be examined in 2 groups:

1st generation: Chlorpropamide, Tolbutamide, Tolazamide, Acetohexamide

2nd generation: Glyburide (Glibenclamide), Glipizide, Gliclazide, Glimepiride

First-generation sulfonylureas are not used today due to their very long half-lives and serious side effects (especially hypoglycemia). 2nd generation sulfonylureas are modern drugs that are still in clinical use due to their low side effects. Sulfonylureas should be preferred in cases where beta cell reserve is thought to be sufficient. Therefore, those with diabetes for less than 7 years are suitable candidates for sulfonylureas. Sulfonylureas are suitable alternatives for those who are of normal weight or underweight and for whom hypoglycemia does not pose a risk (14).

They are administered in single or divided doses daily, depending on the sulfonylurea group used, approximately 30 minutes before the meal. The main side effects are hypoglycemia, weight gain, allergy, skin rash, hepatotoxicity, rarely agranulocytosis, and bone marrow aplasia. When chlorpropamide is used with alcohol, it causes redness of the face. Sulfonylureas are contraindicated in diabetes mellitus due to type 1 diabetes, pancreatectomy, or subclinical inflammation of the pancreas, with a tendency to hypoglycemia. As with all oral antidiabetic drugs, it could never be used in chronic liver disease, renal failure, pregnant women, lactating women, major surgery, trauma, serious infection, sepsis, and acute metabolic decompensation such as ketoacidosis, hyperosmolar coma, lactic acidosis (15).

4.2. Glinides

Glinides stimulate insulin secretion by binding to a different point of sulfonylurea (SUR) receptors on pancreatic β-cells than sulfonylureas, closing the ATP-sensitive potassium channel. It is rapidly absorbed from the gut and subsequently metabolized in the liver, with a plasma half-life of less than one hour. They bind to receptors more quickly and dissociate faster. Thus, the drug causes a brief but rapid insulin stimulation. They are more effective in controlling postprandial hyperglycemia. It is taken before three meals a day. Repaglinide and nateglinide are commercially available. Repaglinide 0.5-1-2 mg tablet contains an active substance, the maximum dose is 16 mg/day. There are 60-120 mg tablets of nateglinide, which is originally a derivative of phenylalanine. The drug is rapidly absorbed from the gut, reaching peak plasma levels within one hour. It is metabolized in the liver and has a plasma half-life of approximately 1.5 hours. It causes rapid and short insulin secretion and is given before meals, thus lowering the postprandial plasma glucose level. Like other insulin secretagogues, its side effects are hypoglycemia and weight gain (16).

4.3. Biguanides (Metformin)

Metformin increases the sensitivity of both the liver and peripheral tissues to insulin. It suppresses both gluconeogenesis and glycogenolysis in the liver. In muscles, it is effective by rising insulin receptor tyrosine kinase activity, Glucose transporter type 4 **(**GLUT 4) number, and glycogen synthesis. More specifically, it lowers fasting and partially postprandial blood sugar. Metformin provides approximately 50 mg/dl reduction in fasting plasma glucose and a 1.5% reduction in HbA1c. The optimal dose is 2 grams per day. Since it does not affect insulin secretion, hypoglycemia is rarely seen. Unlike other antidiabetic agents, it doesn't gain weight, it causes mild weight loss or maintains weight stability. Mainly important side effects are gastrointestinal complaints such as nausea, vomiting, flatulence, abdominal pain, and diarrhea. All effects generally disappear after 15 days with slow dose increases, starting at a low dose. Metformin can also cause a metallic taste in the mouth and vitamin B12 deficiency with prolonged use. It is known that biguanides can cause lactic acidosis, but the incidence of metformin-induced lactic acidosis is very low. However, it is not recommended to be used in the presence of conditions that may facilitate lactic acidosis. Other contraindications should also be considered before initiating treatment with metformin (17).

4.4. Thiazolidinediones

Thiazolidinediones provide glycemic control by reducing insulin resistance. These compounds have a common It has structure of thiazolidine-2-4-dione and each has a different side chain. This dr drug effective in insulin discharging then increases the effect of insulin in peripheral tissues.

Thiazolidinediones bind and activate peroxisome proliferator stimulating receptor-γ (PPAR-γ). This receptor is usually expressed in adipocytes, regulating adipocyte differentiation and expression of adipocyte-specific genes. PPAR-γ is expressed to a lesser extent in muscles and the liver. Among the thiazolidinediones (TZD) group, rosiglitazone has the most potent PPAR-γ ligand (19).

Thiazolidinediones group drugs increase the uptake of free fatty acids by adipose tissue and inhibition of their mobilization. They may also rise the translocation of glucose transporters in muscles and immature adipocytes. They antagonize tumor necrosis factor-α effects. Thiazolidinediones improve insulin sensitivity by increasing glucose utilization in muscle and other tissues in humans. They have been reported to inhibit hepatic glucose production to a lesser extent. It has been shown that serum insulin and free fatty acid levels decrease with thiazolidinediones treatment. Pioglitazone and rosiglitazone are examples of this group of drugs (20).

4.5. Alpha-glucosidase inhibitors (Acarbose, miglitol, voglibose)

First used in the treatment of type 2 diabetes in 1996, acarbose is a purified pseudo tetrasaccharide of microbial origin. It acts only in the gastrointestinal tract and lowers postprandial glucose (14).

Complex carbohydrates are broken down into oligosaccharides by amylase in the small intestine. Oligosaccharides must be decomposed into monosaccharides before they can be absorbed. Oligosaccharides are decomposed into monosaccharides by alpha-glucosidase enzymes (glucoamylase, sucrase, maltase, dextrinase, and isomaltase) located on the brush border of enterocytes. Normally, carbohydrates are rapidly absorbed primarily from the distal duodenum and proximal jejunum. Alpha-glucosidase inhibitors reversibly bind to the enzyme, delaying carbohydrate absorption and absorption and maintaining it throughout the gastrointestinal tract. Thus, it causes a decrease in postprandial plasma glucose in both type 1 and type 2 DM. The mechanism of action of different alpha-glucosidase inhibitors is similar. Acarbose has little effect on isomaltase and no effect on lactase, the enzyme β-glucosidase (21).

Acarbose is less effective than sulfonylurea and metformin. It reduces HbA1c by 0.7-1% and postprandial glucose by 18-72 mg/dl (22).

Efficacy in treatment begins to be seen in the first week and continues for a long time. Absorption of acarbose is not good. In plasma, the active compound only reaches 1-2%. Acarbose is broken down by amylase and bacteria in the small intestine. It is excreted in the urine within 24 hours. The most important advantage of alpha glucose inhibitors is that they have a local effect in the intestine and do not have systemic effects. For this reason, it is especially suitable for elderly diabetic patients. They do not cause weight gain or hypoglycemia. Acarbose should be taken with the first bite at the beginning of each meal, and meals should be rich in complex carbohydrates. It should be started with a single meal a day at a dose of 25-50 mg a day and the dose should be increased gradually. The most important obstacle to the maximum dose (3x100 mg) is the gastrointestinal side effects. With the delay of carbohydrate digestion and absorption in the small bowel, oligosaccharides pass into the large intestine. Bacteria ferment carbohydrates and produce short-chain fatty acids, methane, and carbon dioxide. This condition causes gastrointestinal symptoms such as abdominal pain, gas, and diarrhea. If gastrointestinal side effects come to the fore during titration, sometimes the problem can be solved by reducing the dose, as the side effects will decrease over time (23).

In 25-45% of patients, drug discontinuation may be required due to side effects. May cause an elevation of liver enzymes when used in high doses. Drugs that affect intestinal motility potentially affect the efficacy and gastrointestinal side effects of acarbose, and cholestyramine reduces the antihyperglycemic effects of acarbose. The use of alpha-glucosidase inhibitors is contraindicated in inflammatory bowel disease and malabsorption. It should also not be used in advanced renal failure (17).

4.6. Incretin-based therapies: Dipeptidyl Peptidase-4 Inhibitors

Dipeptidyl Peptidase-4 Inhibitors (DPP-4); By inhibiting the DPP-4 enzyme, they prevent the metabolism of incretin hormones in the circulation. They prolong the duration of the action of glucagon-like peptide-1 (GLP-1). They improve the response of pancreatic alpha and beta cells to glucose (24).

Inhibition of DPP-4 rises prandial insulin secretion while suppressing glucagon secretion. With these effects, by suppressing hepatic glucose production and increasing peripheral glucose use; They degrade postprandial glucose levels in patients with type 2 diabetes (25).

For DPP-4 inhibitors to be effective, there must be a small amount of insulin released. Sitagliptin, saxagliptin, and linagliptin, among DPP-4 inhibitors, have been confirmed in the USA as oral antidiabetic therapy. Linagliptin; is a xanthine-based DPP-4 inhibitor. Even 24 hours after dosing, more than 80% of the DPP-4 enzyme is inhibited. alogliptin; binds strongly and highly selectively to the DPP-4 enzyme. Compared with saxagliptin, saxagliptin a, and vildagliptin, sitagliptin also inhibits the enzymes Dipeptidyl Peptidase-8 and Dipeptidyl Peptidase-9 besides DPP-4. dutogliptin; It is highly water soluble and has low cell permeability. It's binding to plasma proteins is not high. Maximal absorption occurs within 3-4 hours of ingestion and its half-life is 10-13 hours. dutogliptin; its effect on weight change is neutral and similar to placebo in terms of side effects (26).

4.7. Glucagon-like peptide-1 (GLP-1) Analogues

Glucagon-like peptide-1 (GLP-1) is a peptide hormone belonging to the incretin family containing 30 amino acids. GLP-1 is mainly secreted as preproglucagon from enteroendocrine L cells in the small intestine, and a small amount from pancreatic alpha cells and neurons. Proglucagon is converted to GLP-1, Glucagon-like peptide-2, glycerin, and oxyntomodulin in different organs, as the final product, in the bowels. In the brain, preproglucagon is produced in the nucleus tractus solitarius (NTS). GLP-1 can be expressed in neuronal cells in this region and extends to the hypothalamus and some thalamic and cortical regions. With food intake, GLP-1 stimulates insulin release in response to glucose and inhibits glucagon release. GLP-1 receptors haven't only found in pancreatic cells, but also in myocardial cells, vascular endothelium, and the central nervous system. It controls saturation and food intake in the gastrointestinal tract and inhibits glucagon release while ensuring pancreatic beta cell proliferation and survival (27).

In 1992, for the first time, GLP-1 infusion was shown to lower postprandial blood glucose in Type 2 diabetes patients. GLP-1 secretion in humans in answer to food intake is biphasic, with early (after 30-45 minutes) and late (after 60-90 minutes). Release in the early phase occurs via muscarinic receptors after stimulation of the vagus in response to food from L cells. In the late period, glucose, amino acids, long chain, and short-chain fatty acids in small intestines are directly stimulated resulting in metabolite cannot interact with the GLP-1 receptor. Synthetic derivatives of exendin-4 and other GLP-1 analogs (exenatide, liraglutide, lixisenatide, and dulaglutide) have begun to be used in diabetes

with their insulin-like effects. In terms of amino acid sequence, exenatide is 53% homologous to endogenous GLP-1. Liraglutide shows 97% homologous features. Short-acting drugs inhibit gastric emptying and inhibit postprandial blood glucose elevation. Long-acting ones have strong insulinotropic and glucagonostatic effects on fasting glucose levels (28).

GLP-1 analogs (other than dulaglutide) show their effects by easily crossing the blood-brain barrier in experimental models. For the use of short-acting exenatide, permission was granted by the American Medicines and Food Administration ("Federal Drug and Administration", FDA) in 2005, by the European Medicines Agency in 2006, and in 2012 for the use of long-acting exenatidine. Liraglutide was approved by the EMA in 2009 and by the FDA in 2010. In 2013, Lixisenatide was approved and started to be used. GLP-1 receptor agonists are effective in decreasing body weight as well as lowering blood glucose levels. After 21 clinical trials, when the use of placebo, insulin, and GLP-1 receptor agonists was compared in terms of body weight, it was shown that GLP-1 receptor agonists were more effective in decreasing body weight in diabetic, non-diabetic-obese individuals. Food-induced GLP-1 secretion is impaired in prediabetics and diabetics, and pancreatic beta cells are also resistant to endogenous physiological levels of GLP-1. However, high levels of GLP-1 overcome this resistance and cause insulin secretion. It has been reported that hyperglycemia in experimental animals reduces beta cell GLP-1 receptor production and ultimately causes GLP-1 resistance. GLP-1 secretion is normal in most Type 2 diabetes patients. However, resistance to GLP-1 is observed with impaired insulin secretion (29).

The GLP-1 receptor is conjugated with the G protein, and after binding to the receptor, the activation of adenyl cyclase rises the intracellular Cyclic adenosine monophosphate *(cAMP)* level, resulting in the activation of protein kinase A. Then, with the opening of Ca++ channels and increasing Ca++ in the cell, neurotransmitter release increases. However, activation of protein kinase (MAPK) pathways is mediated by PI3K. The production of genes is affected by cellular growth, repair, and differentiation. NTS is secreted from GLP-1 neurons in the brain and these neurons can reach the paraventricular nucleus. They cause satiety and anorexia through the interactions of neurons and their receptors. Extending to the nucleus, these neurons also influence the vagal motor information of the pancreas. Thus, insulin secretion increases and blood glucose is lowered by decreasing glucagon secretion. Intravenous administration of GLP-1 has been shown to dose-dependently reduce food intake and inhibit gastric emptying in obese and normal humans (30).

Because GLP-1 reduces appetite, GLP-1 derivative drugs are allowed to be used in the treatment of obesity. Recently, he has focused on the effects of GLP-1 on brain metabolism and functions. Uncontrolled Type 2 and Type 1 diabetic patient often develop peripheral neuropathy. In addition, gray matter reduction is observed in brain areas related to somatosensory perception. Atrophy is observed in various cortical and subcortical brain areas in type diabetes patients. The relationship between hemoglobin A1c (HBA1c) and cognitive dysfunction has been demonstrated. In addition, cardiovascular changes such as endothelial destruction, ventricular dysfunction, and atherosclerosis are also effective in the deterioration of cognitive functions. GLP-1 receptors have been detected in the central and peripheral nervous systems (31).

4.8. Sodium-glucose Cotransporter-2 (SGLT2) Inhibitors

Glucose reabsorption occurs through transporters such as Sodium-glucose Cotransporters (SGLT) and glucose transporter (GLUT). Glucose reabsorption from the glomerular filtrate occurs via SGLT, independent of insulin. In contrast to the Sodium-glucose Cotransporter, GLUT transporters ensure glucose uptake into insulin-sensitive tissues. SGLT transporters transport glucose using energy (32).

Approximately 90% of the filtered glucose in the kidney is reabsorbed by SGLT2, located in the first part of the proximal tubules, while the remaining 10% is reabsorbed by Sodium-glucose Cotransporter-1 (SGLT1). SGLT2 is a low-affinity, high-capacity carrier, while SGLT1 has a high-affinity, low-capacity carrier (33).

It has been observed that renal tubular glucose excretion rate is approximately 40 mg/dl higher (normally 180-200 mg/dl) in patients with type 2 diabetes. At the same time, increased reabsorption capacity in patients with type 2 diabetes increases the expression of SGLT2 in the proximal tubules. Ultimately, without correcting the hyperglycemia and further increasing it, it causes glucose toxicity. SGLT2 inhibitors have been developed to inhibit glucose reabsorption and ensure renal glucose excretion. SGLT2 inhibitors have provided a new perspective in the treatment of type 2 diabetes mellitus. The first SGLT2 inhibitor found was the natural compound phlorizin found in apple tree bark. The non-selective nature of the phlorizin molecule caused serious gastrointestinal side effects. In addition, its low oral bioavailability prevented its further development (34).

New drugs have been developed that specifically inhibit SGLT2 and do not act on SGLT1, which causes gastrointestinal side effects. Some of the

highly selective oral drugs that inhibit SGLT2 are dapagliflozin, canagliflozin, ipragliflozin, empagliflozin, and ertugliflozin. Most of the SGLT2-inhibitors are similar in structure. SGLT2 inhibitors; There are differences in the rate of binding to SGLT2 compared to SGLT1. SGLT2 inhibitors bind to SGLT1 to a lesser extent than SGLT2; In SGLT1 inhibition, it reduced diarrhea and similar side effects due to glucose-galactose malabsorption (35).

The effects of SGLT2 inhibitors are independent of insulin. Since other oral antidiabetic drugs act through insulin, their effectiveness decreases over time due to deterioration in pancreatic beta cell function. On the other hand, since SGLT2 inhibitors act independently of insulin, there is little decrease in their effectiveness over time. Its unique mechanism of action allows it to be used alone or in combination with other oral antidiabetics and insulins. The magnitude of this effect depends on the blood glucose level and glomerular filtration rate. Following the initiation of SGLT2 inhibitors, the filtered glucose load decreases with the decrease in blood glucose levels. In this case, urinary glucose excretion is also limited. In other words, their effects are proportional to the glucose load in the environment. When blood glucose level decreases, urinary glucose excretion of SGLT2 inhibitors decreases in parallel. This explains why they cause hypoglycemia to a lesser extent. SGLT2 inhibition decreases weight and fat mass by increasing urinary glucose excretion and causing calorie reduction. This effect reduces the two factors that conduce to the pathogenesis of diabetes (excessive calorie intake and overweight). They also cause a mild diuretic effect and moderate blood pressure reduction in patients with type 2 diabetes (36).

SGLT2 inhibitors cause osmotic diuresis. This increases the risk of hypotension and hypovolemia. Their effectiveness decreases in chronic renal failure. An increase in glucose in the urine theoretically increases the risk of genital fungus and urinary tract infections. In two recent studies; SGLT2 inhibitors have been reported to increase plasma glucagon levels while decreasing plasma insulin secretion. The new and unexpected increase in the hormone glucagon causes an increase in hepatic glucose production. The use of glucagon-like peptide-1 analogs, which will suppress the glucagon hormone, together with SGLT2 inhibitors may provide synergistic treatment (37).

4.9. Amylin analoques (pramlintide)

Amylin (IAPP), a peptide hormone, is secreted from the β cells of the pancreas in a coordinated manner with insulin at a ratio of approximately 100:1 (insulin:amylin). Amylin, which slows gastric emptying by increasing satiety,

plays a role in glucose regulation and prevents spikes in blood sugar levels after meals. Amylin, together with insulin and c-peptide, is a hormone secreted from beta cells in response to meals (38).

It has been shown in studies to be an important glucagon-regulating hormone that reduces glucose entry into the circulation after meals, especially by suppressing postprandial glucagon secretion and delaying gastric emptying. Pramlintide is currently administered as a subcutaneous injection. In type 2 DM patients, improvement in postprandial glycemia, a decrease in insulin dose and weight were detected (39).

5. Insulin Therapy

In type 2 diabetes, it is necessary to start treatment in the earlier stages of the disease to prevent insulin resistance, macrovascular risk, and early beta-cell failure. This strategy should definitely include initiating treatment with oral antidiabetics (OAD) in the early period, followed by a continuation of treatment with basal insulin or premixed insulin in the early period in Type 2 diabetes patients that can be suboptimally controlled with oral antidiabetics. Postprandial blood sugar levels in cases that cannot be controlled, intensive insulin therapy is required (40).

While ideal insulin therapy provides good glycemic control by mimicking endogenous insulin secretion, it should not cause adverse effects on the patient's quality of life. At the same time, it should control the basal glucose level by preventing hepatic glucose output and provide normal glucose homeostasis by providing post-meal regulation when necessary. Considering all these, insulin analogues, which show positive differences compared to human insulins, have been developed in order to realize ideal insulin therapy. Insulin analogues have a very important place in the treatment of diabetes with a lower risk of hypoglycemia, pharmacokinetic properties similar to physiological insulin secretion, advantages in glycemic control, and ease of use.

5.1. Long-acting (Basal) Insulin Analoques

5.1.1. Insulin Glargine

Insulin glargine is the first long-acting human insulin analogue. It differs from human insulin due to amino acid differences in the A and B chains. At position 21 in the A chain, asparagine and glulisine were replaced, and the B chain was lengthened by adding 2 arginines to its C-terminus. This modification

in the B chain neutralizes the isoelectric point of the molecule, while the A chain modification provides stability (41).

Thanks to these modifications, insulin glargine is soluble in a slightly acidic solution. However, when injected into the subcutaneous tissue, it forms precipitates in the form of hexamers at neutral pH. Thanks to this structure, insulin glargine dissolves slowly in the long term, providing blood insulin levels, so it has a peak-free profile, its duration of action is extended to 24 hours, and Neutral Protamine Hagedorn (NPH) insulin has lower intra-patient variability than insulin. The use of once-daily insulin glargine in combination with oral antidiabetics increases the compliance and quality of life of patients in the treatment of Type 2 diabetes compared to NPH insulin, thanks to both the flexible administration regimen and lowering the risk of hypoglycemia. Studies with patients with type 1 diabetes show a lower risk of symptomatic and nocturnal hypoglycemia compared to NPH insulin, while insulin glargine provides better Fasting Plasma Glucose (FPG) control and similar hemoglobin A1c (HbA1c) control.

However, a 30-month retrospective analysis shows that insulin glargine therapy provides better HbA1c control compared to NPH insulin in patients with Type 1 diabetes. In the treatment of type 2 diabetes, insulin glargine used together with oral antidiabetics (OAD) has lower symptomatic hypoglycemia and nocturnal hypoglycemia, less weight gain, more treatment satisfaction, better fasting plasma glucose (APG) control, and similar results compared to OAD+NPH insulin treatment. While HbA1c control is available, observational studies indicate better HbA1c control with insulin glargine (42).

5.1.2. Insulin detemir

Insulin detemir is a long-acting basal insulin analog and was obtained by adding myristic acid to lysine in B29 and subtracting threonine from B30 in human insulin. Thanks to insulin detemir myristic acid, it binds to albumin in the subcutaneous tissue and thus becomes a monomer more slowly. Thanks to this feature, its effect lasts longer than human insulin. The duration of action of insulin detemir was found to be peak-free and approximately 24 hours depending on the dose determined. The effect profile of insulin detemir is statistically significantly less variable and more predictable when compared to NPH insulin (43).

Patients using insulin detemir had significantly less glucose variability than patients using NPH. This feature is one of its therapeutic properties. In addition,

detemir causes mainly less weight gain than NPH. Limiting weight gain reduces the physiological barrier associated with initiation and compliance with insulin therapy in patients with Type 2 DM. In addition, detemir is clear and NPH is turbid insulin. The fact that the patient can use insulin without mixing it may also be one of the factors that increase treatment compliance (44,45).

5.2. Rapid-acting (Bolus) insulin analogues

5.2.1. Insulin Aspart

Insulin aspart is produced by substitution of the amino acid proline with aspartic acid at position B28 of insulin. Thanks to this structure, it has less tendency to form hexamers than regular human insulin; This allows insulin aspart to be absorbed faster from the subcutaneous tissue than regular human insulin. The effect of insulin aspart begins approximately 10-20 minutes after subcutaneous injection. The maximum effect is achieved within 1-3 hours after injection. The duration of action is 3-5 hours. In clinical studies in patients with type 1 diabetes, postprandial blood glucose levels were found to be lower with insulin aspart compared to regular human insulin. The insulin aspart group reported a willingness to continue the current treatment due to flexible treatment (46).

5.2.2. Insulin Lispro

Insulin lispro is a fast-acting insulin analogue. In the amino acid chain, proline and lysine are substituted at positions 28 and 29 in the B chain compared to human insulin. In this way, it is absorbed more quickly from the subcutaneous tissue. Maximum insulin concentration is reached faster and in a shorter time with insulin lispro compared to Regular Human insulin (RHI). It has been proven that insulin lispro has a faster onset of action and a shorter duration of action compared to regular human insulin. After insulin lispro is administered subcutaneously, its effect begins within 10-15 minutes. Clinical studies show that Post Prandial Glucose (PPG) levels 1 and 2 hours later with insulin lispro show similar or greater improvement than RHI. The improvement in HbA1c values was similar for the two insulins. With continuous subcutaneous insulin infusion, there is a greater improvement in PPG and HbA1c values compared to RHI with insulin lispro. Insulin lispro is as safe as human insulin. In clinical studies, hypoglycemia rates were similar to regular human insulin (RHI) in patients using insulin lispro (47).

5.2.3. Insulin Glulisine

Insulin glulisine is a fast-acting insulin analogue. With lysine instead of aspargine in the B3 position in the amino acid sequence and glutamic acid instead of lysine in the B29 position, the molecule became more soluble at physiological pH than human insulin and allowed for faster absorption. The absence of zinc in its content prevents the hexamer complex formation of the molecule. In addition, Polysorbate 20 content increases the stabilization of the molecule and prevents the formation of fibrils. It has been proven. Glulisine is both shorter and faster-acting than regular insulin. Insulin glulisine takes effect in about 5-20 minutes after it is inject insulin glulisine is absorbed twice as fast as human insulin (48).

In a study conducted on patients with type 1 diabetes, better PPG and HbA1c control was achieved with insulin glulisine administered before meals. Postprandial glucose (PPG) and HbA1c control are similar to insulin glulisine administered after meals and regular human insulin (RHI) administered before meals. In adolescents and children with type 1 diabetes, insulin glulisine is absorbed more rapidly from the subcutaneous tissue and remains in the systemic circulation for a shorter time than RHI. It is also as safe and well tolerated as insulin glulisine RHI. The duration of action of hypoglycemia RHI and the time to peak level is longer than that of insulin glulisine. Insulin glulisine causes nocturnal hypoglycemia to a lesser extent than regular human insulin. Severe hypoglycemia is observed at a lower rate with insulin glulisine given before and after meals compared to regular human insulin (49).

5.3. Biphasic (Premixed/premixed) insulin analogues

5.3.1. Biphasic Insulin aspart 30 (BIASp 30)

BIASp 30 is a biphasic insulin containing soluble insulin aspart (30%) and protamine insulin aspart (70%), and the pharmacokinetics of aspart are preserved in the mixture. The onset of action after subcutaneous administration is 10-20 minutes. The maximum effect is achieved within 1-4 hours after injection. The duration of action is up to 24 hours. The maximum serum insulin concentration achieved with BIASp 30 is approximately 50% greater than that achieved with Biphasic Human Insulins 30. The time required to reach maximum concentration is approximately half that of biphasic human insulins. According to Biphasic Human Insulins, the onset of action is rapid, so it can be given close to the meal (within the first 0-10 minutes of the meal). In a recent clamp study, BIASp 30

showed a better pharmacodynamic and pharmacokinetic profile with its earlier and higher activity than biphasic human insulin 30 (50).

In randomized studies, biphasic analogues have been shown to provide up to 40% better postprandial control. In an open-label, randomized, 4-period crossover study, BIASp 30 administered immediately before or after a meal provided better PPG control than Biphasic human insulins 30 administered in the same manner. In another comparison study, postprandial glucose increases were 44% lower after dinner and 34% lower after breakfast, and mean postprandial glucose increases were significantly lower (51).

5.3.2. Biphasic insulin lispro

It is a mixture of insulin lispro, which meets the need for prandial insulin, and protamine insulin lispro, which meets the need for basal insulin. They are mixtures in 25/75 or 50/50 ratios. Clinical studies in patients with Type 1 and Type 2 diabetes have shown that patients using insulin lispro have reduced episodes of nocturnal hypoglycemia compared to regular insulin. In a comparative study, it was shown that the peak increase in serum glucose was lower with biphasic insulin lispro than with biphasic human insulin 30. Serum insulin concentration was found to be higher after biphasic insulin lispro 25 compared to biphasic human insulin 30. Clinical studies have shown that insulin lispro controls postprandial hyperglycemia better than regular insulin (52).

References

1. Satman, I., Yilmaz, T., Sengul, A., Salman, S., Salman, F., Uygur, S., ... & TURDEP Group. (2002). Population-based study of diabetes and risk characteristics in Turkey: results of the Turkish diabetes epidemiology study (TURDEP). *Diabetes care*, *25*(9), 1551-1556.

2. UK Prospective Diabetes Study (UKPDS) Group. (1998). Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *The Lancet*, *352*(9131), 837-853.

3. Uusitalo, U., Lee, H. S., Andrén Aronsson, C., Vehik, K., Yang, J., Hummel, S., ... & Norris, J. M. (2018). Early infant diet and islet autoimmunity in the TEDDY study. *Diabetes Care*, *41*(3), 522-530.

4. Sonmez, A., Haymana, C., Bayram, F., Salman, S., Dizdar, O. S., Gurkan, E., ... & Araz, M. (2018). Turkish nationwide survEy of glycemic

and other Metabolic parameters of patients with Diabetes mellitus (TEMD study). *Diabetes research and clinical practice*, *146*, 138-147.

5. https://file.temd.org.tr/Uploads/publications/guides/documents/diabetes-mellitus_2022.pdf (Access Date: 25.01.2023).

6. Association American Diabetes. (2018). Updates to the standards of medical care in diabetes—2018. *Diabetes Care*, *41*(9), 2045-2047.

7. Ziegler, R., & Neu, A. (2018). Diabetes in childhood and adolescence: A guideline-based approach to diagnosis, treatment, and follow-up. *Deutsches Ärzteblatt International*, *115*(9), 146.

8. Akın, S., & Durna, Z. (2012). Lung cancer and care, chronic diseases and care. *İstanbul (Turkey): Nobel Medical Bookstores*, *1*, 161-176.

9. Pop-Busui, R., Januzzi, J. L., Bruemmer, D., Butalia, S., Green, J. B., Horton, W. B., ... & Richardson, C. R. (2022). Heart failure: an underappreciated complication of diabetes. A consensus report of the American Diabetes Association. *Diabetes Care*, *45*(7), 1670-1690.

10. Neu, A., Bürger-Büsing, J., Danne, T., Dost, A., Holder, M., Holl, R. W., ... & Ziegler, R. (2019). Diagnosis, therapy, and follow-up of diabetes mellitus in children and adolescents. *Experimental and Clinical Endocrinology & Diabetes*, *127*(S 01), S39-S72.

11. Uygur, M. M., & Yavuz, D. G. (2017). Diyabet tanısı ve sınıflandırılması. *Turkiye Klinikleri J Nutr Diet-Special Topics*, *3*(3), 120-129.

12. Genuth, S., Alberti, K. G., Bennett, P., Buse, J., Defronzo, R., Kahn, R., ... & Zimmet, P. (2003). Expert Committee on the Diagnosis and Classification of Diabetes Mellitus-American Diabetes Association. Follow-up report on the diagnosis of diabetes mellitus. *Diabetes care*, *26*, 3160-7.

13. Watkins, P. J., Amiel, S. A., Howell, S. L., & Turner, E. (2003). *Diabetes and its management*. John Wiley & Sons.

14. Avery, M. A., Mizuno, C. S., Chittiboyina, A. G., Kurtz, T. W., & Pershadsingh, H. A. (2008). Type 2 diabetes and oral antihyperglycemic drugs. *Current medicinal chemistry*, *15*(1), 61-74.

15. Nathan, D. M., Buse, J. B., Davidson, M. B., Ferrannini, E., Holman, R. R., Sherwin, R., & Zinman, B. (2009). Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes care*, *32*(1), 193-203.

16. German, M. S. (2011). Chapter 17. Pancreatic hormones and diabetes mellitus. Dalam: Gardner DG, Shoback D, eds. Greenspan's basic & clinical endocrinology.

17. Levetan, C. (2007). Oral antidiabetic agents in type 2 diabetes. *Current medical research and opinion*, *23*(4), 945-952.

18. Mudaliar, S., & Henry, R. R. (2001). New oral therapies for type 2 diabetes mellitus: the glitazones or insulin sensitizers. *Annual review of medicine*, *52*(1), 239-257.

19. Lebovitz, H. E. (2001). Insulin resistance: definition and consequences. *Experimental and clinical endocrinology & diabetes*, *109*(Suppl 2), S135-S148.

20. Fürnsinn, C., & Waldhäusl, W. (2002). Thiazolidinediones: metabolic actions in vitro. *Diabetologia*, *45*, 1211-1223.

21. Lebovitz, H. E. (2005). Management of hyperglycemia with oral antihypoglycemic agents in type 2 diabetes. *Joslin's Diabetes mellitus*, 687-710.

22. Krentz, A. J., & Bailey, C. J. (2005). Oral antidiabetic agents: current role in type 2 diabetes mellitus. *Drugs*, *65*, 385-411.

23. DeFronzo, R. A. (1999). Pharmacologic therapy for type 2 diabetes mellitus. *Annals of internal medicine*, *131*(4), 281-303.

24. B Ghatak, S., S Patel, D., Shanker, N., Srivastava, A., S Deshpand, S., & J Panchal, S. (2010). Alogliptin: a novel molecule for improving glycemic control in type II diabetes mellitus. *Current Diabetes Reviews*, *6*(6), 410-421.

25. Hollander, P. A., & Kushner, P. (2010). Type 2 diabetes comorbidities and treatment challenges: rationale for DPP-4 inhibitors. *Postgraduate medicine*, *122*(3), 71-80.

26. Pattzi, H. M. R., Pitale, S., Alpizar, M., Bennett, C., O'Farrell, A. M., Li, J., ... & PHX1149-PROT202 Study Group. (2010). Dutogliptin, a selective DPP4 inhibitor, improves glycaemic control in patients with type 2 diabetes: a 12-week, double-blind, randomized, placebo-controlled, multicentre trial. *Diabetes, Obesity and Metabolism*, *12*(4), 348-355.

27. Calsolaro, V., & Edison, P. (2015). Novel GLP-1 (glucagon-like peptide-1) analogues and insulin in the treatment for Alzheimer's disease and other neurodegenerative diseases. *CNS drugs*, *29*, 1023-1039.

28. Meier, J. J. (2012). GLP-1 receptor agonists for individualized treatment of type 2 diabetes mellitus. *Nature Reviews Endocrinology*, *8*(12), 728-742.

29. Muscogiuri, G., DeFronzo, R. A., Gastaldelli, A., & Holst, J. J. (2017). Glucagon-like peptide-1 and the central/peripheral nervous system: crosstalk in diabetes. *Trends in Endocrinology & Metabolism*, *28*(2), 88-103.

30. Crespo, C. S., Perianes Cachero, A., Puebla Jiménez, L., Barrios, V., & Arilla Ferreiro, E. (2014). Peptides and Food Intake. Front Endocrinol. 5: 58. *Frontiers Media SA*.

31. Brubaker, P. L., & Gil-Lozano, M. (2016). Glucagon-like peptide-1: The missing link in the metabolic clock?. *Journal of diabetes investigation*, *7*, 70-75.

32. Bailey, C. J., Gross, J. L., Pieters, A., Bastien, A., & List, J. F. (2010). Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with metformin: a randomised, double-blind, placebo-controlled trial. *The Lancet*, *375*(9733), 2223-2233.

33. Vestri, S., Okamoto, M. M., De Freitas, H. S., Aparecida Dos Santos, R., Nunes, M. T., Morimatsu, M., ... & Machado, U. F. (2001). Changes in sodium or glucose filtration rate modulate expression of glucose transporters in renal proximal tubular cells of rat. *The Journal of membrane biology*, *182*, 105-112.

34. Ehrenkranz, J. R., Lewis, N. G., Ronald Kahn, C., & Roth, J. (2005). Phlorizin: a review. *Diabetes/metabolism research and reviews*, *21*(1), 31-38.

35. Polidori, D., Sha, S., Mudaliar, S., Ciaraldi, T. P., Ghosh, A., Vaccaro, N., ... & Henry, R. R. (2013). Canagliflozin lowers postprandial glucose and insulin by delaying intestinal glucose absorption in addition to increasing urinary glucose excretion: results of a randomized, placebo-controlled study. *Diabetes care*, *36*(8), 2154-2161.

36. Ptaszynska, A., Hardy, E., Johnsson, E., Parikh, S., & List, J. (2013). Effects of dapagliflozin on cardiovascular risk factors. *Postgraduate medicine*, *125*(3), 181-189.

37. Merovci, A., Solis-Herrera, C., Daniele, G., Eldor, R., Fiorentino, T. V., Tripathy, D., ... & DeFronzo, R. A. (2014). Dapagliflozin improves muscle insulin sensitivity but enhances endogenous glucose production. *The Journal of clinical investigation*, *124*(2), 509-514.

38. Buse, J. B., Weyer, C., & Maggs, D. G. (2002). Amylin replacement with pramlintide in type 1 and type 2 diabetes: a physiological approach to overcome barriers with insulin therapy. *Clinical Diabetes*, *20*(3), 137-144.

39. Turan, E., & Kulaksızoğlu, M. (2015). Tip 2 diyabet tedavisinde güncel yaklaşımlar. *Okmeydanı Tıp Dergisi*, *31*(ek sayı), 86-94.

40. Martin, S., Schneider, B., Heinemann, L., Lodwig, V., Kurth, H. J., Kolb, H., ... & ROSSO Study Group. (2006). Self-monitoring of blood glucose in type 2 diabetes and long-term outcome: an epidemiological cohort study. *Diabetologia*, *49*, 271-278.

41. Barnett, A. H. (2003). A review of basal insulins. *Diabetic Medicine*, *20*(11), 873-885.

42. Ratner, R. E., Hirsch, I. B., Neifing, J. L., Garg, S. K., Mecca, T. E., & Wilson, C. A. (2000). Less hypoglycemia with insulin glargine in intensive insulin therapy for type 1 diabetes. US Study Group of Insulin Glargine in Type 1 Diabetes. *Diabetes care*, *23*(5), 639-643.

43. Heise, T., Nosek, L., Rønn, B. B., Endahl, L., Heinemann, L., Kapitza, C., & Draeger, E. (2004). Lower within-subject variability of insulin detemir in comparison to NPH insulin and insulin glargine in people with type 1 diabetes. *Diabetes*, *53*(6), 1614-1620.

44. Philis-Tsimikas, A. (2008). An update on the use of insulin detemir, with a focus on type 2 diabetes (drug evaluation update). *Expert Opinion on Pharmacotherapy*, *9*(12), 2181-2195.

45. Valensi, P., & Cosson, E. (2005). Is insulin detemir able to favor a lower variability in the action of injected insulin in diabetic subjects?. *Diabetes & metabolism*, *31*(4), 4S34-4S39.

46. Mathiesen, E. R., Kinsley, B., Amiel, S. A., Heller, S., McCance, D., Duran, S., ... & Insulin Aspart Pregnancy Study Group. (2007). Maternal glycemic control and hypoglycemia in type 1 diabetic pregnancy: a randomized trial of insulin aspart versus human insulin in 322 pregnant women. *Diabetes care*, *30*(4), 771-776.

47. Becker, R. H. A., Frick, A. D., Burger, F., Potgieter, J. H., & Scholtz, H. (2005). Insulin glulisine, a new rapid-acting insulin analogue, displays a rapid time-action profile in obese non-diabetic subjects. *Experimental and clinical endocrinology & diabetes*, *113*(08), 435-443.

48. Becker, R. H. A., Frick, A. D., Teichert, L., Nosek, L., Heinemann, L., & Rave, K. (2009). Dose–response relationship of insulin glulisine in subjects with type 1 diabetes. *Diabetes, Obesity and Metabolism*, *11*(1), 60-68.

49. Garg, S. K., Rosenstock, J., & Ways, K. (2005). Optimized basal-bolus insulin regimens in type 1 diabetes: insulin glulisine versus regular human insulin in combination with basal insulin glargine. *Endocrine practice*, *11*(1), 11-17.

50. Heise, T., Heinemann, L., Hövelmann, U., Brauns, B., Nosek, L., Haahr, H. L., & Olsen, K. J. (2009). Biphasic insulin aspart 30/70: pharmacokinetics and pharmacodynamics compared with once-daily biphasic human insulin and basal-bolus therapy. *Diabetes Care*, *32*(8), 1431-1433.

51. McSorley, P. T., Bell, P. M., Jacobsen, L. V., Kristensen, A., & Lindholm, A. (2002). Twice-daily biphasic insulin aspart 30 versus biphasic

human insulin 30: a double-blind crossover study in adults with type 2 diabetes mellitus. *Clinical therapeutics*, *24*(4), 530-539.

52. Wilde, M. I., & McTavish, D. (1997). Insulin lispro: a review of its pharmacological properties and therapeutic use in the management of diabetes mellitus. *Drugs*, *54*, 597-614.

CHAPTER II

HYPERLIPIDEMIA

AKIF DOĞANTEKİN

(MD), Internal Medicine Specialist, Private Gaziantep Emek Hospital, Internal Diseases Clinic, E-mail: akifdogantekin@gmail.com, ORCID: 0000-0001-6078-540X

1. Introduction

Hyperlipidemia (HL) is expressed as an increase in blood levels of lipoproteins with different contents consisting of lipid and protein composition. When we say HL lipid profile, one, more, or all of the parameters such as total cholesterol (TC), low-density lipoprotein (LDL-C), and triglyceride (TG) increase, and high-density lipoprotein (HDL-C) levels decrease. Other medical synonyms are high cholesterol (hypercholesterolemia), high lipoprotein (hyperlipoproteinemia), and high blood fat, which we use to explain to our patients (1).

Lipoproteins are triglyceride, cholesterol, and protein compounds called apoprotein (Apo). Lipoproteins are compounds that function for the control, balance, and transport of blood lipid levels. TGs are obtained from ingested food by intestinal reabsorption. It is a storage state of fat in the body. They are deposited more in the abdominal region in men and the hips in women. Cholesterol is the essential fat of tissues and cells. It is present in the cell membrane as a phospholipid (2).

2. Pathophysiology of Atherosclerosis

The most fundamental development regarding hyperlipidemia was found by a German scientist in 1956. This scientist, who is a pathologist, found that cholesterol deposits in the vascular structure cause atherosclerosis. He also stated that the main cause of atherosclerosis is due to vascular endothelial damage (3).

Endothelial cells are the most important structure for the health of the vascular structure. Vascular structures are composed of three layers. Tunica

intima, media, and adventitia. Endothelial and subendothelial layers are found in the tunica intima layer. The main cell that determines the selective permeability of the vessel and the contraction and relaxation of the elastic fibers in the subendothelial tissue and the smooth muscle in the tunica media is the endothelial cell. Any damage to these vital functions of the endothelium seriously affects the overall hemodynamics of the body. The normal vascular structure is smooth and does not impede the flow of blood. The most important vascular component that provides this is the endothelium. In the case of HL, plaque, which we call atherosclerosis, occurs in this endothelial structure and subendothelial tissue. This causes the narrowing of the vascular lumen, reducing the blood supply of the organs. LDL-C is the most atherogenic blood fat with the highest atherogenic index. With the accumulation of LDL-C in the subendothelial tissue, the secretion of inflammatory cytokines interleukin-1 (IL-1), tumor necrosis factor-α (TNF-α), transforming growth factor-β (TGF-β) increases and inflammation cells in this region It also accumulates (4).

High LDL-C levels increase oxidation in the body. This situation triggers many pathological events such as the domino effect. Macrophages phagocytize oxidized LDL-C to form structures called foam cells. Foam cells accumulate in the subintimal tissue, forming fatty streaks that are the beginning of plaques called atherosclerosis. These lines are not at the level to narrow the lumen and reduce blood flow. Foam cells, called foam cells, are reduced by programmed cell death and undergo necrosis. This necrotic tissue is surrounded by transmigration and proliferation of muscular tissue from the middle layer of the vessel to the intima. The last connective tissue elements surround this necrotic central-muscular tissue structure like a capsule. We call this newly formed tissue fibrous plaque, and this tissue is now the lesion that narrows the vessel lumen and diameter. The necrotic lipid center consisting of foam cell remnants grows larger unless the elevation of LDL-C and TG is treated. This growing plaque turns into an unstable plaque structure. If the plaque capsule ruptures, a plaque structure is formed in which a thrombus is attached as a result of contact with blood, which we call a complicated plaque. Complicated plaque (atherosclerosis) is the most important cause of cardiovascular diseases, which is the number 1 cause of death in our country and worldwide. It causes occlusion in all arteries, especially the coronary arteries, which are the vessels originating from the aorta, and slows down the blood flow. This is what makes HL important to clinicians. The antiatherogenic blood lipoprotein is HDL-C. For this reason, it is popularly known as good or beneficial cholesterol (5).

3. Classification of Hyperlipidemia

We divide HL into 2 groups primary and secondary. The primary is mostly familial, that is, hereditary hyperlipidemia, and the second one represents hyperlipidemia due to the underlying disease or drug use. Treatment of HL primarily requires lifestyle regulation, daily physical activity, and dietary measures. Despite this, if the result is not obtained, the use of drugs, which we call medical treatment, should be started. The most important drug group in medical treatment is 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMG-CoA reductase) enzyme inhibitors, which we call the statin group. Our goal in this treatment is to bring the levels of LDL, which is atherogenic cholesterol, to levels that will not cause cardiovascular complications (6).

Primary hyperlipidemias are divided into 5 groups according to the Fredrickson classification. A disadvantage or defect of this classification is that it does not refer to or evaluate anti-atherogenic cholesterol, and HDL-C levels.

Table 1. Fredricson classification in primary hyperlipoproteinemia (7)

Type	Increased lipoprotein	Cholesterol	TG	Chylomicron
I	Chylomicron	Normal or ⇑	⇑⇑	⇑
IIa	LDL	⇑	Normal	Not
IIb	LDL, VLDL	⇑	⇑	Not
III	β-VLDL	⇑	⇑	can be found
IV	VLDL	Normal or ⇑	⇑	Not
V	VLDL, chylomicron	Normal or ⇑	⇑ ⇑	⇑

Secondary hyperlipidemia, on the other hand, is acquired hyperlipoproteinemia, that is, secondary to the underlying pathology. This type of hyperlipidemia also has a clinical picture similar to the hereditary ones. Pathophysiologically, early-developing atherosclerosis is also present in these patients. The most common causes of secondary hyperlipidemia are diabetes mellitus, insulin resistance, thiazide diuretics, beta-blockers, hypothyroidism, chronic renal failure, alcohol use, western diet, obesity, pregnancy, acromegaly, androgens, glucocorticoids, isotretinoin and cyclosporine (8).

Diabetes mellitus (DM) is a metabolic disease that progresses with decreased insulin levels or insulin receptor insensitivity, not only with carbohydrates but also with an imbalance in fat and protein metabolism. DM is a risk factor for cardiovascular diseases. The most important reason for this is the predisposition to dyslipidemia in patients with diabetes. As insulin functions

decrease in DM patients, free fatty acids increase in the blood. As a result of this increase, TG production increases in the liver. Cholesterol ester transport protein (CTEP) replaces TG-VLDL transport with HDL-K ester transport. As a result of this change, HDL-C rich in TG and VLDL and with more atherogenic potency is synthesized instead of HDL-C with high anti-atherogenic power. This atherogenic HDL-C is degraded by lipoprotein lipase (LPL) and hepatic lipase (HPL) in the liver. This change stimulates the production of TG-rich LDL-C. TG levels increase after meals in DM patients. As a result, the risk of atherosclerosis and ischemic heart disease increases (9).

Diuretics are the first choice drug group in the treatment of hypertension. Taking thiazide diuretics in doses higher than 50 milligrams per day causes an increase of approximately 10% in total and LDL-C levels. They increase the TG level by about 5%. It has been observed that cholesterol levels have returned to normal after use exceeding 1 year. They cause hyperuricemia by increasing uric acid absorption by causing fluid loss from the proximal tubule. Use of more than 25 mg/day causes hyperglycemia. Caution should be exercised in patients with DM and insulin resistance (10).

β-blockers should be used with caution in patients with asthma and diabetes. These 2 diseases make it difficult to control. Propranolol lowers HDL-C levels and increases TG levels.

In hypothyroidism, oxygen use and basal metabolic rate decrease. Sodium and water retention increase. Lipid accumulation makes it difficult to lose weight and even causes weight gain. The fat breakdown is reduced. TC, TG, and LDL-C levels increase. As noted, hypothyroidism increases lipid forms leading to atherosclerosis.

In chronic renal failure, when proteinuria is intense initially, the production of Apo B-containing lipoproteins such as VLDL and LDL in the liver increases. Lipoprotein degradation is reduced and LDL receptor sensitivity decreases. TG increases. There is no specific change in HDL-C level.

Alcohol use increases plasma TG and LDL-C levels. This condition is also associated with cardiovascular disease, alcoholic fatty liver, and pancreatitis. The cause of high TG is increased VLDL secretion, fatty acid flow from adipose tissue to the liver, and impaired lipolysis. Therefore, alcohol use should be discontinued or reduced in patients with a diagnosis of hypertriglyceridemia (11).

For a patient with an HL diagnosis, it is recommended to regulate his diet, to ensure that he reaches the ideal body weight, and to exercise regularly.

Consumption of foods containing saturated fatty acids increases TC and LDL-C levels. Intake of foods containing monounsaturated fatty acids increases HDL-C levels. To reduce LDL-C levels, it is necessary to reduce the amount of fat in the diet and increase the consumption of foods containing polyunsaturated fatty acids (PUFA). One of the PUFAs, omega-3 fatty acids reduce LDL-C synthesis in the liver and thus lowers the TG level. In the distribution of the daily energy source, saturated fatty acids mustn't exceed 7-8%. It is appropriate to take at least 30 gr/day since the fiber taken with food affects reducing cardiovascular diseases. A healthy diet should consist of vegetables, fruits, fiber, whole grains, and fish and contain low levels of FFA (12).

In HL occurring in obese patients, plasma TG and free fatty acids increased and HDL-C levels decreased. Lipolysis increases and in parallel with this, free fatty acid (FFA) release from adipose tissue increases. An increase in FFA increases VLDL production by decreasing LPL activity in adipose tissue and muscle tissue. As a result, the levels of TG and cholesterol esters rich in TG increase. As a result, HDL-C levels decrease. TG-rich LDL-C levels increase. Pro-inflammatory cytokines such as IL-1, IL-6, TNF-α, and adiponectin released from adipose tissue facilitate the formation of HL in obese patients (13).

Acromegaly is a clinical picture characterized by excessive secretion of growth hormones in the body. It is seen with an annual frequency of about 3-15% in the world. The most common cause of mortality in acromegaly is cardiovascular disease. The most common cause of the cardiovascular disease is HL. TC levels are high. DM and insulin resistance are increased in acromegalic patients (14).

The use of drugs containing glucocorticoids increases the volume of fluid in the body, creating a tendency to dysrhythmia and atherosclerosis. Again, the most important reason for this is HL. Daily use of glucocorticoids equivalent to 10 mg prednisone is associated with HL. Cases with long-term use of glucocorticoids at high doses should be followed up for hyperlipidemia (15).

4. Complications of hyperlipidemia

4.1. Atherosclerosis

It is the accumulation of lipid and inflammatory cells that occurs in the intima and media layers of the vascular bed and narrows the vessel lumen. It is the most vital complication of HL. Atherosclerotic plaque consists of 3 components. The first is an atheroma, a mass of macrophages located in the

middle of the plaque. The second component is the cholesterol layer, and the third is the outermost layer with calcium deposits.

4.2. Coronary Artery Disease (CAD)

Atherosclerotic plaque is the most important cause of CAD. Atherosclerosis is the main cause of CAD. The lumen of the coronary arteries that supply the heart muscle narrows. Cardiac hemodynamics is impaired. If this hemodynamics progresses further, damage to the heart muscle occurs. If the patient has a disease such as hypertension, this further increases myocardial hypertrophy. Myocardial injury may occur even earlier. This hypertrophy causes congestive heart failure in the later stages (16).

4.3. Myocardial Infarction (MI)

When the coronary artery lumen narrows and myocardial damage progresses, the inevitable result is MI. This clinical picture occurs as a result of a thrombus formed when the capsule of the complicated plaque in the coronary artery ruptures and comes into contact with the lipid core. There is nearly 100% stenosis here. Up to 30% of MI patients have high cholesterol. This shows that MI is not only caused by HL but is also multifactorial.

4.4. Angina Pectoris

Angina pectoris is a symptom. It is characterized by a feeling of tightness in the chest, pain, and restlessness. There is a decrease in the nutrition of the myocardium or a nearly complete feeding problem. It is a very serious precursor of MI. Cardiac controls and, if necessary, coronary angiography should be performed in a patient with angina symptoms. Angina can be confused with clinical pictures such as muscle pain, reflux, reflux esophagitis. Even when we rule out these diseases, we first check the heart and then rule out other clinical pictures. The reason for this is that the patient does not die due to reflux or muscle pain, but if there is indeed a condition that is a precursor to ischemia, such as angina, mortality may result (17).

4.5. Cerebrovascular disease (CVD)

We call CVD the clinical picture characterized by a decrease or almost complete occlusion of blood flow as a result of atherosclerotic plaque formed in the arteries feeding the brain. Fat and ketone bodies are used by the brain the disruption the transmission of glucose, which is the main food source of the brain, to the brain. This clinical picture is characterized by a decrease in blood

pH, which we call ketosis. Loss of consciousness may develop as a result of metabolic acidosis. The plaque formed is mostly in the carotid and vertebral arteries. If the capsule of the complicated plaque ruptures, a thrombus forms. This thrombus can clog even the thinnest capillaries of the brain, like a kind of stray mine. It causes the clinical picture we call an ischemic stroke. As a result of ischemia, brain cells die and these necrotic tissues become irreversibly dysfunctional. With the reduction of TC and LDL-C levels by around 20%, the risk of stroke is significantly reduced (18).

5. Symptoms of hyperlipidemia

HL is not a disease with specific symptoms. It gives symptoms according to the degree of stenosis in the involved organs and arteries. With the formation of plaque in the cardiac coronary, chest pain and MI occur. A clinical picture ranging from headache, dizziness, brain fog, and convulsions to ischemic stroke and even death occurs due to carotid and vertebral artery stenosis. Since HL is a component of metabolic syndrome, clinical conditions such as insulin resistance, prediabetes, and DM may occur. Xanthelasma formation around the eyes, xanthomas in the tendons, and acne-like lesions on the skin occur (19).

6. Diagnosis of hyperlipidemia

The diagnosis of hyperlipidemia is made with a blood test. We check TG, TC, LDL-C, HDL-C, and VLDL-C levels, which we call lipid profiles, in blood tests. These examinations are done from the age of 20. If the lipid profile is found to be normal, it is repeated at 5-year intervals. If the lipid profile is found to be abnormal, it is followed up with diet and lifestyle changes. If it does not decrease despite this, pharmacological treatment should be arranged. In secondary HL, if the underlying disease is treated more, HL is also treated. Normal levels for the lipid profile are listed below (Table 2).

Table 2. Normal lipid levels (20)

Lipidler	Ideal value	Limits	High
TC	< 200 mg/dl	200-239 mg/dl	> 240 mg/dl
LDL-C	< 100 mg/dl	130-159 mg/dl	> 160 mg/dl ≥ 190 mg/dl (very high)
HDL-C	≥ 60 mg/dl	Male 40-59 mg/dl Female 50-59 mg/dl	Male < 40 mg/dl Female < 50 mg/dl
TG	< 150 mg/dl	150-499 mg/dl	500-1000 mg/dl ≥ 1000 mg/dl (severe)

7. Prevention of hyperlipidemia

Nutrition is the most important factor in the prevention of HL. First of all, if the patient is obese, he should lose weight and reach the ideal weight. Vegetable oils should be preferred. Omega-3 needs should be met by consuming fish at least 2 times a week. 35-40 g of pulp should be taken daily. It would be more accurate to buy whole wheat or bran bread instead of white bread. Bulgur, which has a low glycemic index, should be preferred over rice. To increase fiber intake, fruits, and vegetables should be eaten with their peel. The consumption of chickpeas, lentils, and beans, which are high in protein and low in fat, should be increased. Snacks such as hazelnut, walnut, and almond should be consumed due to both their pulp and their hypolipidemic effects. It would be more appropriate to boil or grill foods instead of frying them. While cooking meat dishes, oil should not be added from the outside and should be cooked in its fat. Margarine, butter, and lard should be avoided. Alcoholic beverages, double-triple instant coffee mixes, and soft drinks such as cola should not be drunk. Oily meat products such as chicken skin, oily fish, fatty meat, sausages, and bacon should be avoided (21).

8. Hyperlipidemia treatment

We have 2 options for the treatment of HL. The first and most important is a lifestyle change. In addition to paying attention to diet, it is important to increase daily physical activity. Because physical activity decreases the level of atherogenic lipids such as TC, LDL-C, and TG, while it increases the levels of anti-atherogenic lipids such as HDL-C. It is recommended to quit smoking and alcohol use. Good, quality, and timely sleep is important as it increases melatonin secretion. It not only reduces lipid levels but also prevents the development of chronic diseases and malignancies with its antioxidant properties.

The second option is drug therapy. If the patient has hereditary HL, coronary artery disease (CAD), or has at least 2 risk factors equivalent to CAD, priority drug therapy should be initiated. Our hypolipidemic drugs are frequently statins, niacin, fibric acid derivatives, bile acid sequestrants, and ezetimibe. Although treatment with a single drug is generally possible, we recommend combined treatments in some extreme cases. We generally recommend lifelong medical treatments and lifestyle changes (22).

REFERENCES

1. Amit G, Vandana S, Sidharth M. Hyperlipidemia: An Updated Review. Inter J of Biopharma & Toxicol Res 1:81-89; 2011.

2. Ankur R, Nidhi D, Seema R, Amarjeet D, Ashok K.Hyperlipidemia- a Deadly Pathological Condition. Inter J Curr Pharma Res 4:15-18;2012.

3. Virchow RP, Thrombose IG. In Gesammelte Abhandlungen zur Wissenschaftlichen Medicin. Frankfurt-am-Main, Meidinger Sohn & Company, S 458-564; 1856.

4. Chin J et al. Association between remnant lipoprotein cholesterol levels and non-alcoholic fatty liver disease in adolescents. JHEP Rep. 2020 Jul 24;2(6):100150.

5. Vallace, P., Vascular endothelium, its physiology and pathophysiology. In: Weatherall DJ et al. Oxford text book of medicine, 3rd ed.Oxford Medical Publications. 1996;2, 2295-2300.

6. Adams SP, Tsang M, Wright JM. Lipid-lowering efficacy of atorvastatin. Cochrane Database Syst Rev. 2015 Mar 12;2015(3):CD008226.

7. Mahley RW, et al. Disorders of lipid metabolism. In: Larsen PR, et al (eds). Williams Textbook of Endocrinology. 10th ed. Philadelphia: Saunders, 2003: 1642-91.

8. Sumino H, Murakami M. Causes and Abnormal Lipid Laboratory Values of Secondary Hyperlipidemia: Endocrine Disease. Rinsho Byori. 2016 May;64(5):513-517.

9. Knopp RH, Retzlaff B, Aikawa K, Kahn SE. Management of patients with diabetic hyperlipidemia. Am J Cardiol. 2003 Apr 3;91(7A):24E-28E.

10. Perez-Stable E, Caralis PV. Thiazide-induced disturbances in carbohydrate, lipid, and potassium metabolism. Am Heart J. 1983 Jul;106(1 Pt 2):245-51.

11. Boudewijn Klop et al. Alcohol and plasma triglycerides. Curr Opin Lipidol. 2013 Aug;24(4):321-6.

12. Yilmaz H O. Hyperlipidemia and Nutrition. Turkish Journal of Health Sciences and Research, 1(2), 2018, 72-82.

13. Klop B, Elte JW, Cabezas MC. Dyslipidemia in obesity: Mechanisms and potential targets. Nutrients 2013;5:1218-1240.

14. Mearns BM. Targeting levels and functions of blood lipids in the prevention of CVD. Nat Rev Cardiol 2011;8:179-80.

15. Poetker DM, Reh DD. A comprehensive review of the adverse effects ofsystemic corticosteroids. Otolaryngol Clin North Am 2010; 43: 753-768.

16. Shepard DR, Jneid H, Thacker HL. Gender, hyperlipidemia, and coronary artery disease. Compr Ther. 2003 Spring;29(1):7-17.

17. Park J, Kim JR, Shin DG, Cho KH. Females with angina pectoris have altered lipoprotein metabolism with elevated cholesteryl ester transfer protein activity and impaired high-density lipoproteins-associated antioxidant enzymes. Int J Mol Med. 2012 Apr;29(4):683-9.

18. Alloubani A, Nimer R, Samara R. Relationship between Hyperlipidemia, Cardiovascular Disease and Stroke: A Systematic Review. Curr Cardiol Rev. 2021;17(6):e051121189015.

19. Stewart J, McCallin T, Martinez J, Chacko S, Yusuf S. Hyperlipidemia. Pediatr Rev. 2020 Aug;41(8):393-402.

20. Turkish Society of Endocrinology and Metabolism, Obesity, Lipid Metabolism, Hypertension Working Group. Dyslipidemia diagnosis and treatment guide – 2021. 9th Edition: October 2021.

21. Saklayen MG. The Global Epidemic of the Metabolic Syndrome. Curr Hypertens Rep. 2018 Feb 26;20(2):12.

22. Malik J et al. Modern Lipid Management: A Literature Review. Cureus. 2020 Jul 24;12(7):e9375.

CHAPTER III

PARANEOPLASTIC NEUROLOGICAL DISEASES

CANSU SARIKAYA

(MD) Neurology Specialist, Sivas State Hospital, Sivas,
e-mail: cansuegilmez@hotmail.com
ORCID: 0000-0002-5790-8488

Introduction

Paraneoplastic syndrome is a dysfunction that occurs in an organ despite the absence of a primary tumor or metastasis. The mechanism is still unclearly explained and autoimmune mechanisms are thought to be responsible. The basic mechanism is composed of the immune response against nervous system-specific antigens expressed in cancer cells. Thus, it can affect any part of the peripheral or central nervous system (1).

Anti-neuronal antibodies are helpful in diagnosis but there may also be syndromes in which the antibody is indefinable. Clinical symptoms and examination are therefore the most crucial steps. Imaging, cerebrospinal fluid (CSF) examination, electroencephalography (EEG), and electromyelography (EMG) examinations can be used in diagnosis (2, 3).

1. Major Paraneoplastic Neurological Syndromes

1.1. Encephalomyelitis

This is an inflammatory condition that affects the dorsal root ganglia, peripheral nervous system, and nerve roots in addition to different regions of the central nervous system. This syndrome might be accompanied by 25% autonomic dysfunction and often with anti-Hu antibodies. This may occur with other cancers, especially small-cell lung cancer. Pleocytosis and protein increase can be seen in CSF examination, and pathology is often detected on EEG (4).

1.2. Limbic Encephalitis

This syndrome is characterized by seizures, memory loss, cognitive dysfunction, and psychiatric symptoms in which limbic structures are involved. This is a paraneoplastic disease usually associated with the distant effect of small cell lung cancer (SCLC) and can also be associated with other cancers such as testicular carcinoma, thymoma, and Hodgkin lymphoma. Anti-Ma and Anti-Hu are the most frequently observed antibodies. The increase in T2 signal, which specifically involves temporal zones, has a high sensitivity on MR imaging. Normal activity or slowing and spike activity can be observed on EEG. Pleocytosis and protein increase can be seen in CSF (5, 6).

1.3. Progressive Cerebellar Syndrome

This syndrome is characterized by progressive cerebellar syndrome over weeks and months. Ataxia, dysarthria, and nystagmus may occur. Cerebellar atrophy may later be seen. It may accompany gynecological and breast cancers. It is often accompanied by anti-Ri and anti-Yo antibodies. There is an extensive loss of Purkinje in the cerebellum in pathology (7, 8).

1.4. Opsoclonus-Myoclonus Syndrome

The syndrome is characterized by high-frequency, involuntary, saccadic eye movements and non-rhythmic myoclonus, and is accompanied by cerebellar involvement and encephalopathy. It is most commonly associated with small cell lung cancer and breast cancer in adults and neuroblastoma in children. Anti-Ri antibody has often been found to be associated (9, 10, 11).

1.5. Sensorial Neuropathy

This occurs due to the involvement of sensory neurons of the dorsal root ganglia and may be accompanied by motor findings due to the involvement of motor nerve roots. It usually starts with paresthesia complaints that have begun in the lower extremities. It is often accompanied by anti-Hu, CV2/CRMP5, and amphiphysin antibodies. Various cancers, especially SCLC, are observable. Diagnosis is made with electrophysiological tests (12, 13).

1.6. Lambert-Eaton Syndrome

This is a progressive syndrome that often starts with proximal muscle weakness in the lower extremities and continues with the upper extremities,

distal muscles, bulbar and ocular involvements. It is often accompanied by autonomic nerve involvement. Antibodies for P/Q-type voltage-gated calcium channels are present in approximately 90% of patients. It may further be accompanied by anti-glial nuclear antibodies, also known as SOX antibodies. The most common accompanying type of cancer is SCLC. Decrement response impression is typical on EMG (14, 15).

2. Other Syndromes

Stiff-Person Syndrome: This syndrome is characterized by simultaneous co-activation of agonist and antagonist muscles that can be triggered or spontaneous. It is often associated with breast cancer and amphiphysin antibodies. Pleostic activity in CSF and continuous motor unit potentials on EMG while at rest are observable (16).

NMDAR Encephalitis: This is associated with anti-NMDA receptor antibodies and is characterized by psychotic disorder, seizures, movement, and autonomic nervous system disorders. Ovarian teratoma is the most common accompanier. In addition to slow waves and epileptic discharges, extreme delta brush findings are also observable on EEG (17, 18).

Paraneoplastic Polyradiculoneuropathy: This occurs in an axonal pattern. The most common antibodies are amphiphysin, CV2/CRMP5, and PCA-2/microtubule-associated protein 1B. It is usually accompanied by small-cell lung cancer and breast cancer (19, 20).

3. Treatment

In paraneoplastic syndromes, rapid treatment of tumor generally contributes significantly to the recovery of the syndrome.

There is insufficient data on responses to various immunosuppressive and immunomodulatory treatments in paraneoplastic syndromes accompanied by intracellular antigens and mediated by T cells. The studies are limited to small case series. High-dose corticosteroid therapy is used.

High-dose methylprednisolone and intravenous immunoglobulin or plasmapheresis therapy are recommended in paraneoplastic syndromes associated with neuronal membrane antibodies. Rituximab and Cyclophosphamide are recommendable in non-responders. The studies show that Rituximab has been increasingly used in the initial treatment regimens, particularly in patients with severe symptoms (21, 22).

4. References

1. Berzero G, Psimaras D. Neurological paraneoplastic syndromes: an update. Curr Opin Oncol. 2018;30(6):359-367.

2. Honnorat J, Antoine JC. Paraneoplastic neurological syndromes. Orphanet J Rare Dis. 2007;2(1):22

3. Darnell RB, Posner JB. Paraneoplastic syndromes involving the nervous system. N Engl J Med. 2003;349(3):1543-1554

4. Graus F, Delattre JY, Antoine JC, et al. Recommended diagnostic criteria for paraneoplastic neurological syndromes. J Neurol Neurosurg Psychiatry. 2004;75(8): 1135-1140.

5. Gultekin SH, Rosenfeld MR, Voltz R, ve ark. Paraneoplastic limbic encephalitis: neurological symptoms, immunological findings and tumour association in 50 patients. Brain. 2000;123:1481.

6. Lawn ND, Westmoreland BF, Kiely MJ, et al. Clinical, magnetic resonance imaging, and electroencephalographic findings in paraneoplastic limbic encephalitis. Mayo Clin Proc 2003;78(11):1363–8.

7. Vogrig A, Bernardini A, Gigli GL, et al. Stroke-like presentation of paraneoplastic cerebellar degeneration: a single-center experience and review of the literature. Cerebellum. 2019;18(5):976-982.

8. McKeon A. Purkinje cell cytoplasmic autoantibody type 1 accompaniments: the cerebellum and beyond. Arch Neurol. 2011;68(10):1282

9. Kun LE, Gajjar A, Pollack IF. Pediatric brain tumors. İçinde: Perry MC (editör), American Society of Clinical Oncology 1999 Educational Book. American Society of Clinical Oncology, Alexandria, 1999.

10. Armangu´e T, Sabater L, Torres-Vega E, et al. Clinical and immunological features of opsoclonus-myoclonus syndrome in the era of neuronal cell surface antibodies. JAMA Neurol. 2016;73(4):417.

11. Pranzatelli MR, Tate ED, McGee NR. Demographic, clinical, and immunologic features of 389 children with opsoclonus-myoclonus syndrome: a cross-sectional study. Front Neurol. 2017;8:468. 25.

12. Graus F, Dalmau J. Paraneoplastic neuropathies. Curr Opin Neurol 2013;26(5): 489–95.

13. Darnell RB, Posner JB. Paraneoplastic syndromes involving the nervous system. N Engl J Med 2003;349(16):1543–54.

14. Titulaer MJ, Lang B, Verschuuren JJ. Lambert-Eaton myasthenic syndrome: from clinical characteristics to therapeutic strategies. Lancet Neurol. 2011;10(12): 1098-1107.

15. Titulaer MJ, Maddison P, Sont JK, et al. Clinical Dutch-English Lambert-Eaton Myasthenic syndrome (LEMS) tumor association prediction score accurately predicts small-cell lung cancer in the LEMS. J Clin Oncol. 2011;29(7):902-908.

16. Murinson BB, Guarnaccia JB. Stiff-person syndrome with amphiphysin antibodies. Neurology. 2008;71(24):1955-1958.

17. Dalmau J, Gleichman AJ, Hughes EG, et al. Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. Lancet Neurol 2008;7(12): 1091–8.

18. Gresa-Arribas N, Titulaer MJ, Torrents A, et al. Antibody titres at diagnosis and during follow-up of anti-NMDA receptor encephalitis: a retrospective study. Lancet Neurol 2014;13(2):167–77.

19. Dubey D, Lennon VA, Gadoth A, et al. Autoimmune CRMP5 neuropathy phenotype and outcome defined from 105 cases. Neurology. 2018;90(2):e103-e110.

20. Dubey D, Jitprapaikulsan J, Bi H, et al. Amphiphysin-IgG autoimmune neuropathy: a recognizable clinicopathologic syndrome. Neurology. 2019;93(20):e1873-e1880.

21. Keime-Guibert F, Graus F, Fleury A, et al. Treatment of paraneoplastic neurological syndromes with antineuronal antibodies (Anti-Hu, anti-Yo) with a combination of immunoglobulins, cyclophosphamide, and methylprednisolone. J Neurol Neurosurg Psychiatry 2000;68(4):479–82.

22. Grativvol RS, Cavalcante WCP, Castro LHM, Nitrini R, Simabukuro MM. Updates in the Diagnosis and Treatment of Paraneoplastic Neurologic Syndromes. Curr Oncol Rep. 2018;20(11):92

CHAPTER IV

NEUROLOGICAL INVOLVEMENT IN BEHÇET'S DISEASE

CANSU SARIKAYA

(MD) Neurology Specialist, Sivas State Hospital, Sivas,
e-mail: cansuegilmez@hotmail.com
ORCID: 0000-0002-5790-8488

1. Introduction

Behçet's disease, first described by Hulusi Behçet in 1937, is an autoimmune, inflammatory disease involving many systems. Mainly musculocutaneous, ocular, vascular, gastrointestinal, and neurological clinical involvements are observable (1).

Main autoimmune and autoinflammatory mechanisms are assumed to play a role in its pathogenesis. However, the underlying etiopathogenesis has still not been fully elucidated. Environmental and infectious processes may affect underlying autoimmune processes. Genetic studies have often shown its relationship with the human leucocytic antigen (HLA)-B51 allele (2)(3)(4).

The disease often occurs in the third decade. It has a similar frequency in men and women. It has a worse prognosis in men. The classic syndrome progresses with oral aphthae, genital ulcers, skin lesions, arthritis, uveitis, and vasculitis. Although neurological involvement is less common than these clinical manifestations, we should consider it may occur in inflammatory central nervous system diseases. (3).

2. Neurological Involvement

Neurological involvement is observed at a rate of 5-10%. It is usually more common in men. Central nervous system involvement is observed more frequently than the peripheral nervous system. Parenchymal or vascular involvement is also observable. Parenchymal involvement is more common in approximately 80% of all cases. Although its clinical presentation depends on the site of

involvement, dysfunction due to white matter involvement, multiple cranial nerve involvement, myelopathy, and acute-subacute onset encephalopathy are frequently observable. Subacute headache, ataxia, and hemiparesis are the main symptoms. They may be in attacks or progressive. In vascular involvement, the clinical presentation is often headache and visual impairment due to intracranial hypertension. On neurological examination, papilledema and 6th cranial nerve involvement are observable. Dural sinus thrombosis and vasculitis may also be observed (5) (6) (7) (8). In the diagnosis of Neurobehçet, it is important to exclude other causes that may lead to similar clinical pictures. Neuroimaging, cerebrospinal examination (CSF), pathergy test, HLA determination, and biopsy can be used for differential diagnosis.

Magnetic resonance (MR) is the gold standard in radiological diagnosis. Typically, T2 hyperintense lesions extending from the brain stem to the diencephalon are observed in parenchymal involvement. Contrast-enhancing lesions can be observed in the acute phase. Atrophy may be observed in the later period. Dural sinus thrombosis is frequently observed in vascular involvement and the diagnosis is made by MR venography.

CSF examination often shows pleocytosis. CSF opening pressure may be high. Oligoclonal band (OCD) positivity is 15-20%.

Genetically, the HLA-B51 allele may be detected. The presence of pathergy is an important parameter for Behçet's disease. However, its negativity does not exclude the diagnosis (9) (10) (11) (12). In the differential diagnosis, multiple sclerosis, cerebrovascular diseases, infectious diseases, brain tumors, neurosarcoidosis, central nervous system vasculitis, and neuroinflammatory diseases must be kept in mind (13) (14).

According to the International Study Group (ISG) criteria, the presence of oral aphtha, genital aphtha, and the ocular lesion is 2 points each; neurological involvement, vascular involvement, and presence of pathergy are evaluated as 1 point each; and a total of 4 points or more is accepted as Behçet's disease (15).

3. Treatment

High-dose intravenous methylprednisolone for 7-10 days is recommended for acute treatment in neurological involvement. Depending on the severity of the relapse, oral steroid therapy can be administered for 3-6 months. The first choice in long-term anti-inflammatory therapy is immunosuppressive agents such as azathioprine. In case of intolerance, mycophenolate mofetil, and methotrexate are preferable (16) (17).

Anti-tumor necrosis factor and thalidomide may be useful in resistant cases (18). Recent studies have reported that infliximab can be used as the first choice in severe cases (19) (20).

4. References

1. Davatchi F, Shahram F, Akbarian M, Gharibdoost F, Nadji A, Chams SH et al. Behçet's disease – analysis of 3443 cases.APLAR Journal of Rheumatology 1997; 1: 2-5.

2. Gül, A., Pathogenesis of Behçet's disease: Autoinflammatory features and beyond. Seminars in Immünopathology, 2015. 37(4): 413-418.

3.Yazıcı H. Behçet syndrome: an update. Curr Rheumatol Rep.2003;5:195–219.

4. Wallace GR. HLA-B*51 the primary risk in Behçet disease. Proc Natl Acad Sci USA 2014;111: 8706-7.

5. Kalra S, Silman A, Akman-Demir G, Bohlega S, Borhani-Haghighi A, Constantinescu SC, et al. Diagnosis and management of Neuro-Behcet's disease: International consensus

6. Borhani Haghighi A, Pourmand R, Nikseresht AR. Neuro-Behçet's disease: A review. Neurologist 2005; 11: 80-89.

7. Kidd D. Neurological complications of Behcet's syndrome. Curr Neurol Neurosc Rep 2012;12:675-9.

8. Siva A, Saip S. The spectrum of nervous system involvement in Behcet's syndrome and its differential diagnosis. J Neurol 2009;56:513-29.

9. Kokturk A. Clinical and pathological manifestations with differential diagnosis in Behcet's disease. Patholog Res Int 2012;2012:690390.

10. Gündüz, T.,et al., Laboratory and clinical correlates of brain atrophy in Neuro-Behçet's disease. J Neurol Sci, 2020. 414: 116831.

11. Borhani-Haghighi A, Kardeh B, Banerjee S, Yadollahikhales G, Safari A, Sahraian MA, Shapiro L. Neuro-Behcet's disease: An update on diagnosis, differential diagnoses, and treatment. Mult Scler Relat Disord. 2019 Dec 23;39:101906. doi: 10.1016/j.msard.2019.101906. Epub ahead of print. PMID: 31887565.

12. McLean BN, Miller D, Thompson EJ. Oligoclonal banding of IgG in CSF, blood-brain barrier function, and MRI findings in patients with sarcoidosis, systemic lupus erythema-tosus, and Behcet's disease involving the nervous system. J Neurol Neurosurg Psychiatry 1995;58:548-54.

13. Uygunoglu U, Siva A. An uncommon disease included commonly in the differential diagnosis of neurological diseases: Neuro-Behçet's syndrome. J Neurol Sci. 2021 Jul 15;426:117436. doi: 10.1016/j.jns.2021.117436. Epub 2021 Apr 20. PMID: 33984547.

14. Mohan MC, Koya JM, Kandaswamy GV, Jaleel VA, Jimnaz PA, Manjuhasan S, Ravindran V. Neuro-Behcet's: a diagnostic challenge. Oxf Med Case Reports. 2015 Jul 1;2015(7):311-3. doi: 10.1093/omcr/omv046. PMID: 26421157; PMCID: PMC4584512.

15. International Team for the Revision of the International Criteria for Behçet's Disease (ITR-ICBD). The International Criteria for Behçet's Disease (ICBD): A collaborative study of 27 countries on the sensitivity and specificity of the new criteria. J Eur Acad Derm Venereol 2014;28:338-47.

16. Akman-Demir G, Saip S, Siva A. Behcet disease. Curr Treat Options Neurol 2011;13:290-310.

17. Akman-Demir G, Serdaroglu P. Neuro-Behçet's disease: A practical approach to diagnosis and treatment. Pract Neurol 2002;2:340-7.

18. Sfikakis PP, Arida A, Panopoulos S, Fragiadaki K, Pentazos G,Laskari K, et al. Brief report: drug-free long-term remission in severe Behçet's disease following withdrawal of successful antitumor necrosis factor treatment. Arthritis Rheumatol.2017;69(12):2380–5.

19. Zeydan B, Uygunoglu U, Saip S, Demirci ON, Seyahi E, Ugurlu S, et al. Infliximab is a plausible alternative for neurologic complications of Behçet disease. Neurol Neuroimmunol Neuroinflamm.2016;3(5):e258

20. Borhani Haghighi A, Safari A, Nazarinia MA, Habibagahi Z, Shenavandeh S. Infliximab for patients with neuro-Behcet's disease: case series and literature review. Clin Rheumatol. 2011 Jul;30(7):1007-12. doi: 10.1007/s10067-011-1726-1. Epub 2011 Mar 24. PMID: 21431864.

CHAPTER V

PAIN AND ITS MANAGEMENT IN COVID-19

İLKNUR TOPAL

(Specialist Dr.), İstanbul Medipol University
Derpatmant of Physical Therapy and Rehabilitation.
dr.ilknurcann@gmail.com
ORCID: 0000-0002-5904-2980

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a new coronavirus that was discovered in Wuhan, China in December 2019 and has since spread throughout the world (1). On March 11, 2020, the World Health Organization (WHO) declared the coronavirus disease 2019 (COVID-19) a global pandemic (2). There are 634,266,503 coronavirus cases and 6,587,925 deaths worldwide as of October 2022 (3). Of the cases identified worldwide, 613,327,547 people have recovered.

The International Association for the Study of Pain (IASP) defines pain as "an unpleasant sensory and emotional experience associated with or resembling that associated with, actual or potential tissue damage" (4). Chronic pain is defined as persistent or recurring pain that typically lasts for more than three months or exceeds normal tissue healing (4). Given the disability, emotional instability, and social isolation it causes, chronic pain poses a significant personal and socioeconomic burden. Its early diagnosis and treatment are crucial for this reason.

Pain can be categorized as nociceptive, neuropathic, nociplastic, or mixed-type based on its pathophysiological categories (5). Nociceptive pain is the most common type of pain caused by nociceptive receptor sensation after tissue injury. Nociceptive pain has a protective function and is also known as physiological or inflammatory pain (5). It is typically characterized as a sharp, throbbing pain that is well localized. Nociceptive pain includes somatic pain, bone pain, and visceral pain. Somatic pain is caused by soft tissue inflammation or trauma in

superficial tissues such as the skin, subcutaneous tissue, and muscles. A sharp stinging pain that can be localized is present. It is caused by the skeletal system as a result of bone pain, fractures, and trauma. It is a sharp pain that is deeply localized. Visceral pain is a type of poorly localized pain that manifests as colic and cramping as a result of internal organ inflammation and distension. Examples include acute appendicitis, and renal or biliary colic pain (5).

Pain resulting from a lesion or dysfunction of the nervous system is called neuropathic pain. Neuropathic pain typically spans the length of the affected neural tissue or structure and is linked to sensory changes like hypo- or hyperesthesia, hypo- or hyperalgesia, allodynia, or paresthesia. It causes symptoms such as burning, electric shock, numbness, needle pricking, and freezing (6).

Pain caused by varying nociception without tissue or somatosensory damage causing peripheral nociceptor activation is referred to as nociplastic pain (7). Examples include fibromyalgia, chronic low back pain, and phantom pain.

Mixed pain occurs when a component of neuropathic pain coexists with nociceptive pain in the same patient. Patients who have persistent pain after unsuccessful lumbar spine surgery are an example of this type of pain sufferer. Mechanical low back pain is the nociceptive component in this case, while radicular lower extremity pain is the neuropathic component(8).

Despite the fact that pain relief is considered a basic human right, the COVID-19 pandemic has forced countries around the world to devote their health systems and resources to intensive care units (ICUs) and other COVID-19-specific facilities. Because chronic pain treatment, like most elective health issues, was deemed non-emergency during the COVID-19 pandemic, all outpatient and elective interventional procedures were reduced or discontinued to reduce the risk of viral spread during this process. Concurrently, home quarantine, fear of illness or death, uncertainty, anxiety about the future, the feeling of being alone due to the inability to access healthcare, and the depression and anxiety that comes with it have all had a negative impact on chronic pain management (9). In addition to the socioeconomic stress it induces, COVID-19 has the potential to induce nociceptive, neuropathic, nociplastic, and mixed-type pain because it is a neurotropic virus, causes the release of various mediators related to tissue damage secondary to the severe inflammation it creates, and causes tissue hypoxia due to hypercoagulability (10).

While COVID-19 patients typically present to the hospital with mild symptoms of an upper respiratory infection, such as fever, coughing, sore throat,

and shortness of breath, the virus can also present itself in a variety of clinical manifestations, from mild upper respiratory infection symptoms to severe acute respiratory distress syndrome (ARDS) (11). Besides those, it is common to observe symptoms like headache, myalgia, joint pain, chest pain, sore throat, and abdominal pain (11). In COVID-19 patients, neuropathic pain has also been reported (11).

By affecting the central and peripheral nervous systems, viral infections can cause neuromuscular symptoms (12). Many viruses, including Epstein-Barr virus (EBV), varicella-zoster virus (VZV), human immunodeficiency virus (HIV), cytomegalovirus (CMV), influenza A, and enteroviruses, have previously been linked to neurological complications (12). In herpes zoster infection, unilateral vesicular lesions on the skin, and long-lasting neuropathic pain and allodynia localized in a specific dermatome have been reported; in HIV infection, neuropathic pain accompanied by burning and mechanical allodynia; and in association with enteroviruses, cases of acute flaccid myelitis and chronic neuropathic pain have been reported (12). COVID-19 has also been linked to a variety of neurological symptoms at the onset or progression of the disease. The most prevalent nonspecific neurological symptom observed in COVID-19 patients is headache, while the most prevalent musculoskeletal symptom is myalgia (11).

2. Pathophysiology of painful conditions

Concerning the mechanisms underlying COVID-19's involvement in the neuromuscular system, a number of theories have been put forth. When Moriguchi et al. (13) reported finding SARS-CoV-2 RNA in the cerebrospinal fluid (CSF) of a patient developing encephalopathy after COVID-19, it was the first time that SARS-CoV-2 invasion of the central nervous system (CNS) had been shown to. It is assumed that both the hematogenous and neuronal pathways can be used to penetrate the CNS, despite the fact that the neuroinvasion mechanism of SARS-CoV-2 is still not completely understood.

The first mechanism that has been proposed in this regard states that the membranous spike proteins of the virus can bind to the angiotensin-converting enzyme 2 (ACE-2) receptor in human cells and directly invade the nervous system (14). Once the virus binds to the ACE-2 receptor, transmembrane protease, serine 2 (TMPRSS-2) provides proteolytic division and preparation of the spike protein that allows the virus to enter host cells (14).

ACE-2 receptors are expressed to a great extent in neurons, across the CNS, including oligodendrocytes, the substantia nigra, ventricles, the middle

temporal gyrus, the posterior cingulate cortex, and the olfactory bulb (15). For this reason, the virus has the ability to infect the mentioned neurons and glial cells throughout the CNS. ACE2 and TMPRSS2 have been reported to co-express in nasal goblet and ciliary epithelial cells, as well as oligodendrocytes (16).

A second theory is that the virus crosses the blood-brain barrier by hematogenously reaching the choroid plexus (17). SARS-CoV-2 can also infect leukocytes, which spread to other tissues in the human body and can then pass to the CNS (17). Leukocytes can then transport viruses to the CNS. Moreover, some chemokines secreted by activated leukocytes have been linked to endothelial damage and elevated blood barrier permeability (18).

A third theory is that the virus spreads transneuronally into the CNS by invading the olfactory bulb (19). The virus is assumed to use the olfactory pathway as its gateway to the brain. In postmortem autopsies, inflammation and perivascular leukocyte infiltration in the olfactory bulb have been shown (20). The virus might also enter the CNS via afferent and enteric nervous system neurons, according to another theory (21).

The situation is slightly different in terms of the involvement of the peripheral nervous system. Molecular mimicry mechanism is more prominent here (11). Involvement of the peripheral nervous system typically occurs through the myelin sheath or an immune-mediated response of Schwann cells (11). Glycoproteins on the virus are similar to structures found in neuronal tissues in humans. This condition triggers an autoimmune response to neuronal tissues.

In terms of the pathophysiology of muscle cell involvement, it is thought that the virus can enter the cell directly via the ACE2 pathway (11). Moreover, another mechanism is the immune complex deposition and the release of cytokines that lead to myositis. The immune similarity mechanism between viral antigens and human muscle cells is also blamed (11).

3. Painful symptoms are seen in COVID-19

3.1. Headache

Headache is the most prevalent neurological symptom linked to COVID-19. It may occur during the acute phase of the infection or as a potential long-term problem following the acute phase. Although the pathogenesis of the headache seen in COVID-19 has not yet been fully explained, it is discussed that proinflammatory mediators and cytokines due to the virus may cause headaches, that the virus may directly invade the trigeminal nerve endings in the nasal cavity, or that vasoconstriction and oxidative stress caused by endothelial damage may affect the trigeminal nerve and cause headaches (22, 23). In a meta-analysis,

the frequency of headaches was reported as 10.9% (24). Another meta-analysis, which included 3,598 patients, revealed that 11–14% of patients experienced headaches (25). Headache may accompany other symptoms and signs in cases of COVID-19 as well as be the primary reason for presenting to the hospital. Uygun et al. (26) reported that the headache seen in COVID-19 patients was bilateral, resistant to analgesics, and of longer duration, was associated with anosmia/ageusia and gastrointestinal complaints, and, contrary to expectations, was more common in males.

It is critical to identify patients who are at risk of headaches for a long time after contracting COVID-19 to help prevent this consequence because headaches can decrease a person's quality of life and, depending on their severity, can impact activities of daily living. A patient who had previously had migraines under control did not respond to the usual effective acute treatment, according to a case study examining the treatment of refractory headaches in COVID-19 patients (27). That study also pointed out that anticonvulsants may help with refractory headaches while posing the least risk of side effects and drug interactions.

3.2. Arthralgia-Myalgia

Myalgia and arthralgia are common comorbid symptoms in COVID-19 patients. According to one study, 15% of patients had arthralgia and 44% had myalgia (28). Cioffi et al. (29) reported that at the onset of COVID-19, 32% of patients had arthralgia and 19% had muscle pain. Long-Quan Li et al. (30) reported the prevalence of myalgia in patients who survived COVID-19 as 35.8%, while another meta-analysis reported it to be 21.9% (31). In another study, 50% of patients suffer from ed myalgia (32). Myalgia and fatigue were reported to be more common in the elderly than in young people in a study of 1,420 European patients (33). Corsini Campioli et al. (34) reported that myalgia continued for an average of 23 days following the end of viral shedding. According to a Cochrane review on the subject, the specificity and sensitivity of complaints of myalgia and arthralgia, respectively, were 45–91% and 19–86%, respectively (35). Studies have also suggested that low back pain, similar to myalgia, may be one of the first signs of COVID-19 (36). Abdullahi et al. reported a 10% prevalence of low back pain in COVID-19 patients in a meta-analysis (37).

3.3. Myositis-Rhabdomyolysis

There have been 9 cases of myositis and rhabdomyolysis linked to COVID-19 to date (11). It has been shown that fatigue, muscle pain, and loss of strength are predominant in these cases, creatine phosphokinase levels are elevated,

and these symptoms may be accompanied by hematuria (11). Of the patients reported in a study, only 4 patients complained of myalgia, and another patient complained of myalgia, fever, and dyspnea without muscle weakness (38). Another patient presented to the clinic complaining of leg tingling, numbness, and persistent muscle twitching (39). One patient had macroscopic hematuria, three had microscopic hematuria, and all had elevated levels of serum creatine phosphokinase (39). Five patients recovered with conservative treatment, while two patients required mechanical ventilation (40).

3.4. Critical Illness Myopathy

In patients who have been in the ICU for an extended period, the clinical picture involving cognitive, physical, and psychological disorders seen after discharge from the ICU, which has a negative impact on quality of life, has been termed post-intensive care syndrome (PICS) (41). In patients admitted to an ICU, critical illness myopathy, critical illness polyneuropathy, and muscular atrophy can be seen (41). Muscle weakness due to the use of corticosteroids may also develop. All these can disrupt muscle coordination and cause pain in muscles and joints. Six COVID-19 patients with critical illness myopathy have been reported as of yet (42). All six patients had acute flaccid quadriparesis. Their electrophysiological tests revealed a myopathic pattern. These patients had slightly elevated levels of creatine kinase.

4. Visceral pain

4.1. Abdominal pain

The SARS-CoV-2 virus can cause symptoms and signs in a variety of internal organs. In COVID-19, abdominal pain is a frequently reported symptom, particularly in the pediatric age range. The reported frequency ranges from 1 to 14.5% of the cases (43). Abdominal pain may also involve many underlying pathologies. Diarrhea, mesenteric lymphadenitis, renal or hepatic damage, and testicular pain may also manifest as abdominal pain (44).

4.2. Testicular pain

There are case studies describing patients who developed atypical testicular and abdominal pain after contracting SARS-CoV-2 (44, 45). These studies have linked this condition to the presence of high concentrations of ACE-2 in renal and testicular tissues. Considering the high expression of ACE2 in spermatogonia, Sertoli cells, and Leydig cells, it is plausible that SARS-CoV-2

binding to ACE-2 receptors in the testicle causes inflammation and facilitates testicular damage and orchitis in infected patients (45, 46). On the other hand, Paoli et al. (47) demonstrated that a patient who tested positive for the virus through a nasopharyngeal swab had no viral mRNA in the patient's sperm or urine. Holtmann et al. (48) discovered no mRNA in urine, sperm, or testicular tissue in a patient with moderate COVID infection, but they did discover a decline in sperm quality. Corona et al. (46) postulated that the orchitis-like syndrome associated with COVID-19 could be caused by vasculitis as a result of abnormalities in coagulation and segmental vascularization of the testis.

4.3. Chest pain

Chest pain may stay for a long time both during and after the disease's progression. Symptoms such as chest pain, palpitations, and tachycardia that persist for up to 6 months after the disease may be a sign of permanent cardiac problems (49). In one study, based on radiological examinations, permanent cardiac abnormalities were reported in 78% of patients who recovered from coronavirus, and myocardial inflammation was reported in 60% of the patients (50). Additionally, there was no correlation between the severity of acute coronavirus disease and the incidence of cardiac sequelae in that study (50). Another study that looked at athletes recovering from COVID-19 revealed that 46% of them had myocardial inflammation (51). Clinicians need to look into cases of post-COVID chest pain for potential cardiac diseases even though not all cases are suggestive of underlying cardiac abnormalities.

Persistent chest pain is one of the long-term symptoms experienced frequently by people recovering from SARS-CoV-2. It was shown that 13% of 130 SARS-CoV-2 patients who recovered had persistent chest pain at least 60 days after infection (52). Similarly, 10% of patients in a 274-patient retrospective study reported chest pain symptoms after a coronavirus infection (53). There are several mechanisms that have been proposed for post-COVID chest pain. The first is that SARS-CoV-2 can cause myocardial cell damage via the ACE2 receptor (54). Hypercoagulability and endothelial damage may also be at the root of cardiac problems (54). Patients who present with long-term chest pain after coronavirus infection should be properly examined for pulmonary embolism, which can be fatal as a complication in high-risk patients (55).

5. Chronic Pain and Neuropathic Pain

Chronic pain is a major concern, particularly for COVID patients admitted to an ICU. There have been reports of chronic pain developing also in patients

who have been in the ICU for an extended period (41). The clinical picture called PICS syndrome involving cognitive, physical, and psychological disorders seen after discharge from an ICU, which has a negative impact on quality of life, has been termed persistent inflammation, immunosuppression, and catabolism syndrome (PIICS) (41). PIICS usually emerges after an event that triggers a systemic inflammatory response. After the acute inflammatory response and initial infection, patients experience a compensatory anti-inflammatory response (56). Patients suffer immunosuppression, which is known as PIICS, once this compensatory response is disproportionately aggressive for the amount of initial inflammation (56). In patients admitted to an ICU, critical illness myopathy, critical illness polyneuropathy, and muscular atrophy can be seen (41). Muscle weakness due to the use of corticosteroids may also develop. All these can disrupt muscle coordination and cause pain in joints (41). Chronic pain prevalence after discharge from ICU has been reported to be 14–77% (57). Acute pain, prolonged ventilation and immobility, neuromuscular block, recurrent prone position, and neurological damage are all potential risk factors for chronic pain in these patients (41). The patient's age and overall physical condition also increase the likelihood that they will experience chronic pain after an infection. Elderly patients and those with underlying comorbidities, especially hypertension, bee more likely to experience chronic pain after coronavirus treatment (41, 58).

On the other hand, patients who are in intensive care for a long time may experience symptoms of neuropathic pain (57). This condition can last for a long time after discharge. There have even been cases where neuropathy has been observed for nearly 5 years in nerve conduction studies (59). Even if electrophysiology tests come back normal, minor nerve fiber damage may still cause neuropathic pain symptoms like numbness and paresthesia to last for many more months (60).

Chronic pain can occur in patients who have not been admitted to intensive care. Attal et al. (12) have predicted that given the data examined after previous viral infections, neuropathic pain may develop early or within weeks as a result of COVID-19, and early diagnosis and treatment strategies should be established in this respect. Early study series have reported that 2.3% of patients hospitalized for COVID-19 infection may experience neuropathic pain (61). The incidence of chronic pain was 13.7% in the study by Topal İ et al. (62), which examined 501 patients with COVID-19 infection. These patients experienced pain that was mostly localized to the back, neck, and waist regions, with sporadic spread to the arms or legs but no dermatomal spread. Various degrees of burning

neuropathic pain symptoms were present in some of the patients. Aksan et al. (63) treated a case with severe pain, burning, and allodynia involving the trapezius and paraspinal region in the neck and back (C1–L5) on the second day of hospitalization, they followed up in the hospital with a COVID-19 diagnosis. The patient did not respond to a non-steroidal anti-inflammatory drug (NSAID) but did benefit from gabapentin treatment. While experiencing COVID-19, a patient described by McWilliam et al. (64) developed neuropathic pain that was localized in the distal extremity. Despite the patient's partial response to pregabalin treatment, the patient recovered during a steroid withdrawal regimen.

6. Pain Management in COVID-19 Patients

6.1. Pharmacological Pain Management

6.1.1. Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) and Paracetamol

NSAIDs inhibit the arachidonic acid cascade by inhibiting cyclooxygenase (COX) and affecting prostaglandin biosynthesis. They produce an analgesic effect in this way. NSAIDs are classified into two categories as non-selective COX inhibitors (such as ibuprofen, aspirin (acetylsalicylate), diclofenac, and naproxen) and selective COX2 inhibitors (such as celecoxib, rofecoxib, etoricoxib, lumiracoxib, and valdecoxib).

There are several arguments against using NSAIDs in COVID patients, even though they are often the first treatment option that comes to mind for post-COVID pain. There have been concerns about the symptoms of COVID-19-related viral upper respiratory tract infections getting worse in people taking NSAIDs while the pandemic was still going on (65). The safety of ibuprofen in COVID-19 was called into question after a report by a French infectious diseases expert who observed four children developing decompensation and severe symptoms at an early stage of infection after they were given ibuprofen (66). The report was initially confirmed by the French Minister of Health and the WHO. However, after reviewing the available data, the WHO issued its recommendations, emphasizing that there is no evidence of decompensation in COVID-19 patients following NSAID use (65). The WHO found no evidence for the mentioned hypothesis in its review of 73 studies involving adults and children treated with NSAIDs for respiratory tract infection (67). Indomethacin, on the other hand, was found by Amici et al. (68) to have *strong antiviral activity* against *canine coronavirus in vitro and human SARS-CoV in vivo* when administered at

a concentration dose of 1 mg/kg, by significantly inhibiting virus replication and by protecting the host cell from virus-induced damage. According to Fang et al. (69), however, ibuprofen use in diabetic and hypertensive patients receiving angiotensin II type-I receptor blockers increased ACE-2 expression, which may assist in COVID-19 infection. Kotsiou et al. (70) reported that NSAID before to hospitalization for the treatment of symptoms of community-acquired pneumonia was linked to pneumonia exacerbation, prolonged hospitalization, and more severe pleural effusions. A number of studies posit that when treating COVID-19, this effect should also be taken into account (71, 72).

As a result, no study to date has reported higher mortality in COVID-19 patients treated with ibuprofen (73). The WHO does not advise switching or stopping NSAIDs for patients who are receiving chronic treatment for a suspected or confirmed SARS-CoV-2 infection, despite the fact that there is debate surrounding this matter. It will be less risky, however, in suspicious cases if ibuprofen is substituted with paracetamol or metamizole, especially when taken over-the-counter (74). Paracetamol can be favored as the main medication, particularly in patients with fever or headaches.

Metamizole does not interact with therapeutic agents commonly used to treat SARS-CoV-2 (74). It also affects the main protease of SARS-CoV-2 (Mpro), inhibiting its transcription and replication (75). However, the use of metamizole in COVID-19 patients is questionable due to its association with agranulocytosis, which can occur suddenly (76).

6.1.2. Opioids

While the use of opioids for pain management in ICUs is unavoidable, the issues associated with their use in COVID patients are becoming recognized. In patients infected with COVID-19, the cellular immune system, in particular, is suppressed (77). Lymphocytopenia is a key indicator of this. Opioids used to treat pain can also suppress the immune system. According to Flores et al., morphine induced adrenal-dependent lymphopenia in an animal model and lowered the response to mitogenic stimulation by about 70% (78). Suppression of immunity after administration of fentanyl depends on the dose (79). The immunosuppressive properties of fentanyl are reduced earlier during treatment than during morphine therapy (79). It is unclear exactly how oxycodone suppresses the immune system. Wiese et al. revealed that the immunosuppressive properties of opioids influence infection frequency (80). For COVID patients, buprenorphine and tramadol are suggested for pain management because they

cause less immune system suppression (81). These do not prolong viral shedding because they do not have immunosuppressive qualities (82).

Opioids can also be used to treat coughing and to combat shortness of breath in addition to pain. Opioids have been shown to alleviate shortness of breath in patients with chronic obstructive pulmonary disease (COPD) (83). In their meta-analysis, Extrome et al. (83) found that small doses of opioids were safe and effective in reducing shortness of breath. While tramadol and oxycodone are recommended here, it is important to remember that they can suppress COVID-19 symptoms. Fentanyl and morphine are not generally advised.

6.1.3. Gabapentinoids

COVID-19, a neurotrophic virus, is expected to cause neuropathic pain by involving the central and peripheral nervous systems. Patients with COVID-19 who have peripheral neuropathy may require the addition of gabapentinoids to their treatment plan (84). Gabapentin and pregabalin are calcium channel α2-δ ligands commonly used to treat neuropathic pain. Pregabalin acts more quickly than gabapentin (85). They are well tolerated in general and have similar side effects (86). Aksan et al. (63) treated a case with severe pain, burning, and allodynia involving the trapezius and paraspinal region in the neck and back (C1–L5) on the second day of hospitalization they followed up in the hospital with a COVID-19 diagnosis. The patient did not respond to an NSAID but did benefit from gabapentin treatment. Due to a lack of research, estimating the potential of gabapentinoids in the treatment of SARS-CoV-2-induced neuropathy is challenging. Because they have the potential to reduce respiratory drive, combining them with opioids for treatment can be dangerous (87). For this reason, for drug combination necessities, duloxetine is a better option than gabapentinoids (87).

6.2. Non-Pharmacological Pain Management

6.2.1. Physical therapy modalities

Despite the lack of research on the use of physical therapy modalities for pain management in SARS-CoV-2 infected patients, physical therapy modalities appear to be a viable option given their effectiveness in nociceptive and neuropathic pain. Applications of electrotherapy, in particular, are recommended for patients suffering from neuropathic or chronic pain (88, 89). Transcutaneous electrical nerve stimulation (TENS) can be practiced in both acute and chronic

pain (88). TENS is one of the techniques that have been proven to be successful in treating neuropathic pain (90). TENS works by activating central mechanisms to activate μ-opioid receptors in the spinal cord and brain stem at low frequencies while providing analgesia through δ-opioid receptors at high frequencies. A randomized controlled trial showed that low-frequency TENS was superior to a placebo in lowering pain and discomfort in diabetic neuropathy patients (91). Similarly, in a randomized controlled trial carried out by Forst et al. (92), low-frequency TENS contributed a significant enhancement in neuropathic pain scores. As a result, TENS may be effective in treating painful peripheral neuropathy.

Laser is another physical therapy agent that can be employed to treat neuropathic pain. In patients suffering from neuropathic pain, very low laser levels have been demonstrated to be effective (93). When used at a low level, laser therapy enhances functional ability while also reducing pain and inflammation. Low-frequency laser therapy was shown to significantly reduce pain in 36 patients with postherpetic neuralgia by 55.3% (94). Techniques for neurostimulation, including transcranial magnetic stimulation and cortical electrical stimulation (CES), spinal cord stimulation, and deep brain stimulation, have also been found to be effective in treating neuropathic pain (95). Therefore, neuropathic pain experienced by COVID-19 patients can be treated using these electrotherapy techniques, which are effective in treating neuropathic pain types that are similar to it.

In order to lessen inflammatory responses in the lungs during the COVID-19 pandemic, some hospitals advised using ultra-shortwave diathermy (USWD) for patients in the severe and critical categories. When the coagulopathy aspect of COVID is considered, however, concerns have been raised that the use of USWD may result in pulmonary fibrosis (96). Dominguez-Nicolas (97) reported that low-field thoracic magnetic stimulation could increase oxygen saturation levels in a study of 17 COVID-19 patients. Similarly, the anti-inflammatory effects of infrared and electromagnetic fields were demonstrated in a study on human cell cultures infected with COVID-19 (98). This information has alleviated concerns about using physical therapy modalities in COVID-19 patients.

Patients with COVID-19 who are experiencing acute musculoskeletal pain are typically advised to rest, apply cold, apply compression, and elevate their body parts. Many COVID-19 patients have cardiovascular, respiratory, renal, and neurological comorbidities that limit their functional capacity. Evidence-based exercise programs should be the main focus of rehabilitation disciplines to optimize peripheral muscle strength and respiration.

Sarcopenia is an unavoidable complication that is expected in elderly patients who are kept in long-term isolation at home due to the pandemic as well as in patients hospitalized in long-term intensive care. In addition to exercise therapy, neuromuscular electrical stimulation (NMES) can be used to treat sarcopenia (99).

Physical therapy modalities, in conjunction with an individually planned rehabilitation program, can be used to manage pain in COVID patients.

6.2.2. Exercise and Physiotherapy applications

Physical activity levels worldwide have dropped significantly as a result of social isolation and physical inactivity during the COVID-19 pandemic, raising the risk of comorbidities and mental disorders. However, given that exercise can protect against COVID-19 and reduce mortality and morbidity, it is inescapable that it will be incorporated into the treatment regimen (100, 101). Aside from enhancing muscle strength, decreasing shortness of breath, improving balance and coordination, and improving mental status by reducing stress, exercise is also essential for pain management (88, 102). According to Goethals et al. (103), it is concerning that the levels of independence, autonomy, and mental health of elderly people are negatively affected during the quarantine and that public health campaigns to encourage physical exercise at home for elderly people should be carried out. SA sedentary lifestyle may also increase the risk of neuropsychiatric effects, decreased cognitive levels, sarcopenia, chronic pain, and, most notably, cardiovascular disease. According to Narici et al. (104), during the COVID-19 epidemic, muscle fiber denervation and rapid loss of muscle mass may occur due to increased levels of physical inactivity, which is associated with damage to the neuromuscular junction and disruption and suppression of muscle protein synthesis. They reported that physical inactivity may also affect glucose homeostasis and reduce insulin sensitivity, and in addition, there may be impairments at all levels of the oxygen delivery and consumption cascade, including aerobic capacity, peripheral circulation, and muscle oxidative function. And this is linked to insulin resistance, muscle loss, and fat accumulation.

Previous research has shown that low-intensity exercise has an immunomodulatory effect by increasing anti-inflammatory cytokines (105). Exercise recommendation to COVID-19 patients was avoided at the start of the epidemic due to the possibility of myocarditis and the concern that oxygenation might be lowered. However, evidence obtained during the pandemic has demonstrated that exercise reduces the severity of COVID-19, emphasizing

the significance of exercise in both COVID and non-COVID individuals (106). Leandro et al. (105) suggested doing moderately intense physical exercise at home because the immunomodulation caused by exercise can help enhance the immune response to the progression of SARS-CoV-2 infection. Regular exercise may help lower the risk of COVID-19 infection and minimize cardiopulmonary sequelae during recovery following the illness, according to Heffernan and Jae et al. (107). With the right exercise program that was started on the 18th day of a patient's illness and continued for 30 days, the 50-year-old patient who had myocarditis caused by COVID-19 was able to achieve full independence (108). A multi-modal exercise program, myofascial relaxation techniques, and massage have been recommended for patients suffering from chronic or neuropathic pain (88). It has been reported that fascia-based manual therapy applications can help relieve pain in post-COVID patients (109).

7. Conclusion

COVID-19 patients may present with many mechanisms that are still not known, including pain symptoms such as myalgia, arthralgia, sore throat, headache, and peripheral neuropathies, as well as pain due to PICSs. For pain treatment, each patient requires an individualized approach that is multidisciplinary and takes into consideration the person's comorbidities. It is crucial to develop strategies for COVID-19 patients by being cautious of side effects foranyl treatment methods and making use of the experience acquired to date in pain management, even though there is no disnitive information to restrict the use of analgesics in pain treatment.

References

1. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVİD-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. JAMA 2020;323(13):1239.

2. World Health Organization. WHO director-general's opening remarks at the media briefing on COVİD-19—11 March 2020 [Internet]. Geneva: World Health Organization; 2020 [cited at 2020]. Available from: https://www.who.int/dg/ speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-COVID-19---11-march-2020

3. https://www.worldometers.info/coronavirus/. Erişim tarihi 28 Ekim 2022.

4. IASP. https://www.iasp-pain.org/terminology? navItemNumber= 576# Pain, Accessed 10th Jan 2019

5. Stucky C. Mechanisms of pain. PNAS. 2001;98:11845–11846.

6. Bates D, Schultheis DC, Hanes MC, at al. A Comprehensive algorithm for management of neuropathic pain. Pain Med. 2019;20:2-12.

7. Trouvin AP, Perrot S. New concepts of pain. Best Pract Res Clin Rheumatol. 2019 Jun;33(3):101415.

8. D'Mello R, Dickenson AH. Spinal cord mechanisms of pain. Br J Anaesth. 2008;101(1):8–16.

9. Pubtillo F, Giglio M, Brienza N at al. Impact of COVID-19 pandemic on chronic pain management: Looking for the best way to deliver care. Best Pract Res Clin Anaesthesiol. 2020; 34(3):529-537.

10. Clauw Dj, Häuser W, Cohen SP, Fitzcharles mA. Considering the potential for an increase in chronic pain after the COVID-19 pandemic. Pain. 2020;161(8):1694.

11. Paliwal VK, Garg RK, Gupta A, Tejan N. Neuromuscular presentations in patients with COVID-19. Neurol Sci. 2020;41(11):3039-3056.

12. Attal N, Martinez V, Bouhassira D. Potential for increased prevalence of neuropathic pain after the COVID-19 pandemic. Pain Rep. 2021;6(1):e884.

13. Moriguchi T, Harii N, Goto J, at al. A first case of meningitis/encephalitis associated with SARS-Coronavirus-2. Int J Infect Dis. 2020;94:55-58.

14. Desforges M, Le Coupanec A, Dubeau P at al. Human coronaviruses and other respiratory viruses: underestimated opportunistic pathogens of the central nervous system? Viruses. 2019 Dec 20;12(1):14.

15. Chen R, Wang K, Yu J, Chen Z, Wen C, Xu Z. The spatial and cell-type distribution of SARS-CoV-2 receptor ACE2 in human and mouse brain. Front Neurol. 2021;11:573095.

16. Sardu C, Gambardella J, Morelli MB, Wang X, Marfella R, Santulli G. Hypertension, Thrombosis, Kidney Failure, and Diabetes: Is COVID-19 an Endothelial Disease? A Comprehensive Evaluation of Clinical and Basic Evidence. Clin Basic Evid. 2020;9(5);1417.

17. Desforges M, Le Coupanec A, Brison E, Meessen-Pinard M, Talbot PJ. Neuroinvasive and neurotropic human respiratory coronaviruses: potential neurovirulent agents in humans. Adv Exp Med Biol. 2014;807:75-96.

18. Stamatovic SM, Shakui P, Keep RF, et al. Monocyte chemoattractant protein-1 regulation of blood–brain barrier permeability. J Cereb Blood Flow Metab. 2005;25(5):593-606.

19. Swanson PA, 2nd, McGavern DB. Viral diseases of the central nervous system. Curr Opin Virol. 2015;11:44–54.

20. Agyeman AA, Chin KL, Landersdorfer CB, Liew D, Ofori-Asenso R. Smell and Taste Dysfunction in Patients With COVID-19: A Systematic Review and Meta-analysis. Mayo Clin Proc. 2020 Aug;95(8):1621-1631

21. Amirian ES. Potential fecal transmission of SARS-CoV-2: current evidence and implications for public health. Int J Infect Dis. 2020;95:363-370.

22. Bolay H, Gül A, Baykan B. COVID-19 is a real headache. Headache. 2020;60(7):1415-1421.

23. Varga Z, Flammer AJ, Steiger P, et al. Endothelial cell infection and endothelitis in COVID-19. Lancet. 2020; 395:1417-8.

24. Pinzon RT, Wijaya VO, Buana RB, Al Jody A, Nunsio PN. Neurologic Characteristics in Coronavirus Disease 2019 (COVID-19): A Systematic Review and Meta-Analysis. Front Neurol. 2020;11:565.

25. Borges do Nascimento IJ, Cacic N, Abdulazeem HM, et al. Coronavirus infection (COVID-19) in humans: A scoping review and meta-analysis. J Clin Med. 2020;9:941.

26. Uygun Ö, Ertaş M, Ekizoğlu E, Bolay H, Özge A, Orhan EK, at al Headache characteristics in COVID-19 pandemic-a survey study.Front Neurol. 2020;21(1):121

27. Becker WJ, Findlay T, Moga C, Scott NA, Harstall C, Taenzer P. Guideline for primary care management of headache in adults. Can Fam Physician. 2015;61(8):670-679.

28. Schett G, Manger B, Simon D, et al. COVID19 revisiting inflammatory pathways of arthritis. Nat Rev Rheumatol. 2020;16:465-70.

29. Ciaffi J, Meliconi R, Ruscitti P, et al. Rheumatic manifestations of COVID-19: a systematic review and meta-analysis. BMC Rheumatol. 2020;4:65.

30. Li LQ, Huang T, Wang YQ, at al. COVID-19 patients' clinical characteristics, discharge rate, and fatality rate of meta-analysis. J Med Virol. 2020;92(6):577-583.

31. Zhu J, Zhong Z, Ji P, Pang J, Zhang J, Zhao C. Clinicopathological characteristics of 8697 patients with COVID-19 in China: a meta-analysis. Fam Med Community Health. 2020;8(2):e000406.

32. Lechien JR, Chiesa-Estomba CM, De Siati DR, at al. Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study. Eur Arch Otorhinolaryngol. 2020;277:1-11.

33. Lechien JR, Chiesa-Estomba CM, Place S, at al. Clinical and epidemiological characteristics of 1420 European patients with mild-to-moderate coronavirus disease 2019. J Intern Med. 2020;288:335–344.

34. Campioli CC, Cevallos EC, Assi M, Patel R, Binnicker MJ, O'Horo JC. Clinical predictors and timing of cessation of viral RNA shedding in patients with COVID-19. J Clin Virol. 2020;130:104577.

35. Struyf T, Deeks JJ, Dinnes J, et al; Cochrane COVID-19 Diagnostic Test Accuracy Group. Signs and symptoms to determine if a patient presenting in primary care or hospital outpatient settings has COVID-19 disease. Cochrane Database Syst Rev. 2020;7:CD013665.

36. Puntillo F, Giglio M, Brienza N, et al. Impact of COVID-19 pandemic on chronic pain management: Looking for the best way to deliver care. Best Pract Res Clin Anaesthesiol. 2020;34:529-37.

37. Abdullahi A, Candan SA, Abba MA, et al. Neurological and musculoskeletal features of COVID-19: a systematic review and metaanalysis. Front Neurol. 2020;11:687.

38. Zhang Q, Shan KS, Minalyan A, O'Sullivan C, Nace T. A rare presentation of coronavirus disease 2019 (COVID-19) induced viral myositis with subsequent rhabdomyolysis. Cureus. 2020;12(5):e8074.

39. Chan KH, Farouji I, Abu Hanoud A, Slim J. Weakness and elevated creatinine kinase as the initial presentation of coronavirus disease 2019 (COVID-19) Am J Emerg Med. 2020;38(7):1548.e1-1548.e3.

40. Borku Uysal B, Ikitimur H, Yavuzer S, Islamoglu MS, Cengiz M. Case report: a COVID-19 patient presenting with mild rhabdomyolysis. Am J Trop Med Hyg. 2020;103:847-850.

41. Kemp HI, Corner E, Colvin LA. Chronic pain after COVID-19: implications for rehabilitation. Br J Anaesth. 2020;125(4):436-440.

42. Madia F, Merico B, Primiano G, Cutuli SL, De Pascale G, Servidei S. Acute myopathic quadriplegia in COVID-19 patients in the intensive care unit. Neurology. Advance online publication. Neurology. 2020;95(11):492-494.

43. Tsai PH, lai WY, lin YY, luo YH, lin YT, Chen HK, et al. Clinical manifestation and disease progression in COVID-19 infection. journal of the Chinese medical Association. 2021; 84(1):3-8.

44. Kim j, Thomsen T, Sell n, Goldsmith Aj. Abdominal and testicular pain: An atypical presentation of COVID-19. The American journal of Emergency medicine. 2020;38(7):1542.e1e3.

45. La Marca A, Busani S, Donno V, Guaraldi G, Ligabue G, Girardis M. Testicular pain as an unusual presentation of COVID-19: a brief review of SARS-CoV-2 and the testis. Reprod Biomed Online. 2020;41(5):903–906.

46. Corona G, Baldi E, Isidori AM, at al. SARS-CoV-2 infection, male fertility and sperm cryopreservation: a position statement of the Italian Society of Andrology and Sexual Medicine (SIAMS) (Società Italiana di Andrologia e Medicina della Sessualità) J Endocrinol Invest. 2020;43(8):1153–1157.

47. Paoli D, Pallotti F, Colangelo S, at al. Study of SARS-CoV-2 in semen and urine samples of a volunteer with positive naso-pharyngeal swab. J Endocrinol Invest. 2020;43(12):1819–1822.

48. Holtmann N, Edimiris P, Andree M, Doehmen C, Baston-Buest D, Adams O, Bielfeld AP. Assessment of SARS-CoV-2 in human semen—a cohort study. Fertil Steril. 2020;114(2):233–238.

49. Yong SJ. Long COVID or post-COVID-19 syndrome: putative pathophysiology, risk factors, and treatments. Infect Dis. 2021;53(10):737-754

50. Puntmann VO, Carerj ML, Wieters I, at al. Outcomes of cardiovascular magnetic resonance imaging in patients recently recovered from coronavirus disease 2019 (COVID-19) JAMA cardiology. 2020;5(11):1265-1273.

51. Rajpal S, Tong MS, Borchers J, at al. Cardiovascular magnetic resonance findings in competitive athletes recovering from COVID-19 infection. JAMA cardiology. 2021;6(1):116–118.

52. Carvalho-Schneider C, Laurent E, Lemaignen A, at al. Follow-up of adults with noncritical COVID-19 two months after symptom onset. Clin Microbiol Infect. 2021;27(2):258–263.

53. Osikomaiya B, Erinoso O, Wright KO, at al. Long COVID': persistent COVID-19 symptoms in survivors managed in Lagos State, Nigeria. BMC Infect Dis. 2021;21(1):1-7.

54. Ni W, Yang X, Yang D, at al. Role of angiotensin-converting enzyme 2 (ACE2) in COVID-19. Crit Care. 2020;24(1):1–10.

55. Varatharaj A, Thomas N, Ellul MA, at al. Neurological and neuropsychiatric complications of COVID-19 in 153 patients: a UK-wide surveillance study. The Lancet Psychiatry. 2020;7(10):875–882.

56. Oronsky B, Larson C, Hammond TC, at al. A review of persistent post-COVID syndrome (PPCS). Clin Rev Allergy Immunol. 2021:1–9.

57. Kemp HI, Laycock H, Costello A, Brett SJ. Chronic pain in critical care survivors: a narrative review. Br J Anaesth 2019; 123: e372e84

58. Mao L, Jin H, Wang M, at al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. JAMA Neurol. 2020;77(6):683–690.

59. Fletcher SN, Kennedy DD, Ghosh IR, et al. Persistent neuromuscular and neurophysiologic abnormalities in long-term survivors of prolonged critical illness. Crit Care Med 2003;31: 1012e6

60. Angel M, Bril V, Shannon P, Herridge M. Neuromuscular function in survivors of the acute respiratory distress syndrome. Can J Neurol Sci 2007; 34: 427-32.

61. Guadarrama-Ortiz P, Choreño-Parra JA, Sánchez-Martínez CM, Pacheco-Sánchez FJ, Rodríguez-Nava AI, García-Quintero G. Neurological aspects of SARS-CoV-2 infection: mechanisms and manifestations. Front Neurol. 2020 Sep 4;11:1039.

62. Topal İ, Özçelik N, Atayoğlu AT. Post-COVİD-19 pain syndrome: a descriptive study in Turkish population. Korean J Pain 2022;35(4):1-7.

63. Aksan F, Nelson [EA,] Swedish KA.A COVİD-19 patient with intense burning pain.J Neurovirol. 2020;26(5):800-801.

64. McWilliam M, Samuel M, Fad Alkufri FH. Neuropathic pain post-COVID-19: a case report. BMJ Case Rep. 2021;14(7):e243459.

65. Russell B., Moss C., Rigg A., Van Hemelrijck M. COVID-19 and treatment with NSAIDs and corticosteroids: Should we be limiting their use in the clinical setting? Ecancermedicalscience. 2020;14:1023.

66. Day M. Covid-19: European drugs agency to review safety of ibuprofen. BMJ. 2020;368:m1168.

67. World Health Organization The Use of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) in Patients with COVID-19. [(accessed on 5 June 2020)]; Available online: https://www.who.int/news-room/commentaries/detail/the-use-of-non-steroidal-anti-inflammatory-drugs-(nsaids)-in-patients-with-covid-19

68. Amici C, Di Caro A, Ciucci A, et al. Indomethacin has a potent antiviral activity against SARS coronavirus. Antivir Ther. 2006;11(8):1021–1030.

69. Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? Lancet Respir Med. 2020;2600(20):30116.

70. Kotsiou OS, Zarogiannis SG, Gourgoulianis KI. Prehospital NSAIDs use prolong hospitalization in patients with pleuro-pulmonary infection. Respir. Med. 2017;123:28–33.

71. Micallef J., Soeiro T., Jonville-Béra A.-P., French Society of Pharmacology and Therapeutics Non-Steroidal anti-inflammatory drugs, pharmacology, and COVID-19 infection. Therapie. 2020;S0040-5957:30092–30095.

72. Yousefifard M, Zali A, Zarghi A, Madani Neishaboori A, Hosseini M, Safari S. Non-Steroidal anti-inflammatory drugs in management of COVID-19: A systematic review on current evidence. Int. J. Clin. Pract. 2020:e13557.

73. Rinott E, Kozer E, Shapira Y, Bar-Haim A, Youngster I. Ibuprofen use and clinical outcomes in COVID-19 patients. Clin. Microbiol. Infect. 2020;26(9):1259.e5-1259.e7.

74. Bein B., Bachmann M., Huggett S., Wegermann P. SARS-CoV-2/COVID-19: Evidence-Based recommendations on diagnosis and therapy. Geburtshilfe Frauenheilkd. 2020;80:491–498.

75. Aly O. Molecular docking reveals the potential of aliskiren, dipyridamole, mopidamol, rosuvastatin, rolitetracycline and metamizole to inhibit COVID-19 virus main protease. ChemRxiv. 2020

76. Schönhöfer P., Offerhaus L., Herxheimer A. Dipyrone and agranulocytosis: What is the risk? Lancet. 2003;361:968–969.

77. Diwan S. Covid-19 pandemic: Implications on interventional pain practice-a narrative review. Pain Physician. 2020;23:311-318.

78. Flores LR, Wahl SM, Bayer BM. Mechanisms of morphine-induced immunosuppression: Effect of acute morphine administration on lymphocyte trafficking. J. Pharmacol. Exp. Ther. 1995;272:1246–1251.

79. Pettus K, Cleary JF, de Lima L, Ahmed E, Radbruch L. Availability of internationally controlled essential medicines in the COVID-19 pandemic. J. Pain Symptom Manag. 2020;60:48-51.

80. Wiese A.D., Griffin M.R., Schaffner W., Stein C.M., Greevy R.A., Mitchel E.F., Grijalva C.G. Long-Acting opioid use and the risk of serious infections: A retrospective cohort study. Clin. Infect. Dis. 2019;68:1862–1869.

81. El-Tallawy Sn, nalamasu R, Pergolizzi JV, Gharibo C. Pain management during the COVID-19 pandemic. Pain and Therapy. 2020:1-14.

82. Davis M.P. Twelve reasons for considering buprenorphine as a frontline analgesic in the management of pain. J. Support. Oncol. 2012;10:209–219.

83. Ekström M, Nilsson F, Abernethy AA, Currow DC. Effects of opioids on breathlessness and exercise capacity in chronic obstructive pulmonary disease: A systematic review. Ann. Am. Thorac. Soc. 2015;12:1079-1092.

84. Devlin JW, O'Neal HRJ, Thomas C, at al. Strategies to optimize ICU liberation (A to F) bundle performance in critically Ill adults with coronavirus disease 2019. Crit. Care Explor. 2020;2:e0139.

85. Pop-Busui R, Boulton AJM, Feldman EL, at al. Diabetic neuropathy: A position statement by the american diabetes association. Diabetes Care. 2017;40:136–154.

86. Zilliox LA. Neuropathic pain. Continuum (Minneap. Minn) 2017;23:512–532.

87. Gomes T, Juurlink DN, Antoniou T, Mamdani MM, Paterson JM, van den Brink W. Gabapentin, opioids, and the risk of opioid-related death: A Population-based nested case–control study. PLoS Med. 2017;14:e1002396.

88. Machado F. Physiotherapy in the management of pain in musculoskeletal manifestations after COVID-19. 2021.

89. Postigo-martin P, Cantarero-Villanueva I, lista-Paz A, Castro-martín E, Arroyo-morales m, Seco-Calvo j. A COVID-19 rehabilitation prospective surveillance model for use by physiotherapists. journal of Clinical medicine. 2021;10(8):1691.

90. Jin DM, Xu Y, Geng DF, et al.: Effect of transcutaneous electrical nerve stimulation on symptomatic diabetic peripheral neuropathy: A meta-analysis of randomized controlled trials. *Diabetes Res Clin Pract* 2010; 89: 10–5.

91. Kumar D, Marshall HJ. Diabetic peripheral neuropathy: Amelioration of pain with transcutaneous electrostimulation. *Diabetes Care* 1997; 20: 1702–5.

92. Forst T, Nguyen M, Forst S, et al. Impact of low frequency transcutaneous electrical nerve stimulation on symptomatic diabetic neuropathy using the new Salutaris device. *Diabetes Nutr Metab* 2004;17:163-8.

93. Giuliani A, Fernandez M, Farinelli M, et al. Very low level laser therapy attenuates edema and pain in experimental models. *Int J Tissue React* 2004; 26: 29-37.

94. Iijima K, Shimoyama N, Shimoyama M, et al. Effect of repeated irradiation of low-power He-Ne laser in pain relief from postherpetic neuralgia. *Clin J Pain* 1989; 5: 271-4.

95. Lefaucheur JP, Drouot X, Menard-Lefaucheur I, et al. Neurogenic pain relief by repetitive transcranial magnetic cortical stimulation depends on the origin and the site of pain. *J Neurol Neurosurg Psychiatry* 2004;75:612-6.

96. Yu HP-m, jones AY, Dean E, liisa laakso E. Ultra-shortwave diathermy-a new purported treatment for management of patients with COVID19. Physiother Theor Pr. 2020;36(5):559-63.

97. Dominguez-nicolas SM, manjarrez E. Low-field thoracic magnetic stimulation increases peripheral oxygen saturation levels in coronavirus disease (COVID-19) patients: a singleblind, sham-controlled, crossover study. medRxiv. 2021

98. Pooam M, Aguida B, Drahy S, jourdan N, Ahmad M. Therapeutic application of light and electromagnetic fields to reduce hyper-inflammation triggered by COVID-19. Communicative & Integrative Biology. 2021;14(1):66-77.

99. Kalirathinam D, Guruchandran R, Subramani P. Comprehensive physiotherapy management in Covid-19-a narrative review. Scientia medica. 2020;30(1):e38030-e.

100. Fallon K. Exercise in the time of COVID-19. Aust j Gen Pract. 2020;49(Suppl 13):1-2.

101. Ranasinghe C, Ozemek C, Arena R. Exercise and well-being during COVID 19-time to boost your immunity. Expert Review of Anti-Infective Therapy. 2020;18(12):1195-200.

102. Jiménez-Pavón D, Carbonell-Baeza A, lavie Cj. Physical exercise as therapy to fight against the mental and physical consequences of COVID-19 quarantine: Special focus in older people. Progress in Cardiovascular Diseases. 2020;63(3):386.

103. Goethals L, Barth N, Guyot J, Hupin D, Celarier T, Bongue B. Impact of Home Quarantine on Physical Activity Among Older Adults Living at Home During the COVID-19 Pandemic: Qualitative Interview Study. JMIR Aging. 2020 ;3(1):e19007

104. Narici, GM. De Vito, M. Franchi, et al. Impact of sedentarism due to the COVID-19 home confinement on neuromuscular, cardiovascular and metabolic health: Physiological and pathophysiological implications and recommendations for physical and nutritional countermeasures. Eur J Sport Sci 2021;21(4):614-635.

105. Leandro CG, De Silva WTF, Lima-Silva AE. Covid-19 and exercise-induced immunomodulation. Neuroimmunomodulation. 2020;27(1):75-78.

106. Barker-Davies Rm, O'Sullivan O, Senaratne KPP, et al. The Stanford Hall consensus statement for post-COVID-19 rehabilitation. Brit j Sport med. 2020;54(16):949-59.

107. Heffernan KS, Jae SY. Exercise as medicine for COVID-19: An ACE in the hole? Med Hypotheses 2020;142:109835.

108. Butler K, Clancy MJ, Adler J, Tevald MA. Acute rehabilitation of a patient with COVID-19 myocarditis: a case report. Phys Ther. 2021;101(1):190.

109. Sharkey J. Fascia focused manual therapy interventions-proposed treatment for postCOVID syndrome. Integrative journal of medical Sciences. 2021;8.

CHAPTER VI

COPD AND COMORBIDITIES

M. ARZU ÖZKARAFAKILI

Göğüs Hastalıkları Uzmanı, S.B.Ü. Şişli Hamidiye Etfal Eğitim Araştırma Hastanesi aaarzup@yahoo.com
ORCID: 0000-0002-8345-4539

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a heterogenous and multi-component lung disease, characterized by dyspnea, cough, and sputum production (1). It is a preventable and treatable clinical entity that is affecting millions of people worldwide. Today, it is a global healthcare problem with rising morbidity and mortality rates by climate change, global warming, air pollution, and tobacco use. However, despite the evolution of knowledge about the pathophysiology of COPD and the disease processes, the question "why do only 1/5 of smokers have airflow limitation?" remains to be answered (2). As the aging population increases, COPD becomes a higher burden for health care system economics.

These individuals have exertional dyspnea, their exercise performance and oxygen uptake are limited due to airflow obstruction and hypoxemia. This is the main concern about COPD and its components that it comprises accompanying diseases such as cardiovascular disorders, depression, cognitive impairment, metabolic and musculoskeletal implications, and lung cancer (3). Some of these develop independently of COPD, but some of them are causally related. On the other hand, the symptoms of comorbidities in COPD may be overlooked and differential diagnosis can be difficult (4). Moreover, the presence of COPD itself is one of the most known comorbidities that negatively affects many clinical conditions. Comorbidities may occur in any severity stage of COPD (2).

When associated with other diseases, the impairment in clinical outcomes of COPD becomes more deteriorating (4). These factors make us recognize COPD as a systemic and progressive disease which is a challenge for physicians.

Global Initiative of Obstructive Lung Disease (GOLD) is a comprehensive workshop, studies on diagnosis, management, and prevention of COPD since 2001. GOLD publishes its global strategy on COPD annually. The summary of the last statement of GOLD in 2023 recommends proactive interventions in the early phase of COPD which targets inflammatory and systemic components of the disease rather than the lung functions are an area of particular interest (5).

2. Comorbidities

2.1. Cardiovascular Diseases

Cardiovascular diseases frequently coexist with COPD and have an important impact on disease course and prognosis. (GOLD) Congestive heart failure and ischaemic heart disease processes are closely linked to COPD presence. The prevalence of heart failure is up to 20-70% in COPD which is an independent predictor of mortality and treatment with selective b-1 blockers is strongly recommended in these individuals (6). An exacerbation of COPD may be worsened heart failure and worsening of heart failure may lead to COPD exacerbation. The addition of noninvasive ventilation to conventional therapy dramatically improves the clinical status in patients of exacerbation who present with hypercapnic respiratory failure or acute pulmonary edema (7,8).

Several studies reveal that respiratory impairment is strongly associated with hypertension, diabetes, and cardiovascular diseases (4). Interestingly, it is also shown that; the patients whose pulmonary function tests(PFT) are in the normal range but have respiratory symptoms, also have a risk of cardiovascular system diseases as high as GOLD stage 3 or 4 patients. The symptomatic patients with normal PFT are not a negligible proportion. Additionally, these comorbidities have adverse effects on all-cause mortality and hospitalization in a period of 5-year follow-up (4). Hospital admissions either with respiratory causes or not are an important part of the overall burden of COPD (9). It should be kept in mind that cardiovascular events (myocardial infarction, unstable angina, transient ischemic attack, death) are the most frequent nonrespiratory causes of hospital admissions in COPD patients following their exacerbation-related hospitalization (10). The 90-day mortality of acute myocardial infarction, ischemic stroke, and intracranial hemorrhage is associated with hospitalization due to COPD exacerbation(10).

Atrial fibrillation is common in COPD and there is a strong association between atrial fibrillation and lower FEV1(11). As the bronchodilators

particularly short-acting b2 agonists are potentially pro-arrhythmic agents, physicians should be cautious in using these medications. (12) The presence of atrial fibrillation may trigger a COPD exacerbation and vice versa.

Cardiovascular disorders are generally associated with age and some traditional risk factors like smoking, physical inactivity, and poor diet. These are shared risk factors for COPD and cardiovascular diseases but the significant interaction may be explained by chronic systemic inflammation and some other undefined conditions (13). Ischaemic heart disease should be evaluated in all COPD patients according to their risk factor profile. The functional capacity and autonomic control of patients with COPD are impaired due to dyspnea which causes a great loss in physical activities. In this sense, as COPD negatively affects functional performance, cardiovascular diseases are the worst outcomes of COPD (14). Smoking may increase inflammatory status and susceptibility to respiratory infections (15). Airway remodeling and alveolar destruction which are caused by an inflammatory response, protease anti-protease imbalance, apoptosis, and impaired repair mechanisms of the lung are the key issues in the pathogenesis of COPD (16). Systemic inflammation, an increase in oxidative stress, predisposition to atherosclerosis cause adverse cardiovascular events in individuals with COPD (6).

Hypertension is frequently seen in COPD and may have serious effects on prognosis (17). Selective beta-blockers are the essentials of the treatment according to current guidelines(18). Diastolic dysfunction occurs as a consequence of sub-optimally treated hypertension and control of blood pressure which may trigger acute exacerbation that requires hospitalization (14).

Studies with large cohorts show that peripheral vascular disease is more common in COPD than expected as a consequence of atherosclerotic heart disease (19). It negatively affects the quality of life and health status of the individuals (19). It should be kept in mind when a COPD patient with a risk factor for vascular diseases is admitted.

2.2. Lung Cancer

Lung cancer is in the first ranking of death caused by malignant diseases worldwide (20). As most lung cancer cases are diagnosed at an advanced stage, prevention strategies and early detection are crucial because of the poor survival rates (21). COPD is known to be an independent risk factor for lung cancer even if the individuals do never smoke (22). Tobacco use is a common risk factor for COPD and lung cancer but genetic susceptibility, pulmonary inflammation, the

alteration in DNA methylation, and irregular lung repair mechanisms in COPD seem to contribute to lung cancer development (23). The major preventive method is controlling tobacco use and smoking cessation (24). The chest tomography finding of emphysema combined with airflow obstruction determined with PFT is the strongest risk for COPD patients for lung cancer development. Age >55, smoking history>30 pack/years, presence of emphysema on chest tomography, presence of airflow obstruction on PFT with FEV1/FVC ratio <0,7, Body mass index<25kg/m2 and having a family history of lung cancer are the accepted common risk factors for developing lung cancer (GOLD). So, screening with low-dose chest computed tomography is reported to be useful to improve survival in lung cancer. It is particularly recommended in adults between 50-80 years who have an anamnesis of 20-pack-year smoking history, are active smokers, or quit smoking within the past 15 years (25,26). Air pollution, biomass fuel, or asbestos exposure are the other risk factors for lung cancer (27).

2.3. Bronchiectasis

The prevalence of bronchiectasis is not to be underestimated in COPD patients and more frequent use of chest tomography provides us with this knowledge (28). These patients with bronchiectasis are more often males who have more sputum production and exacerbate more often, poorer spirometric values, chronic colonization with Pseudomonas aeroginosa, and increased mortality. These patients may need longer antibiotic therapies and physicians should be cautious in using inhaled corticosteroids as they are prone to lower respiratory tract infections (29).

2.4. Obstructive Sleep Apnea

The combination of obstructive sleep apnea (OSA) and COPD together make the prognosis poor as these patients experience more frequent hypoxemic and hypercapnic episodes (30). Their apneic periods are more profoundly hypoxemic and they develop daytime pulmonary hypertension with more cardiac arrhythmias (30). The utility of positive pressure ventilation for these individuals who have overlap syndrome reduces exacerbations, emergency department admissions, and hospitalization (31).

2.5. Metabolic Syndrome and Diabetes

Diabetes and metabolic syndrome are both more commonly seen in COPD (32). Insulin resistance is associated with an increased risk for COPD

development in females. Several studies show that diabetes has an adverse effect on prognosis of COPD (32).

2.6. Gastroesophageal reflux

It is known that gastroesophageal reflux is an independent risk factor for COPD exacerbations although the pathogenetic mechanisms remain unexplained (33).

2.7. Osteoporosis

Low bone mineral density and bone fractures are commonly seen in COPD patients regardless of glucocorticoid use, age, smoking, and exacerbation history (34). The use of inhaled corticosteroids has relations with fractures which is shown in several studies although not fully proven. Osteoporosis is associated with low fat-free mass, reduced body mass index, and emphysema and is frequently underdiagnosed(35). It is unfortunately related to poor quality of life and prognosis (34). Besides, COPD patients should be checked for vitamin D deficiency.

2.8. Anemia

Anemia due to chronic disease is often present in COPD subjects who have concomitant cardiovascular and metabolic disorders, are more dyspneic, have worse PFT values and exercise capacity, and exerted more severe exacerbations with increased risk of mortality (36). Iron deficiency anemia is also seen in COPD which is due to dysregulated iron metabolism and systemic chronic inflammation (37). Anemia needs to be investigated in case of diagnosis whether a treatable cause is present.

2.9. Polycythemia

It is defined as hemoglobin >17 g/dl in men and >15 g/dl in women. Secondary polycythemia is historically known as a common co-existing entity in COPD but getting decreased due to the widespread use of long-term oxygen therapy (38). In large cohort studies, COPD patients of the male sex who are living at high altitudes, active smokers with decreased DLCO, and severe hypoxemia have an increased risk for secondary polycythemia (38). Obstructive sleep apnea and smoking also cause secondary polycythemia in patients with COPD (38). The finding of secondary polycythemia in COPD may be related to the presence of uncorrected hypoxemia, coexisting interstitial lung disease, or pulmonary

vascular disorders like pulmonary hypertension, venous thromboembolism, and mortality (39).

2.10. Depression, Anxiety, Cognitive impairment

As the patient's dyspnea gets more profound, the consequence is physical inactivity and the development of depression. Anxiety and depression are commonly accompanied by COPD but are frequently not recognized. On the other hand, both have a negative effect on the prognosis of COPD particularly in females of younger age, smokers with lower FEV1 value, and those having cardiovascular disease (40), Moreover, the incidence of committing suicide is higher in COPD patients than ones who do not have COPD. Anxiety and depression should be treated appropriately and encourage the patients for pulmonary rehabilitation as physical exercise positively affects the depressive mood (41). Cognitive impairment is seen in up to 32-56 % of COPD patients, depending on the extensivity of diagnostic assessment (42). It is related to the deterioration of physical activities of daily life and quality of health status regardless of the spirometric severity of COPD(43). Cognitive impairment increases the risk of hospitalization and the duration of hospital stay during the acute exacerbation period (44). It also affects cooperation during using inhaler drugs.

3. References

1. Celli B, Fabbri L, Criner G, et al. Definition and Nomenclature of Chronic Obstructive Pulmonary Disease: Time for its Revision. Am J Respir Crit Care Med 2022.

2. Yang IA, Jenkins CR, Salvi SS. Chronic obstructive pulmonary disease in never-smokers: risk factors, pathogenesis, and implications for prevention and treatment. Lancet Respir Med 2022; 10(5): 497-511.

3. Barnes PJ, Celli BR. Systemic manifestations and comorbidities of COPD. Eur Respir J 2009; 33(5): 1165-85

4. Mannino DM, Thorn D, Swensen A, Holguin F. Prevalence and outcomes of diabetes, hypertension, and cardiovascular disease in COPD. Eur Respir J 2008; 32(4): 962-9. 4

5. GLOBAL STRATEGY FOR PREVENTION, DIAGNOSIS, AND MANAGEMENT OF COPD: 2023 Report

6. Bhatt SP, Dransfield MT. Chronic obstructive pulmonary disease and cardiovascular disease. Transl Res 2013; 162(4): 237-51.

7. MacDonald MI, Shafuddin E, King PT, Chang CL, Bardin PG, Hancox RJ. Cardiac dysfunction during exacerbations of chronic obstructive pulmonary disease. Lancet Respir Med 2016; 4(2): 138-48

8. Masa JF, Utrabo I, Gomez de Terreros J, et al. Noninvasive ventilation for severely acidotic patients in respiratory intermediate care units : Precision medicine in intermediate care units. BMC Pulm Med 2016; 16(1): 97

9. Dransfield MT, Criner GJ, Halpin DMG, et al. Time-Dependent Risk of Cardiovascular Events Following an Exacerbation in Patients With Chronic Obstructive Pulmonary Disease: Post Hoc Analysis From the IMPACT Trial. J Am Heart Assoc 2022; 11(18): e024350.

10. Wang M, Lin EP, Huang LC, Li CY, Shyr Y, Lai CH. Mortality of Cardiovascular Events in Patients With COPD and Preceding Hospitalization for Acute Exacerbation. Chest 2020; 158(3): 973-85

11. Buch P, Friberg J, Scharling H, Lange P, Prescott E. Reduced lung function and risk of atrial fibrillation in the Copenhagen City Heart Study. Eur Respir J 2003; 21(6): 1012-6

12. Salpeter SR, Ormiston TM, Salpeter EE. Cardiovascular effects of beta-agonists in patients with asthma and COPD: a meta-analysis. Chest 2004; 125(6): 2309-21.

13. Le Jemtel T, Padeletti M, Jelic S, et al. Diagnostic and Therapeutic Challenges in Patients With Coexistent Chronic Obstructive Pulmonary Disease and Chronic Heart Failure. *J Am Coll Cardiol.* 2007 Jan, 49 (2) 171–180.https://doi.org/10.1016/j.jacc.2006.08.046

14. Bhatt SP, Dransfield MT. Chronic obstructive pulmonary disease and cardiovascular disease. Transl Res 2013; 162(4): 237-51

15. Wen Qi Gan, S.F. Paul Man, Don D. Sin, The Interactions Between Cigarette Smoking and Reduced Lung Function on Systemic Inflammation, Chest, Volume 127, Issue 2, 2005, Pages 558-564, ISSN 0012-3692, https://doi.org/10.1378/chest.127.2.558.

16. James C Hogg, Pathophysiology of airflow limitation in chronic obstructive pulmonary disease, The Lancet, Volume 364, Issue 9435, 2004, Pages 709-721, ISSN 0140-6736, https://doi.org/10.1016/S0140-6736(04)16900-6.

17. Divo M, Cote C, de Torres JP, et al. Comorbidities and risk of mortality in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2012; 186(2): 155-61.

18. Dransfield MT, McAllister DA, Anderson JA, et al. beta-Blocker Therapy and Clinical Outcomes in Patients with Moderate Chronic Obstructive

Pulmonary Disease and Heightened Cardiovascular Risk. An Observational Substudy of SUMMIT. Ann Am Thorac Soc 2018; 15(5): 608-14.

19. Houben-Wilke S, Jorres RA, Bals R, et al. Peripheral Artery Disease and Its Clinical Relevance in Patients with Chronic Obstructive Pulmonary Disease in the COPD and Systemic Consequences-Comorbidities Network Study. Am J Respir Crit Care Med 2017; 195(2): 189-97.

20. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015; 136(5): E359-86.

21. Tanoue LT, Tanner NT, Gould MK, Silvestri GA. Lung cancer screening. Am J Respir Crit Care Med 2015; 191(1): 19-33.

22. Caramori G, Casolari P, Cavallesco GN, Giuffre S, Adcock I, Papi A. Mechanisms involved in lung cancer development in COPD. Int J Biochem Cell Biol 2011; 43(7): 1030-44.

23. Houghton AM. Mechanistic links between COPD and lung cancer. Nat Rev Cancer 2013; 13(4): 233-45

24. Dhariwal J, Tennant RC, Hansell DM, et al. Smoking cessation in COPD causes a transient improvement in spirometry and decreases micronodules on high-resolution CT imaging. Chest 2014; 145(5): 1006-15

25. de Torres JP, Bastarrika G, Wisnivesky JP, et al. Assessing the relationship between lung cancer risk and emphysema detected on low-dose CT of the chest. Chest 2007; 132(6): 1932-8. 56.

26. Wilson DO, Leader JK, Fuhrman CR, Reilly JJ, Sciurba FC, Weissfeld JL. Quantitative computed tomography analysis, airflow obstruction, and lung cancer in the pittsburgh lung screening study. J Thorac Oncol 2011; 6(7): 1200-5. 57.

27. Lin HH, Murray M, Cohen T, Colijn C, Ezzati M. Effects of smoking and solid-fuel use on COPD, lung cancer, and tuberculosis in China: a time-based, multiple risk factor, modelling study. Lancet 2008; 372(9648): 1473-83.

28. Ni Y, Shi G, Yu Y, Hao J, Chen T, Song H. Clinical characteristics of patients with chronic obstructive pulmonary disease with comorbid bronchiectasis: a systemic review and meta-analysis. Int J Chron Obstruct Pulmon Dis 2015; 10: 1465-75. 89. Du Q, Jin J, Liu X, Sun Y.

29. Bronchiectasis as a Comorbidity of Chronic Obstructive Pulmonary Disease: A Systematic Review and Meta-Analysis. PLoS One 2016; 11(3): e0150532.

30. Chaouat A, Weitzenblum E, Krieger J, Ifoundza T, Oswald M, Kessler R. Association of chronic obstructive pulmonary disease and sleep apnea syndrome. Am J Respir Crit Care Med 1995; 151(1): 82-6.

31. Weitzenblum E, Krieger J, Apprill M, et al. Daytime pulmonary hypertension in patients with obstructive sleep apnea syndrome. Am Rev Respir Dis 1988; 138(2): 345-9.

32. Cebron Lipovec N, Beijers RJ, van den Borst B, Doehner W, Lainscak M, Schols AM. The Prevalence of Metabolic Syndrome In Chronic Obstructive Pulmonary Disease: A Systematic Review. COPD 2016; 13(3): 399-406

33. Ingebrigtsen TS, Marott JL, Vestbo J, Nordestgaard BG, Hallas J, Lange P. Gastro-esophageal reflux disease and exacerbations in chronic obstructive pulmonary disease. Respirology 2015; 20(1): 101-7

34. Bon J, Fuhrman CR, Weissfeld JL, et al. Radiographic emphysema predicts low bone mineral density in a tobaccoexposed cohort. Am J Respir Crit Care Med 2011; 183(7): 885-90. 1

35. Jaramillo JD, Wilson C, Stinson DS, et al. Reduced Bone Density and Vertebral Fractures in Smokers. Men and COPD Patients at Increased Risk. Ann Am Thorac Soc 2015; 12(5): 648-56

36. Xu Y, Hu T, Ding H, Chen R. Effects of anemia on the survival of patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis. Expert Rev Respir Med 2020; 14(12): 1267-77.

37. Martinez-Rivera C, Portillo K, Munoz-Ferrer A, et al. Anemia is a mortality predictor in hospitalized patients for COPD exacerbation. COPD 2012; 9(3): 243-50.

38. Zhang J, DeMeo DL, Silverman EK, et al. Secondary polycythemia in chronic obstructive pulmonary disease: prevalence and risk factors. BMC Pulm Med 2021; 21(1): 235.

39. Nakamura A, Kasamatsu N, Hashizume I, et al. Effects of hemoglobin on pulmonary arterial pressure and pulmonary vascular resistance in patients with chronic emphysema. Respiration 2000; 67(5): 502-6.

40. Ng TP, Niti M, Tan WC, Cao Z, Ong KC, Eng P. Depressive symptoms and chronic obstructive pulmonary disease: effect on mortality, hospital readmission, symptom burden, functional status, and quality of life. Arch Intern Med 2007; 167(1): 60-7. 1

41. Bolton CE, Bevan-Smith EF, Blakey JD, et al. British Thoracic Society guideline on pulmonary rehabilitation in adults. Thorax 2013; 68 Suppl 2: ii1-30

42. Pierobon A, Ranzini L, Torlaschi V, et al. Screening for neuropsychological impairment in COPD patients undergoing rehabilitation. PLoS One 2018; 13(8): e0199736.

43. Cleutjens F, Spruit MA, Ponds R, et al. Cognitive impairment and clinical characteristics in patients with chronic obstructive pulmonary disease. Chron Respir Dis 2018; 15(2): 91-102

44. Chang SS, Chen S, McAvay GJ, Tinetti ME. Effect of coexisting chronic obstructive pulmonary disease and cognitive impairment on health outcomes in older adults. J Am Geriatr Soc 2012; 60(10): 1839-46

CHAPTER VII

THE ROLE OF BCL-2 FAMILY PROTEINS IN CANCER PROGRESSION AND THEIR RELEVANCE TO CANCER THERAPY

RUMEYSA DUYURAN[1] & HÜLYA ÇIÇEK[2]

[1](Ph.D.), Gaziantep University, Institute of Health Sciences, Department of Medical Biochemistry.
rduyuran@hotmail.com
ORCID: 0000-0002-7110-0303

[2](Prof. Dr.), Gaziantep University, Faculty of Medicine, Department of Medical Biochemistry. drhulyacicek@hotmail.com
ORCID: 0000-0002-1065-1582

1. Introduction

Members of the Bcl-2 (B-cell lymphoma gene-2) protein family are the guardians of the genetically conserved mitochondrial apoptotic pathway. This family has 20 members; some are inhibitors of apoptosis, while others stimulate apoptosis and are defined as proapoptotic genes.

The viability of the cell depends on the ratio of proapoptotic and antiapoptotic members of this family. Regulation of apoptosis is provided by the Bcl-2/Bax gene family. Members of the Bcl-2/Bax gene family are located on the membrane of the endoplasmic reticulum as well as the membranes of mitochondria and nuclei. The pro-apoptotic Bcl-2 family members in the cell are the most important part of a balance mechanism that decides whether the cell will survive or not. This said equilibrium state is regulated at the transcriptional or posttranslational level in response to cellular cues.

Many studies on mitochondrial diseases reveal some degree of helplessness of the cell against mitochondrial damage. This damage is called the starting point of an important biochemical process called apoptosis or programmed cell death.

Many physiological events, death, and life decisions are at the mitochondrial level, where the stoichiometry of pro- and antiapoptotic Bcl-2 family members determines the fate of the cell. Understanding this process reveals the various physiological contexts in which the proteins involved in this biological pathway are important and their role in the development of many human cancers and will lead to the development of better chemotherapeutic drugs for treatment. Understanding and grasping the activation process offers great potential in the therapeutic intervention of many diseases such as cancer and autoimmune disorders.

Apoptosis signaling is under the control of complex interactions between BCL-2 family members, BH3 proteins from the pro-apoptotic protein group, and BAX and BAK, apoptosis effectors. Pro-survival BCL-2 proteins can inhibit them either by binding directly to BAX and BAK or by binding only to BH3 proteins, thus preventing them from activating apoptosis effectors. BAX and BAK proteins also differ in their ability to bind to BCL-2 proteins. While BAX can interact with all BCL-2 proteins, BAK is only related to MCL-1 and BCL-XL proteins (1).

2. BCL-2 Family and Its Role in Tumor Formation

The way a cell and tissue escapes apoptosis is considered to be the hallmark of cancer (2). Defects in the control of apoptosis that contribute to cancer prognosis, spread, and resistance to therapy may result from abnormally increased expression of pro-survival proteins or abnormally decreased expression of proapoptotic proteins. Excessively increased levels of BCL-2 family proteins, that is, very high expression of BCL-2 proteins, are closely associated with the development and poor prognosis of many cancers (3-5). Abnormal overexpression of BCL-2 family proteins may also result from chromosomal translocations or increased gene transcription (6).

Abnormally reduced levels of proapoptotic BCL-2 family proteins were observed in various cancers; The reduction of proapoptotic members of the BCL-2 family has also been associated with the development of cancer and treatment resistance. Resistance to cancer treatment causes clinically poor results. Defects in the intrinsic apoptotic pathway, due to overexpression of BCL-2 proteins or abnormal reduction of proapoptotic BCL-2 family members, can render many cells resistant to therapy, both malignant and malignant and non-transformed cells, to anti-cancer therapeutics. This was first demonstrated when lymphoid cells from BCL-2 transgenic mice were found to be resistant to several DNA-damaging anti-cancer agents and glucocorticoids (1, 7, 8).

For these reasons, since proapoptotic BH3 proteins are critical initiators of apoptosis, a focus should also be placed on developing new therapeutic strategies that increase the expression of these proapoptotic proteins (9). It is stated in studies that this treatment will be obtained either with drugs that can directly affect and increase the expression of BH3 proteins or with drugs that can inhibit negative regulators of their expression. Again, many studies have traditionally stated that chemotherapeutic drugs, especially drugs that can induce DNA damage, only induce the expression of BH3 proteins (10).

There is substantial evidence that cellular metabolism can affect the levels of pro-apoptotic BCL-2 family members. In other words, it has been shown that changes in tumor cell metabolism increase the power of malignant cells to survive apoptosis. The biochemical pathway known as the PI3K/AKT pathway provides a link between cell proliferation and cell metabolism. If this pathway is in cancer, that is, the PI3K/AKT pathway, for example, the expression of oncogenic kinases, is often abnormally activated and supports glucose metabolism (11, 12).

3. Bcl-2 Family and Anti-cancer Treatment

In recent studies, it has been extensively investigated that cancer cells do not lose their apoptotic cell feature, but that several Bcl-2 family members lose their function and prevent the activation of this mechanism, and the development of compounds to activate or inactivate members of this family(13). Only the levels of BH3 molecules are thought to reactivate the apoptotic pathway in the tumor cell of an agonist (14). While molecules that mimic BH3 proteins have great potential as ammunition in the fight against cancer, these compounds require BAX or BAK proteins to be functionally active (15). Where chemotherapeutic drug therapy causes chemoresistance mutations in the bax gene instability pathway or results in cancer types that are highly associated with increased proteasomal degradation of the Bax protein, such as prostate adenocarcinoma, BH3 mimetics will be of little help. Therefore, it is of additional importance to understand how Bax/Bak activation results in apoptosis (16, 17).

4. Conclusion

Members of the BCL-2 protein family constitute important regulators of apoptosis. Abnormalities in the expression of pro-survival or pro-apoptotic members of the BCL-2 protein family can promote tumor development and render malignant cells resistant to anti-cancer therapy. A detailed understanding

of the control of apoptosis and how different subsets of BCL-2 family proteins interact with each other has been developed. The understanding reached as a result of these studies has led to the development of new anti-cancer drugs called BH3-mimetics, which can directly activate the apoptosis mechanism by inhibiting pro-survival BCL-2 proteins.

It aims to develop effective and tolerable treatment programs for BH3-mimetic drugs and to explore what other anti-cancer agents can be combined with these drugs to achieve effective and safe cancer treatment. It is believed that only gaining a clearer understanding of how the expression of proapoptotic BH3 proteins is regulated will lead to insights that can be exploited to develop new therapeutics that increase the expression of these cell death-initiating constructs. Such agents are expected to cooperate with BH3-mimetic drugs and standard chemotherapeutics in killing malignant cells.

Although the discovery of the function of the prototypical member of this family, Bcl-2, is not very old, there are many studies in the literature, both in vitro and in vivo. According to widely accepted models, the stoichiometry of pro- and anti-apoptotic molecules decides whether the adapter molecules Bak and Bax oligomerize lead to mitochondrial dysfunction and apoptosis. Although many studies have been carried out to understand the conformational change of these protein structures during apoptosis, the answers to the questions about the mitochondrial dysfunction of Bax and Bak have still not been fully found. Understanding the mechanisms in this process will go a long way in developing new algorithmically engineered drugs.

5. References

1. Meijerink JP, Mensink EJ, Wang K, Sedlak TW, Slöetjes AW, De Witte T, et al. Hematopoietic malignancies demonstrate loss-of-function mutations of BAX. Blood, The Journal of the American Society of Hematology. 1998;91(8):2991-7.

2. Hanahan D. Hallmarks of cancer: new dimensions. Cancer discovery. 2022;12(1):31-46.

3. Adams JM, Cory S. The Bcl-2 protein family: arbiters of cell survival. Science. 1998;281(5381):1322-6.

4. Reed JC. Bcl-2–family proteins and hematologic malignancies: history and prospects. Blood, The Journal of the American Society of Hematology. 2008;111(7):3322-30.

5. Perciavalle RM, Opferman JT. Delving deeper: MCL-1's contributions to normal and cancer biology. Trends in cell biology. 2013;23(1):22-9.

6. Diepstraten ST, Anderson MA, Czabotar PE, Lessene G, Strasser A, Kelly GL. The manipulation of apoptosis for cancer therapy using BH3-mimetic drugs. Nature Reviews Cancer. 2022;22(1):45-64.

7. Knight T, Luedtke D, Edwards H, Taub JW, Ge Y. A delicate balance–The BCL-2 family and its role in apoptosis, oncogenesis, and cancer therapeutics. Biochemical pharmacology. 2019;162:250-61.

8. Yamaguchi R, Lartigue L, Perkins G. Targeting Mcl-1 and other Bcl-2 family member proteins in cancer therapy. Pharmacology & therapeutics. 2019;195:13-20.

9. Lagares D, Santos A, Grasberger PE, Liu F, Probst CK, Rahimi RA, et al. Targeted apoptosis of myofibroblasts with the BH3 mimetic ABT-263 reverses established fibrosis. Science Translational Medicine. 2017;9(420):eaal3765.

10. D'Aguanno S, Del Bufalo D. Inhibition of anti-apoptotic Bcl-2 proteins in preclinical and clinical studies: a current overview in cancer. Cells. 2020;9(5):1287.

11. Ediriweera MK, Tennekoon KH, Samarakoon SR, editors. Role of the PI3K/AKT/mTOR signaling pathway in ovarian cancer: Biological and therapeutic significance. Seminars in cancer biology; 2019: Elsevier.

12. Kitagishi Y, Matsuda S. Diets involved in PPAR and PI3K/AKT/PTEN pathway may contribute to neuroprotection in a traumatic brain injury. Alzheimer's Research & Therapy. 2013;5:1-7.

13. Zhang L, Yu J, Park BH, Kinzler KW, Vogelstein B. Role of BAX in the apoptotic response to anticancer agents. Science. 2000;290(5493):989-92.

14. Li B, Dou QP. Bax degradation by the ubiquitin/proteasome-dependent pathway: involvement in tumor survival and progression. Proceedings of the National Academy of Sciences. 2000;97(8):3850-5.

15. Deng J, Carlson N, Takeyama K, Dal Cin P, Shipp M, Letai A. BH3 profiling identifies three distinct classes of apoptotic blocks to predict response to ABT-737 and conventional chemotherapeutic agents. Cancer cell. 2007;12(2):171-85.

16. Oltersdorf T, Elmore SW, Shoemaker AR, Armstrong RC, Augeri DJ, Belli BA, et al. An inhibitor of Bcl-2 family proteins induces regression of solid tumors. Nature. 2005;435(7042):677-81.

17. Van Delft MF, Wei AH, Mason KD, Vandenberg CJ, Chen L, Czabotar PE, et al. The BH3 mimetic ABT-737 targets selective Bcl-2 proteins and efficiently induces apoptosis via Bak/Bax if Mcl-1 is neutralized. Cancer cell. 2006;10(5):389-99.

CHAPTER VIII

POSTMENOPAUSAL OSTEOPOROSIS

YURDAGÜL BAHRAN MUŞTU

(Dr.), Karaman Training and Research Hospital
yurdagulbahran@gmail.com
ORCID:0000-0002-1452-0125

1. Introduction

Osteoporosis is a metabolic bone disease that causes low bone mineral density, deterioration of bone microstructure, increased bone fragility, and increased risk of fracture.(1) The most important complication due to osteoporosis fractures.Many secondary health problems may occur due to fractures and may ultimately lead to increased mortality. Osteoporosis can be diagnosed and treatment can be planned before a fracture occurs with the screening performed today. Therefore, early detection of osteoporosis and treatment planning is important in terms of preventing complications.It is possible to make many different classifications for osteoporosis. Osteoporosis is evaluated in 2 groups primary and secondary, considering the factors affecting bone metabolism: (1)

Primary osteoporosis is also divided into two; (1,2)
1) Type 1 Osteoporosis (Postmenopausal osteoporosis)
2) Type 2 Osteoporosis (Senile osteoporosis)

About five years before the last menstrual period, the decrease in bone mass begins to accelerate. The annual bone loss in this period is around 1% and 10% in the perimenopausal period.(1)Osteoporosis-related fractures are mostly seen in vertebrae, proximal femur, and distal radius. These fractures occur mostly as a result of minor traumas. These fractures are defined as low-energy fragility fractures, which develop in the case of mechanical loading at a level that does not cause a fracture in a normal bone. In osteoporotic patients, these fragility fractures cause physical and functional limitations and an increase in mortality and morbidity. (3)Especially hip fractures are directly related to mortality.

Mortality rates in the first two years in women with hip fractures are reported to be 12-20%.(4,5) In postmenopausal women, fractures mostly occur in the vertebrae.However, they are often detected late because they are asymptomatic. In a study, vertebral fractures were found to affect mortality in the first 5 years, similar to hip fractures.(3,6)

2. Clinical risk factors

Bone mineral density measurement is used in the clinical diagnosis of osteoporosis.However, even if BMD is found to be normal or borderline, the patient may develop fractures. Osteoporosis is a multifactorial disease. Detailed knowledge of risk factors, good analysis of modifiable risk factors, and intermittent screening are important for preventing osteoporosis and minimizing the risk of fracture.

Non-modifiable risk factors are female gender, age, early menopause, family history,previous fragility fracture, and history of osteoporosis-related diseases.

Modifiable risk factors; vitamin D deficiency, insufficient calcium intake, poor diet, low BMI(body mass index)≤19 kg/m2,alcohol use and smoking, immobilization, history of osteoporosis-related diseases

In a multicenter study investigating risk factors in postmenopausal women, the factors with the highest risk were reported as insufficient sun exposure (53.3%), sedentary life (52.9%), and insufficient calcium intake in childhood and adulthood (41.9% and 45.1%).(7)

Some clinical parameters that pose a risk for osteoporotic fracture development are listed below;

Table 1: Fracture risk factors :(8-10)

Female gender
Old age
Smoking and alcohol use
Previous fragility fracture
Low BMI)≤19 kg/m2
Having used ≥5 mg/day prednisone or its equivalent for at least 3 months
Falls
Presence of diseases that may lead to osteoporosis
History of drug use that may lead to osteoporosis
History of hip fracture in parents
Individual and environmental factors that may facilitate falls

For this reason, the Fracture Risk Assessment Scale called FRAX was developed in 2008. (11)Accordingly, the risk of hip and a major osteoporotic fracture (vertebra, humerus, distal radius) in the next ten years can be calculated in patients who are considered osteopenic according to bone mineral density. According to the FRAX scoring, those who are recommended to be treated for osteoporosis are the patient group with a major osteoporotic fracture risk of≥20% and a hip fracture risk of≥3%. (4,8)FRAX is evaluated using a computer program and varies according to the epidemiological structure of societies. Many countries have their specific inquiry page (https:/ /www.shef.ac.uk/FRAX/tool.jsp?lang:tu). In a study conducted in our country using the FRAX scoring system, it was shown that 8.6% of women with a history of fracture over the age of fifty and 13.6% of women without a history of fracture were osteoporosis treatment candidates.(12)For example, glucocorticoid, alcohol use, and smoking were included in the evaluation, but the duration and dosage of use were ignored, and the lack of consideration of lumbar vertebrae values in BMD measurement, the number of previously developed fractures, and the lack of evaluation of diseases other than rheumatoid arthritis are among the disadvantages of FRAX. According to the risk calculated with FRAX, the decision on pharmacological treatment should be made by considering the clinic.

3. Examination

Clinical symptoms of osteoporosis are not obvious. Findings such as back pain, increased kyphosis, and shortening of height should be emphasized. Spinous process tenderness on physical examination is a warning for vertebral fracture.Shortening of 2 cm in the last 1 year and 4 cm according to the height measurement of the youth period should be considered pathological.(13)In the differential diagnosis, it should be alerted in terms of secondary causes of osteoporosis.

4. Laboratory

Some tests should be requested primarily for the differential diagnosis of secondary osteoporosis and some systemic diseases. These are haemograms, serum calcium, urea, creatinine, liver function tests, parathormone, 25-OH vitamin D, TSH/T4, alkaline phosphatase, albumin, phosphorus, and 24-hour urine calcium value.

5. Monitoring and Diagnosis

DXA(Dual X-ray Absorptiometry) to evaluate bone mineral density, thoracic and lumbar vertebral graphics are requested for scanning for vertebral fracture.The purpose of direct radiographs is to examine the possible presence of vertebral fracture, to detect conditions that may cause false negativity in DXA (degeneration, scoliosis, etc.), and to make a differential diagnosis of back pain. In addition to absorption techniques for the diagnosis of osteoporosis, methods such as conventional computerized tomography and quantitative ultrasonography can also be used in a narrow group of indications.

DXA measurement of lumbar vertebrae and proximal femur gives bone mineral density. Osteoporosis is diagnosed according to the BMD measurement values obtained. In addition to diagnosing with BMD measurement with DXA, it allows for evaluating the risk of fracture, making a pharmacological treatment decision, and monitoring the response to treatment.BMD indicates the mineral content in each square centimeter scanned in grams (g/cm2). T and Z scores are used when DXA results are evaluated in terms of osteoporosis.(1,14)The value obtained by comparing the BMD values of the patient with the BMD measurement values of young adults of the same sex gives the T score, and the comparison of the BMD values of the patient with the BMD values of the adults of the same age and sex gives the Z score.

It is the T score used in the diagnosis of osteoporosis in postmenopausal women.BMD is closely related to bone strength.BMD measurements are not healthy in the presence of vertebral and hip osteoarthritis, osteophytes, fractures, kyphosis, scoliosis, aortic calcification, gallstones, and prosthesis, and may give a higher result than it is. In these cases, the use of quantitative computed tomography is recommended.(15)In the diagnosis of osteoporosis, anteroposterior L1-L4 total, total proximal femur, and femoral neck measurements are the regions that should be evaluated in BMD.In the presence of primary hyperparathyroidism, morbid obesity, in cases where hip and vertebrae measurements cannot be performed (spinal surgery, hip arthroplasty, etc.) distal radius measurement is recommended.(16)

The situations in which the Turkish Society of Endocrinology and Metabolism recommends asking for BMD can be listed as follows;

- Patients aged fifty years and older with a history of fractures,
- All women aged sixty five and over(with or without clinical risk factors),
- Perimenopausal women,and women aged fifty-sixty-nine years(with clinical risk factors),

• Those who use drugs that may cause bone loss or low bone mass (such as glucocorticoids) or have a disease (such as rheumatoid arthritis)

• Monitoring the response to treatment in patients under treatment for osteoporosis.

Although there are different opinions on DXA measurement intervals in guidelines and reviews, annual DXA measurement is performed in the follow-up of osteoporosis treatment according to the social security institution reimbursement system in our country. In some special cases, measurement can be performed at more frequent intervals.

6. Treatment

The main goals in the treatment of osteoporosis are to increase bone strength, minimize the risk of fracture, increase physical capacity, and reduce mortality and morbidity rates.(4)Treatment can be divided into 2 pharmacological and nonpharmacological;

6.1. Nonpharmacological treatment;

6.1.1. Adequate intake of calcium and vitamin D:

The amount of calcium that should be taken daily in the postmenopausal period is 1000-1200 mg/day. If the recommended amount cannot be met by diet, supplementation is necessary. The basic supplement forms are calcium citrate and calcium carbonate.Postmenopausal women should take 800-1200 U vitamin D supplements daily.(17)Although some foods such as salmon, liver, egg yolk, and butterare rich in vitamin D, adequate vitamin D intake is not possible with diet.

6.1.2. Protein intake:

A daily protein intake of 1g/kg is recommended for bone health.

6.1.3. Smoking and alcohol:

Smoking has an accelerating effect on bone loss, its cessation is a must for bone health.(8,18)It is recommended that the daily alcohol intake is not more than 20 grams.(8,17)

6.1.4. Exercise:

Regular muscle strengthening and weight-bearing exercises are recommended to prevent fractures and reduce the risk of falls.Weight-bearing

exercises such as brisk walking for at least thirty minutes three times a week help to protect the bone tissue. (8)Posture and balance exercises should also be added to the treatment plan.

6.1.5. Additional dietary recommendations:

Coffee consumption (over 3 cups), and caffeinated and carbonated drinks should be limited. Daily salt intake should not exceed 2100 mg.

6.2. Pharmacological treatment:

The conditions in which pharmacological treatment should be planned in postmenopausal women aged fifty years and over are as follows ;(4)

* Vertebral, total hip /femoral neck T score ≤-2.5 SD

*Fragility fracture, hip or vertebral fracture detected clinically or by imaging,

*Low bone mass and a ten-year risk of hip fracture calculated by FRAX ≥ 3% or a ten-year risk of osteoporosis-related fracture ≥ 20% or presence of other risk factors

Table 2: Drugs used to treat osteoporosis

Medication	Method of use	Dosage	Characteristics of use	Warnings
Bisphospho-nate Drugs			Drink plenty of water before meals in the morning. Afterward, it is recommended to stay in an upright position for at least thirty minutes.	*It should not be used routinely by patients with Gfr<30-35 Ml/min
Alendronate sodium	Oral	70 mg /week 10 mg/day,	*	*
Alendronate sodium+D3	Oral	70mg+2800/5600 IU/week	*	*
Risedronate sodium	Oral	5 mg/day, 35 mg/ hf consecutive 2 days, 75 mg/month 150 mg/month	*	*
Ibandronic acid	Oral /Iv	150 mg/month,3 mg/3 month	Iv form with at least 15-30 sec injection	*
Zolendronic acid	Iv infusion	5 mg/year	With the infusion of at least 15 minutes	Adequate fluid intake before and after injection is important Flu-like side effects may occur after injection, antipyretic treatment may be given
Denosumab	Subcutaneous injection (SC)	60 mg/6 month		Care should be taken in terms of hypocalcemia. May cause cellulitis-like skin rash
Teriparatide	Subcutaneous injection (SC)	20 mg/day		It is not recommended for use in patients with a high risk of hypercalcemia, bone malignancy, osteosarcoma, or bone metastasis.
Raloxifene	oral	60 mg/day		Contraindicated in the presence of venous thromboembolism
Strontium ranelate	oral	2 g/day sachet		Not recommended for use in severe renal failure

Although efficacy on reduction in fracture risk is an important parameter in treatment decision-making in patients with osteoporosis, many factors such as concomitant diseases of the patient, potential side effects of the drug, cost of the drug, method of use, drug tolerance and compliance of the patient should be considered.

6.2.1. Bisphosphonates

Table 2 shows bisphosphonate drug groups, usage, and doses.Upper gastrointestinal side effects of bisphosphonates are one of the common problems. Oral bisphosphonates should not be preferred in patients with oesophageal diseases or in patients who cannot comply with the form of use. When using the drug, care should be taken in terms of GFR.It should not be used in patients with a GFR value of ≤30-35 ml/min.Undesirable side effects such as osteonecrosis of the jaw may develop during the use of these drugs, although rare.Care should be taken in dental controls and oral hygiene should be observed. Atypical femur fractures are one of the rare complications of chronic bisphosphonate treatment. In particular, patients who have been using bisphosphonate group drugs for a long time should be alerted.

6.2.2.Denosumab may be preferred in patients who develop fractures secondary to osteoporosis or who are unresponsive or intolerant to other treatments.

6.2.3.Teriparatide is approved for use for a maximum of 2 years in postmenopausal women at high risk for fractures.Teriparatide is within the scope of reimbursement for 1.5 years in our country. A rebound effect may be observed when treatment is discontinued. Therefore, antiresorptive therapy is recommended after teriparatide treatment is discontinued.(19)

6.2.4.Hormone replacement therapy (HRT is an indication for antiresorptive therapy and can be used if these drugs cannot be tolerated, It is recommended to use the minimum possible dose for a maximum of 2 years.

6.2.5.Selective estrogen receptor modulators (SERM): *In* cases where bisphosphonates cannot be tolerated or their use is contraindicated, it can be preferred in the treatment of those in the high-risk group for invasive breast cancer.

6.2.6.Strontium ranelate may be preferred as the 2nd or 3rd step in postmenopausal women who do not have fractures and cannot use bisphosphonate and denosumab.(4,8)

REFERENCES

1. Cosman F,de Beur S J,LeBoff M S,Lewiecki EM,Tanner B,Randall S,Lindsay R.Clinician's Guide to Prevention and Treatment of Osteoporosis. Osteoporos Int 2014;25:2359-2381

2. Hannan MT,Felson D,Dawson-Hughes B,Tucker KL,Cupples LA,et al.Risk Factors for Longitudinal Bone Loss in Elderly Men and Women:The Framingham Osteoporosis Study.J Bone Miner Res 2000;15(4):710-720.

3. Ioannidis G,Papaioannou A,Hopman WM,et al.Relation between fractures and mortality:results from Canadian Multicentre Osteoporosis Study. CMAJ.2009;181:265-71.

4. AACE Medical Guidelines for clinical practice for the diagnosis and treatment of postmenopausal osteoporosis.Endocrine Practice 2010:16(Suppl 3):1-37.

5. Parfitt AM.The coupling of bone formation to bone resorption:A critical analysis of the concept and of its relevance to the pathogenesis of osteoporosis.

6. Colon –Emeric C,Kuchibhatla M,Pieper C,Hawkes W,Fredman L,Magaziner J,Zimmerman S,Lyles KW,The contributionof hip fracture to risk of subsequent fractures:data from two longitudinal studies.Osteoporosis Int.2003;14:879-83.

7. Kutsal YG,Savaş S,İnanıcı F,Özdemir O,Karahan S,Doğan A,Hizmetli S,Kamanlı A,Kuran B,Öncel S,Sarıkaya S,Şenel K,Uğurlu H,Yazgan P.The frequency of the clinical risk factors in postmenapausal osteoporosis.2013;28:256-62.

8. Cosman F,de Beur S J,LeBoff M S,Lewiecki EM,Tanner B,Randall S,Lindsay R.Clinician's Guide to Prevention and Treatment of Osteoporosis. Osteoporos Int 2014;doi 10.1007/s00198-014-2794-2.

9. Clinician's Guide to Prevention and Treatment of Osteoporosis. National Osteoporosis Foundation;Washington,DC:National Osteoporosis Foundation;2014.

10. Kanis JA,McCloskey EV,Johansson H,et al.European guidance for the diagnosis and management of osteoporosis in postmenapausal women. Osteoporosis Int 2012;doi:10.1007/s00198-012-2074-y.

11. Kanis JA(World Health Organisation Scientific Group).Assesment of Osteoporosis at the Primary Health Care Level:WHO Scientific Technical

Report.Sheffield,UK:WHO Collaborating Centre for Metabolic Bone Diseases,University of Sheffield,2008.

12. Tuzun S,Eskiyurt N,Akarırmak U,Sarıdoğan M,Johansson H,McCloskey E,Kanis JA.The impact of a FRAX-based intervention threeshold in Turkey:the FRAX-TURK study Arch Osteoporos.2012;7:229-35.

13. Brand RA.50 Years Ago in CORR:The Appearance of Osteoporosis in Ambulatory Institutionalized Males Clin Orthop Relat Res.2011;469:2076-7.

14. Watts NB,Adler RA,Bilezikian JP,et all. Osteoporosis in men:an Endocrine Society clinical practice guideline .J Clin Endocrinol Metab 2012;97:1802.

15. Baim S,Binkley N,Bilezikian JP,et all.Official Positions of the International Society for Clinical Densitometry and executive summary of the 2007 ISCD Position Development Conference.J Clin Densitom 2008;11:75.

16. International Society for Clinical Densitometry.2013 ISCD Official Positions –Adult.www.iscd.org/official-positions/2013-iscd-official-positions-adult/(Accessed on November 14,2013)

17. National Osteoporosis Foundation.Clinician's guide to prevention and treatment of Osteoporosis,Washington D.C.2014.

18. Harinarayan CV,Marwah R,Sahay R,Babhulkar S.Clinical Practice Guidelines on postmenapausal osteoporosis:An executive summary and recommendations.Journal of Midlife health 2013;4 107-126.

19. Clinician's Guide to Prevention and Treatment of Osteoporosis. National Osteoporosis Foundation;Washington,DC:National Osteoporosis Foundation;2013.

CHAPTER IX

DIVINATION AND EXTISPICY IN MESOPOTAMIAN MEDICINE

TUĞBA GENCER[1] & AHMET ÖZDINÇ[2]

[1](MSc. Researcher), Department of Medical History and Ethics, Istanbul University-Cerrahpasa Cerrahpasa Faculty of Medicine, Istanbul, Turkey. tugbaajan@gmail.com
ORCID: 0000-0003-1560-999X

[2](Asst. Prof. Dr.), Department of Medical History and Ethics, Istanbul University-Cerrahpasa Cerrahpasa Faculty of Medicine, Istanbul, Turkey. ahmet.ozdinc@iuc.edu.tr
ORCID: 0000-0002-0012-6637

1. Introduction

From the beginning of their existence, ancient humans asked questions about life and death, nature, the origin and order of the universe, and their place in that order. Ancient humans tried to explain the phenomena they did not understand by creating faith based on cause and effect. Accordingly, the sun that illuminated the earth during the day, and the stars and planets that surrounded it at night, were placed in the sky by deities for the good of humanity, along with all the terrestrial elements. Thus, each element was sacred and carried messages from the deities to humanity. Within this animistic framework, people saw everything in the world as transmitting deities' messages to humanity. (1) The seasons, weather conditions, animal movements, the positions of the stars and planets, the birth forms that started the life cycle, and the state of newborns conveyed messages from supreme powers and were harbingers of what would happen to humans. (1) All such signs were meticulously followed and recorded, leading to the development of divination methods. By doing penance, making sacrifices, and consecrating various offerings to the gods, ancient humans tried to avert adverse fates and ensure long, healthy lives and a safe future. (1) Thus, the

Mesopotamian people aimed to control their destinies and *nam*,[1] and determine their fates. For Mesopotamians, divination and extispicy were essential for providing information about the unknown, warning about the future, and discovering the causes of disasters and illnesses. (2) Deities held the supreme power to send diseases, and all the catastrophes humans experienced were due to deities' anger and displeasure, the breaking of taboos, and the committing of sins. Moreover, diseases were explained as punishments for sins against the gods, such as neglecting them or provoking their wrath. (3) In the Mesopotamian cuneiform tablets, diseases are often recorded as caused by gods or by "the power of evil spirits" (*miqit temi*) that "take the soul prisoner" (***šane*** *ṭemi*)[2] or "influence the soul" (*Nakir temi*)[3]. (4) God-generated diseases came from "the hand of the deities" (miqit ***šame***), (4) "the hand of the goddess" (*kt Ištar*), or the hand of Sin (*kt Sin*). (3). Also, for these ancient people, evil demons, such as jinn and afreet, were powerful beings that brought disease and epidemics to torment those whom they wished to punish. This situation was depicted in the epic poem *Atra-hasis* (exceedingly wise) recorded in Akkadian in the eighteenth century BC. In this epic, the deities became angry with humans and intended to decimate their populations by sending demons to inflict epidemics. (3) The epic mentions that the deities first sent a plague to the people through afreet, followed by famine, drought, and finally, massive floods. The name *Atra-hasis* is given in the Epic of Gilgamesh as *Utnapishtim*, and the story of Atrahasis which is recorded in various versions resembles accounts of the flood in the Epic of *Gilgamesh*. (5) This epic, which was transferred to the Hittites through the Hurrians, was referred to as *Atra(m)haši* by the Hittites. (5)

In Mesopotamian health practices, although medical methods (such as surgical practices and herbal treatments) were not ignored, (6) the outcomes of diseases largely depended on the will of supernatural powers and the influence

1 In Sumerian, the word *nam* means fate, and fate-misfortune is expressed as *nam-nu-tar*. In Mesopotamian belief, a demon named *Namtar* was responsible for all kinds of diseases, death, and fate, especially plague. For the use of the word *nam*, see Halloran (2006: 35, 124–125), and for *namtar* in the Mesopotamian belief system, see Black JA, Green A, Rickards T. Mezopotamya mitolojisi sözlüğü: Tanrılar, ifritler, semboller. İstanbul: AramYayıncılık; 2003.

2 *Šane ṭemi*/*Šinit temi* means a rapid change in mood and sudden deterioration of the mind. For the meaning and use of words, see 7. Oppenheim AL, Reiner E. The Assyrian dictionary of the Oriental Institute of the University of Chicago. Vol. 17. "Š" Part III. Chicago: The Oriental Institute; 2008).

3 The word *Nakir* means stranger, outsider, or enemy and has been used in such forms as *nakaru, nakru*, and *nakiru* (see 7. Ibid.)

of deities, spirits, afreet, and jinn. Based on the principle of "if I give, you also give," certain magical rites, such as offering regular gifts and sacrifices to the supreme powers, were deemed to bring relief, and people often resorted to extispicy and divination methods. Such efforts were thought to be necessary for the continuing health of people and indispensable for diagnosing and treating diseases.

This study first addresses the relationship between diseases and divination in Mesopotamia and Anatolia and then focuses on extispicy and hepatoscopy as means to diagnose diseases. We conducted this research because extispicy and divination, which were indispensable for Mesopotamian medicine and formed the basis of secular medicine, are important in the history of medicine. In this study, we examined cuneiform tablet texts, ancient sources, valuable works by Bottero and Kramer (7, 8), and cuneiform texts held in the Metropolitan Museum in New York. We also considered Scurlock et al.'s book *Diagnoses in Assyrian and Babylonian Medicine (9)*, which was based on tablet translations.

2. The Relationship between Diseases and Divination

Medical practices in Mesopotamia began with the Sumerians and were continued by the Akkadians, Babylonians, and Assyrians. The accumulated experience and evolving methods formed the basis of Hittite medicine in Anatolia. (10) Diseases were mainly attributed to demons, evil spirits, and deities in Sumerian, Babylonian, Assyrian, and Hittite medicine, in line with the belief structure of the people of that period (i.e., the way they perceived and interpreted the world). The Mesopotamian pantheon, which influenced Hittite medicine and was based mainly on animistic and naturistic foundations, contained hundreds of deities and supernatural beings. (3) Among these, the deities Anu, Enlil, Ea, Sin, Šamaş, Ishtar, and Adad undertook specific tasks and had supreme power over health. In addition, the healing goddesses Gula, Marduk, and Ea were linked with divination, resurrection, and thunder. (8) (11) Among the demons, the following were primarily responsible for specific diseases: *Namtar* for throat-related diseases, fate, and death (associated with plague); *Asakku* for emaciation and tuberculosis; *Akhkazu* for lung-related diseases; *Alal* for chest ailments; *Gigim* for entrail problems; *Idpa* for malaria; *Labartu* for sexual diseases; *Ti'u* for headache; *Ummu* for fever; *Bennu* for epilepsy; and *Sidanu* for dizziness. The medical records of the period reveal which organs the afreet affected and how. For instance, "*Idpa* was effective for the head, *Namtar* for life, *Alal* for the chest, *Gigim* for the entrails, and *Telal* for the hands." (12) Entreating deities

with various rituals, wearing protective amulets, asking for forgiveness for sins, making sacrifices and atonement, (8) engaging in divination to discover the reasons for diseases, and magical rites were the primary treatment methods for diseases caused by demons and angry spirits. (3)

Among the ancient rites, records of the *Namburbi* and Šurpu rituals provide information about how religious healing/purifying ceremonies were performed. Jeremy Black derived information about magical Šurpu rites from tablet translations, which were valuable to our study. Black (13) stated that Šurpu rites were performed when the patient who needed help did not know which of his actions had angered the deities. He claimed that these rites could be performed when patients were anxious, restless, sleepless, suffering from delirium or headaches, or had tetanus and could not speak. In the rites:

> all possible 'sins' are exhaustively enumerated, including the effects of the 'oath' — either a broken oath returning in the form of a curse, or an oath sworn in good faith but arousing thereby magical powers which could be sources of evil. The 'burning' is a part of the ritual in which the patient peels an onion into the fire, strips date from a branch into the fire, or unravels matting into the fire, all the while reciting incantations in which the 'undoing' of his sins is compared to the activity he is performing. Finally, the magician extinguishes the fire and the sins. (13)

Apart from Šurpu and *Namburbi* (exorcism), prayer rites, in various forms, were practiced to reach deities through objects and by assigning meanings to the chosen. Rituals began with the patient being isolated and confined to a thatched hut or a drawn circle. Next, the patient was washed and shaved because purification and cleansing were essential for *Nanburbi* rites. During the ritual, tamarisk fronds were used to sprinkle holy water, and incense was used as a disinfectant. Later, the area would be swept and cleaned, and a goat would be sacrificed for penance, if necessary. (13) Objects of sacrifice could be animals, stones, or plants. Another way of practicing *Namburbi* rites was explained in a different tablet record, as follows:

> In the rite, the patient must take a goat or a chosen object to his bed at night. The next day, a pit is dug, and the patient is laid down in this pit along with his goat (or selected object). Later, the throat of the goat and the patient pretended to be cut. However, while a blunt knife is preferred for the patient, a sharp knife is preferred for

> the goat, by having its throat cut. The remarkable point here is that the selected object or goat used in the rite is put in the place of the patient by dressing it in the patient's clothes and lighting incense as atonement for the patient. It is for this reason that, after the death of the goat, mourning takes place, and it [the goat] is treated as a human being. Afterward, all the distress of the patient and the trouble that has happened to him are buried with the goat, or the selected object is thrown into the river. The patient is now free from disease and can continue to live. (7)

A similar practice was evident in the *Tarpalla* and *Nakuśśi* ceremonies of the Hittites, despite time and geographical differences. The common aspect of both rites was the use of living and inanimate objects to which disease and all evil elements were transmitted as surrogates and a means of communication with the gods. The intention was the same: to eliminate disease and a terrible fate by "destroying one of the chosen objects and releasing the other" through special rites. Thus, a terrible fate could be overcome, diseases would disappear, and purification would be provided. (14)

However, the people who conducted these ceremonies—the priests—were as important as the rituals for the people of the period. They organized the rites, fought the disease demons when necessary, and practiced medicine. Information on the subject, including archaeological data, medical prescriptions, and letters, can be found in tablet texts and extispicy and divination records, most of which are housed in the Library of Ashurbanipal. Dating back to the seventh century BC and located at Nineveh, the library originally contained copies of written sources from earlier periods. Source texts have also been found in Nippur, Sippar, Nimrud, and Sultantepe. In addition, numerous tablet texts were discovered in Hattusa, the capital of the Hittites near Bogazkoy (an inner region of Turkey), which complete the broken, lost, or unreadable Babylonian tablet texts. (15)

Sumerian *gig* and Akkadian *marāṣu, marṣu*, and *Salā'u* ideograms were used in the sense of "sickness" and "being sick." The most common ideograms were *marāṣu* and *murşu*. (16) Priests conducted the medical practices of the period, organized rituals when necessary, and played an active role in the medical diagnosis and treatment of diseases. (11) In Mesopotamia, there were three such occupational groups—"priest-physician," "sorcerer-physician," and "interpreter-priest"—who were responsible for health practices, divination, and sorcery and were referred to in the records as *Asû* (17), *Ašipu* (18), and *Barû* (17),

respectively. Physicians in the *Asû* ("someone who knows water") class applied natural treatment methods, such as plant-based drugs, mineral concoctions, and animals. The *Ašu* were the physicians of the period, practicing the art of healing and using the scientific approaches of the time. (11) The *Mašmaššu*(*m*) or *Ašipu*, who worked with the *Ašu*, served as "exorcists of evil" and played a significant role in fighting diseases, organizing rites, and undertaking the tasks of "priest-sorcerers" by extracting jinn, performing exorcisms, and conducting purification. (13) The *Ašipu*, who were the temple staff and focused on the magical and religious components of the medicine, possessed a higher social status than the *Ašu*. Their responsibilities were cleaning and purifying houses, temples, and other official institutions linked with their profession. Apart from the *Asû* and *Ašipu*, another group of officials named *Bwas*were specialist physicians. They were usually officials who interpreted dreams, practiced divination, and prophesied by examining the entrails of sacrificial animals. (13) Some tablet texts record that the *Asû* who used the primitive medical treatments of the period resorted, from time to time, to olive oil haruspicy and used magical and divination methods to fight diseases. The preceding information is referred to in many letters and prescriptions of the period concerning *Ašipu* and *Barû*.

3. Divination Records and Hepatoscopy: "Extispicy–Haruspicy"

Based on the tablet texts that have survived to this day, most divination methods were based on empirical forms of divination and extispicy. As a result of detailed observations and examinations over an extended period, data were obtained, developed, and copied repeatedly by the priests and their students, eventually forming a "manual" for reference and educational purposes. (8) The methods of divination were quite varied, including communicating with the dead through dreams (*necromancy*), interpreting the shapes of oil spills on water (*lecanomancy*), considering the directions and shapes of arrows thrown on the floor (*belomancy*), observing stars and celestial bodies (*astrology*), birth defects and signs, and animal behaviors. (3) Visions were also induced through different methods, as follows: İškar *Bārûtu* (interpreting sacrificial animals' entrails), (19) *Šumma izbu* (abnormal births), *Alamdimmû* (face reading/ interpreting), *Enūma Anu Enlil* (sky-related), *Šumma ālu* (earth-related), *and* İškār *Zaqīqu* (dreams). (20) The practitioners of these methods were primarily *Barû* and *Ašipû*, who were referred to as šu-maš-gíd-gíd in Sumerian and *bārū* in Akkadian, respectively. (21) The priest-physicians deciphered all the obscure signs of the deities on earth, provided information to people about their futures,

and helped people overcome diseases and disasters by performing special rituals, such as the *namburbû* ceremonies. (13) Those who practiced divination became institutionalized over time, formed a distinct professional class, and continued their profession under different names in various periods and regions.

When considering the content of the divinations, most of which come from the Esarhaddon and Ashurbanipal Libraries, (22) they were sorted according to the titles of *Enūma Anu Enlil*, *Šumma izbu*, *Šumma ālu*, *İškār Zaqīqu, Alamdimmû* and studied in a detailed manner, separately. Sentences are described as "main" and "sub" sentences in a structured linguistic pattern. Accordingly, in each record, the first sentence (i.e., the main sentence) indicates a ***šumma*** (if) assumption, and the second sentence (i.e., the sub-sentence) provides a "judgment." (7) According to this structure, this paper now considers some of the tablet texts relating to diseases.

3.1. Šumma Izbu Records

The *Izbu* series, which contains 24 tablets and hundreds of divinations, considers all the abnormal births, disabilities, and imperfections of humans and animals. In these records, the divinations are categorized according to their content: 1) birth defects resembling animal characteristics, 2) babies with missing limbs, 3) babies with deformed or missing body parts, 4) babies with misplaced body parts, and 5) babies with extra body parts. (22) Some of the divinations were as follows:

> [If] a woman gives birth and (the foetus) has two heads – there will be a fierce attack against the land and the king will give up his throne. For births with missing limbs: [if] a woman gives birth [and] (the foetus) has no eyes, no mouth, and no hands – the advisers of the land will leave it and the king will be killed in his own palace. [If] a woman gives birth and (the foetus) has the head of a wolf – there will be massacres in the land and [If] a woman gives birth and (the foetus) has two heads – there will be a fierce attack against the land and the king will give up his throne. (22) From another list: [If] a woman gives birth and (the newborn) has a wolf's head, there will be massacres in the lands of the kingdom. (23)

Similarly, some of the comments about animal births were as follows:

> [If] a sheep is born like a ram, its heart and organs are one, and it has two bodies up to its hips, chaos will prevail, (24) [if] a defective

> lamb has two eyes at the front of its head and two eyes in the back of its head, the kingdom will have a powerful reign, and [if] a ewe gives birth to a two-headed, eight-legged, one-vertebrated lamb, there will be civil war and turmoil in the country. (7)

As can be seen from these examples, all unusual defective births aroused fear and curiosity in the people of the period, and their concerns about the future played an active role in the development of divination methods, such as those found in the *izbu* records. Experiences and simple observations underpinned predictions of the future, and they found a place in the divination texts. (7) However, some generalizations and assumptions were made without an experiential foundation. According to the soothsayers of the period, if a woman (or animal) gave birth to twins or triplets, it was assumed that she (or it) could give birth to quadruplets, quintuplets, sextuplets, septuplets, or even octuplets. Hence, as seen in the preceding examples of birth defects, if a newborn had three eyes, it was assumed that another newborn could have four or five eyes. (7)

Although most of the predictions were based on magical and empirical foundations, were used to generalize, and contained impossible, extraordinary, and unscientific interpretations that related to supernatural forces, some records were updated by different civilizations over time and opened the way to discoveries with positive value. (7) The *Alandimmû*, another divination series, undoubtedly contributed to the progress of medicine and was effective in developing medical diagnostic and prediction texts known as *Sakikkû*.

3.2. Šumma Alu Corpus "Alamdimmû" Records

The physiological characteristics of the human body were prominent in these records. Dating back to the early Babylonian period, the *Alamdimmû* were first systematized and arranged in a series by *Esagil-kīn-apli*. According to the records, anatomical elements, such as abnormalities, disorders, moles, and spots (right/left/above/below), were evaluated separately according to gender, and the effect of all these characteristics on behavior and fate was considered great length. (2) Some of them are as follows:

> [If] (a black birthmark) is (above his) left (eyebrow): he will be contented [if] there is a *kittabru* (a kind of mole) fleck on his upper lip, be it inside, be it outside: god will provide him with plenty of food, [if] it (=*umsatu* fleck) is on the surface of his tongue on the right side: he will be overwhelmed by blasphemy (2), [if] a (man's)

> face is full of black spots (*ramitu*[4]), he will die, [if] a man's chest hair curls upward, he will be a slave, but [if] it curls downward, he will have losses, [if] a hair turns inward, (the man) will be gloomy and have losses, [if] he has *kittabru* spots on the side of his feet (spreading upward or downward), he will be successful wherever he goes. (7, 25)

Every factor concerning the human body from head to toe, including the reactions of the body and *sakikku*, which were considered in this series, influenced divination about the diagnosis and treatment of diseases.

4. Diagnosis and Prognosis of Diseases: Sakikkû/ SA.GIG "Symptoms"

The *Sakikkû* series, consisting of 40 tablets and considering the meaning of *signs/symptoms,* was organized by *Esagil-kīn-apli*, a scholar of the period, during the reign of Babylonian king *Adad-apla-iddina*. As *ištu muhhi adi šēpi,* the series includes texts about "head to toe" diseases. Furthermore, the texts organize diagnoses, prognoses, and therapeutics according to the subject. (2) Hence, these 40 tablet texts can be summarized as follows:

> (Tablets 1–2): all of the ominous occurrences that might take place as the *Ašipu* was on his way to the patient's house, (Tablets 3–14): began with headaches and progressed down the body in head-to-toe order, (Tablets 15–16): entries organized in accordance with the number of days the patient had been sick, (Tablet 17): phases of illness and times of day, (Tablets 18): a discussion of fevers and attendant signs and symptoms, (Tablets 19–21): divided off illnesses with fever from illnesses where the pulse rate was normal, (Tablets 22-23): infectious diseases, (Tablets 26–30): entries relating to neurology, an apparent subspecialty of the *Ašipu's* craft, (Tablet 31): enteric fever, (Tablet 32): skin lesions, (Tablets 36,37,40): women and infants. (9)

The *sakikku* texts, which contain more serious observations and diagnoses than other divination records and consider disease symptoms, such as "the color

4 *Ramitu* was often used as a term for a lesion resembling a sunspot. 26. Scurlock JA, Andersen BR. Diagnoses in Assyrian and Babylonian medicine: Ancient sources, translations, and modern medical analyses. Urbana: University of Illinois Press; 2005. xxiii, p. 879.

of the patient, his fever and pulse, smell, and discoloration of urine," reflect the ideas of modern medicine. Although the approach to diseases is still faith based, comments about specific symptoms of diseases and treatments are noteworthy for the period. (7) At this point in history, most of the assumptions underpinning the medical diagnosis and treatment texts are positive and based on observation. However, this positive attitude underpinning the assumptions does not apply to sub-sentences (i.e., judgments). Judgments were made according to the theological understanding of the period, and the causes and consequences of diseases were explained as being caused by supernatural beings. Consequently, diagnosis and treatment were conducted by the *Ašipu* of the period, and disease and treatment methods were mainly shaped by the theological world of the *Ašipu*, which included divination and magic.

In this context, the first two series of the collection of 40 tablets begin with the elements *Ašipu* might encounter when visiting patients and consider how illnesses should be diagnosed according to these elements. Thus, unusual omens relate to diseases, such as "[if] the *Ašipu* comes across a pink pig, the patient will get a blister" and "[if] he comes across a black pig, (the patient) will risk dying." (7)

However, diseases can be diagnosed by examining the patient from head to toe and paying attention to each part of the limbs. (7) In this context, many symptoms and variables related to the same issues are essential for medical diagnoses and predictions. For example, when a patient with a complaint is examined from head to toe, the elements to be considered are as follows:

> "[If] the (patient's) nose bleeds ...," "[if] water comes from the nose …," "[if] the tip of the nose is wet …," "[if] the tip of the nose is hot or cold …," "[if] the tip of the nose is yellow …," "[if] the tip of the nose has a red rash …," "[if] the tip of the nose has a white rash …," "[if] the tip of the nose has a red and white rash ...," "[if] the tip of the nose has a black rash ..." For the patient's mouth, "[if] the patient's mouth is red ...," "[if] the patient's mouth is black ..." For the color of the urine: "[if] the color of the urine is red...," "[if] he cannot urinate ..." (9)

For the diagnosis of a disease, coldness, hotness, wetness, dryness, and color differences in the nose and other limbs were significant for the prognosis. For each symptom, the cause and duration of the disease are given, along with assumptions about whether the person will live or die, as follows: "the work

of god, the work of demons, the work of ghosts, the effect of the curse, etc." Within this framework, the examples from medical diagnosis texts, including the *sakikku* texts, relate to supernatural forces that cause diseases and illnesses.

4.1. Supernatural Powers That Cause Disease

Godborne Diseases*:** "[If] a burning pain is firmly established in his abdomen on the right side and he drips blood, "hand" of Adad; he will die. (9) [If] If he was wounded on his abdomen or on the right side of his abdomen and he vomits blood (and he has been sick) for thirty-one days, "hand" of Nergal; he will die." (9) "[If] a baby stands up in his first, second, and third year but cannot stand in his fourth year, can eat bread but cannot talk because the jaw is locked, (this) is the work of ***Šulpaea [the weather god Adad], and [the baby] will not recover." For infants with such symptoms, the *ašipu* advised that they should be left to die or thrown into a river alive because a cure was impossible. This advice is quoted from Stol's tablet translation (26). In another tablet text, this advice also applies to an epileptic baby having a seizure: "If *Bellum*, the ifrit and lord of the roofs, influences the birth of the child, the child's father's house (family) will fall apart at the foot of his bed. So that his father's house does not fall apart, you must bury (the child) as if it were a stillborn child and wait; (thus) evil will disappear." Throwing a baby into a river or burying it alive reflects the exorcism rites of the *Nanburbi* rites mentioned previously. The *Ašipu*, helpless in the face of disease and interpreting diseases according to personal beliefs, found remedies in purification rituals. The text continues, "If the buried child begins to cry where he is buried, and his hard arms and legs relax and begin to move, then the evil has left the child." (26) Here, the fate of the buried child depends on his or her power of resistance underground, but sacrificing the child is recommended.

However, diseases other than epilepsy or seizures are considered caused by gods; hence, "[if] the patient screams 'my head, my head!' this is God's work." Here, which side of the head hurts is important: "[If] his "right" temple hurts him, "hand" of ***šamaš***. [(If) his] "left" [temple] hurts him, "hand" of *Ištar*. (This is because) the right side (of the face) is "hand" of *Ištar* (and) the left side (of the face) is "hand" of ***šamaš***. (9) The goddess *Ištar* is generally associated with urethritis, venereal diseases, and the disease of love; therefore, "[if] (a person) falls sick on the first day, puts his hand on his stomach, his hands and feet are cold, the person talks without knowing what they are saying, stands up and sits down, this is the hand of *Dilbat*," "the hand of *Ištar,"* and "(the person) will

die." "[If] a person feels a burning in the genitals and upper abdomen, a twinge in the liver, and pain in the arms, feet, and stomach, this person has a venereal disease, and this is the work (hand) of the goddess *Ištar*." (9) "[If] the person's body is covered with red skin bumps and their face is yellow, this is the work (hand) of the goddess *Ištar*, and (the patient) has a (venereal) disease." (11)

***Ghost-Borne Diseases*:** "[If] the patient continues to ask for more water but has a normal body temperature, tremors in the hands, the blood flows swiftly toward the hands, and the patient moans from the beginning of the night to midnight, this is the work of a ghost." "[If] both the hands and feet of the patient are shaking at the same time, and the whole body burns with fever, this is the work of a ghost." "[If] a ghost captures a person, the person gets a fever, the body temperature is either too hot or too cold, and this ghost-related terror continues day and night ..." (9).

***Demon-Based Diseases*:** Separate names were used for diseases according to letters in the texts. For example, since the epilepsy seizures mentioned under godborne diseases were believed to be delivered by demons, some diseases, including epilepsy (*miktu*), were referred to by different names, such as *dimutu* and *di'u*. The word *di'u* was also used for malaria, which was attributed to heat stroke in other medical diagnostic texts. According to the narrative, *dimutu* or *dimmu* "comes out of hell ... and the "demons" haunting this patient wrap him with this disease because he [or she] insulted the protective god and the god abandoned them!" (25) Some depictions of demon-related diseases are as follows: "[If] (the person's) body becomes inflamed because of disease, the arms and legs weaken, ... the mouth becomes full of saliva, the person experiences a fit of coughing, becomes speechless, and is exhausted ..." (11) In another text, a disease is described with different symptoms:

> The curse falls upon men like an evil devil. The screaming voice is his. The bad voice is his. The curse is the cause of the disease. The curse strangles the man like a lamb. The evil devil enters his torso and makes him bleed. The voice of the female devil, who causes trouble, is like that of a hyena. She takes over management and command. (12)

The methods for combatting all diseases considered demonic or god- or spirit-based are prayers, rites, and the wearing of *pazuzu* amulets.

However, hundreds of divinations appear in the 40 tablets, several of which have already been discussed. In general, symptoms of the respiratory

tract, gallbladder, urinary tract, reproductive organs, anus, arms, and legs may be considered one by one in different scenarios.

The divination records, including the medical diagnosis texts discussed in this paper, are just a few of the thousands of tablet texts. Undoubtedly, these divination lists are significant in highlighting the medical practices of the period, and they certainly had a great influence on the lives of the people of the period. Thus, stars, meteors, time, the calendar, environmental factors, rivers, settlements, the characteristics of plants, births, the behavior of animals, and particularly the physical appearance and behavior of humans and the choices they made in their dreams were the subjects of divination in a world where every sign was perceived as an omen. This also encouraged humans to examine and observe the world in which they lived, the body's anatomical structures, and their functioning. The tablets, which were developed and copied repeatedly for hundreds of years, constituted a manual used by the health experts of the period, but they moved beyond Mesopotamia, blended with different cultures, evolved, and were incorporated into those different cultures' health practices.

Haruspicy was another method developed in parallel with divination to answer all questions regarding everything, from diseases to politics. Haruspicy was crucial for the people of the period. It involved examining animals' entrails, water, bones, and stones. (27) Among the types of haruspicy, extispicy (*hepatoscopy*) was the main divination method applied in health contexts. It is thought that extispicy was first systematized and developed in Mesopotamia, especially in the Sumerian, Akkadian, Third Ur Dynasty, Babylonian, Assyrian, and Elamite cultures. Over time, "extispicy" became an indispensable method for treating diseases and resolving administrative issues in different geographies and languages (Syrian, Iranian, Anatolian, Greek, Etruscan, and Roman) adapted to their own sociocultural and belief structures. (19)

5. Extispicy (hepatoscopy)

Extispicy, used for diagnosing diseases in Mesopotamia, was seen as a complementary method in the medical practices of the period. (11) Haruspicy was one of the main methods used to clarify deities' demands or opinions on any issue. Performed in sacrificial rites from Mesopotamia to the Roman Empire, haruspicy was first practiced in Mesopotamia and spread to the Ancient Near East and the Mediterranean Sea. (19)

In Mesopotamia, people believed that blood was essential for life. Since the liver contains more blood than the other organs, it was seen as the most

critical organ in the body, the center of emotions and excitement, and the soul's residence. (28) In Mesopotamia, people believed that natural events were omens delivered by unknown superpowers. The people of the period saw the liver itself as an omen, believing that they could learn the opinions and behaviors of deities and supreme powers, the correctness of their own actions, and the courses of diseases through animal livers. (29) In this context, a divination system was developed based on sacrificing lambs and sheep and examining their livers (29). For these extispicies, opinions about the disease were sought in traces on the liver, including the sacrificial animal's entrails, using various models (see Figures 1–2). (29) On clay models, most of which were made of clay and terracotta and used by the *Baru*, notes were engraved to guide the interpreter-priest. Accordingly, models, other visual finds, ancient texts, and recorded reports provide enlightening information about extispicy (Figures 3–4). In particular, the British Museum Ashurbanipal Library Project conducted by Finck (30) obtained detailed information about guiding formulae and diviners from studies of tablet texts discovered in the Ashurbanipal Library. It is known that Babylonian diviners obtained data from the livers of sheep, which were examined through extispicy procedures under the title of "divination questions" or "questions for the sun god." During the Assyrian period, the title used was "extispicy reports." The characteristic (pillow) shape of the reports is distinctive in form and is generally addressed to the great sun god šamaš. Within this framework, the divination process started with the supplication "Šamaš, great lord, give me a firm positive answer to what I am asking you" Answers were then received via the diviner who examined the liver. (30)

In this context, all written and visual data shed light on how the divination practices of the period were conducted. Haruspicy was performed in a separate ritual: "In rites performed at different times of the day, a fire is burned in front of the God's statue by the priests. On the table behind the fire are four pots containing sesame wine, bread, honey, cream, and salt. After making the fire, the *Baru* sacrifices the sheep at a ceremony. Later, he takes out the sacrificial liver and compares it with the clay model." (28) A diviner diagnosed the disease and gave information about it after detailed examinations of the size, color, and various parts[5] of the liver, the changes on its surface, and the folds within it. (29)

5 The "caudate lobe" was designated and used as a finger (*Akk, Ubanu*) for parts of the liver in the haruspicy records. For explanation and prediction, the soothsayers evaluated the "finger" as a solid triangle with three surfaces. They mostly interpreted the signs by defining the right, middle, and left surfaces of the "caudate lobe," which they called the

Any lesions, changes in the liver, or holes made by liver worms were interpreted as good or bad omens. If the divination had an evil purpose, counterrites were organized, and appropriate remedies were recommended. (31) However, an animal's liver was only one of many organs used for extispicy. The lungs, colon, heart, spine, and sternum could also be studied by a diviner as a means of divination. The gallbladder was perceived as part of the liver. (31) For example, some of the omens regarding the gallbladder and liver were as follows:

> [If] the gallbladder is covered with meat, the ruler of the country will die, [if] there is an abnormality on the right side of the middle part of the gallbladder, the middle part of the country will fall into chaos and the people will scatter, [if] there are three kidneys and three holes (*pilšu*) on the right side of the gallbladder and the liver has two gates, there will be chaos in the city... This chaos in the divination changes into the withdrawal of the army, severe snow, dissolution of the family, and a child's death according to the period and person. (7)

However, extispicy and haruspicy were alternative methods that were applied in different geographies and cultures, such as the Etruscan, Greek, Roman, Anatolian, Syrian, and Iranian cultures, and developed according to their languages and beliefs. (32) In particular, the divination and extispicy records and liver models (Figures 5 and 6) of the Hittites, an Anatolian kingdom influenced greatly by Mesopotamian culture, are significant in terms of the spread and continuity of extispicy. Records show that extispicy, expressed as *kuš* in the Hittite language, was mainly used to prevent disasters, such as diseases and epidemics. The relationship between diseases and deities and the importance of extispicy in communicating with deities show its significance. Some examples are as follows: A woman questioning the misfortunes that occur at a birth through haruspicy[6], the third Hattušili resorting to haruspicy to discover which physician and drug could treat his eye disease, the second Murshili writing the plague texts, and the Hittite prince Kantuzili attempting to learn his fault (33). The prayer text of Kantuzili:

"finger" (see. 31. Spar I, Lambert WG. Cuneiform Texts in the Metropolitan Museum of Art II: Literary and Scholastic Texts of the First Millennium BC: Brepols; 2005. p.173)

6 The tablet text including the Hittite Papanikri Ritual, performed to ward against misfortunes occurring at birth, mentioned that haruspicy was practiced to discover the reasons behind misfortunes. Tablet text: KBo V 1 D.y. I (CTH 476)

> But (now) may God come from the depths of his heart and open his will and consent. May he grant (explain to) me my fault, that I may accept my fault. May God speak to me in my dream, may God open his will to me, may he introduce my mistake to me, so that I know. Or let the soothsayer speak to me, (or) let the diviner call out to me (by reading) the liver. (10)

The role of the Hittites is exemplary in terms of the continuity of fortunes, and some believe that the Etruscans absorbed this extispicy technique into their culture from the Hittites (Figure 7). (10) Another view is that the technique was transferred to Greek culture from Egypt, Phoenicia, and Rome. Although the extispicy in these cultures differed little in form and method, there is no significant alteration (Figure 8). Apart from sheep, lambs, goats, oxen, wild geese, chickens, dogs, horses, and frogs were also used for extispicy in Ancient Greece and Rome with the same aim. (32) Extispicy was performed for hundreds of years to deal with many issues, including diseases; political, administrative, and military decisions; and everyday desires. In this regard, the Roman philosopher Cicero (106–43 BC) stated, *extis enim omnes Fere utuntur* (no society or king on earth does not use divination), summarizing his view of haruspicy and its importance. (32)

6. Conclusion

Although divination and extispicy differed in temporal and spatial contexts in different periods and cultures, the practices reflected the meanings that society/culture attributed to matter and mystery according to its needs. Unlike modern humans, for the first humans, the earth around them existed for an eternity that they could not understand. The sunrise and sunset, the darkness at night, the many events that occurred, the weather, the changes in their bodies, and the reactions of those bodies were difficult to understand. These inexplicable happenings frightened them. To allay these fears and concerns, they first created totems, portraying the supreme power in *zoomorphic* (animal) forms that eventually evolved into *anthropomorphic* (human) forms, aiming to keep the power they attributed to deities benign. In their rituals and ceremonies, the people of the period presented sacrifices and offerings to deities with humanlike qualities and aimed to please and serve them to gain their favor. The deities with which an individual established intimacy could ensure a peaceful and prosperous life, protection from disease and evil, a healthy future, and provide warning of and

assistance with future events. For thousands of years, people tried to eliminate misfortune by using advanced divination methods, which were seen as cures for people's fears, worries, and concerns about living healthy lives.

FIGURE CAPTIONS

Figure 1

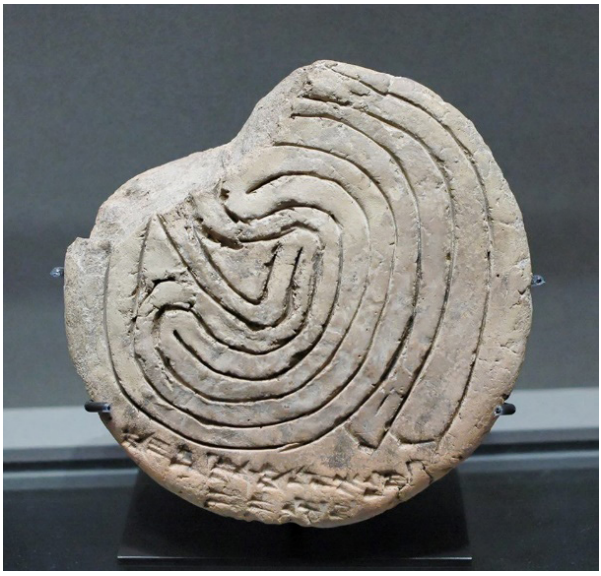
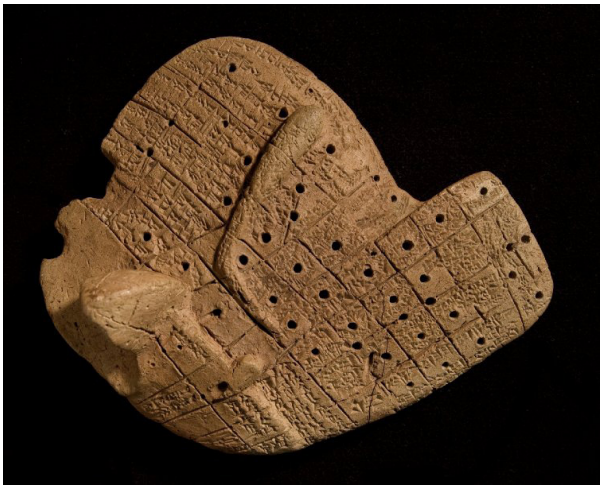


Figure 1: Animal Gut Model Containing Gunpowder Divination Instruction

Louvre Museum, Env. No: AO6033
It is written on: "Left and Right, Meets at the top right and ends here."
2nd millennium BC
Photo: Marie-Lan Nguyen

Figure 2



Front

Back

Figure 2 (Front): Liver Model

British Museum, Env no: ME92668
Babylonian Period, 1990-1600 BC
Mari/Sippar, Southern Iraq

Figure 3

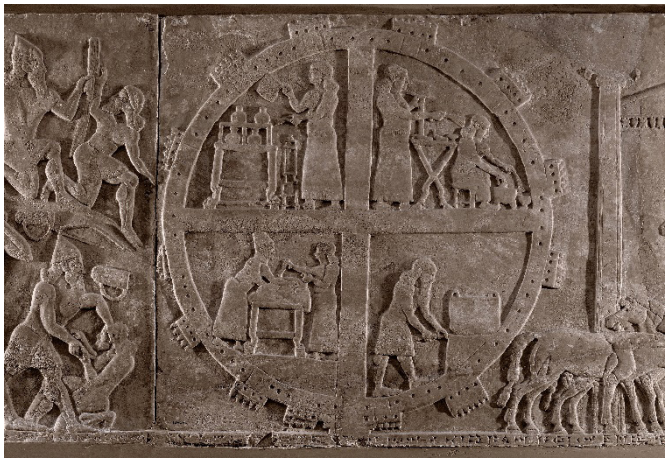


Figure 3: The Scene of Divination by Examining the Sacrificial's Entrails

British Museum, Env. NO: COA0129638II.
Kalhu (Nimrud) 9th century BC. The relief is located to the northwest of the Ashurnasirpal Palace, (The scene of removing the liver of the animal sacrificed by Baru is seen in the lower left corner of the slab).

Figure 4

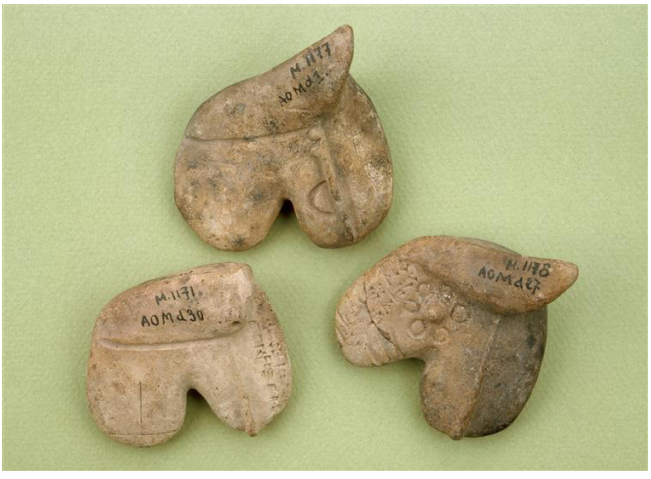


Figure 4: Liver Model

Louvre Museum. Env. NO: AO19830, AO19833, AO19832
Neo-Sumerian Period, 2150, 2000 BC
Mari
Photo: Chritian Jean

Figure 5

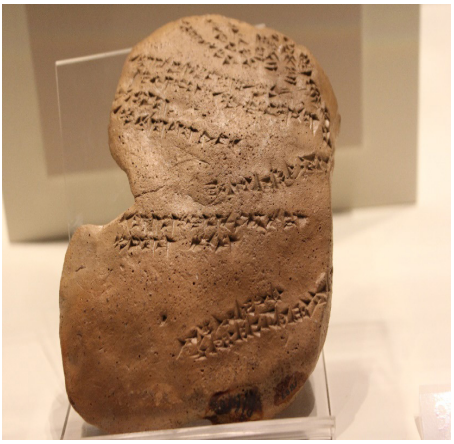


Figure 5: Liver Model Made of Clay Belonging to the Hittites,

Ankara Museum of Civilizations Photo: Tuğba Gençer

Figure 6

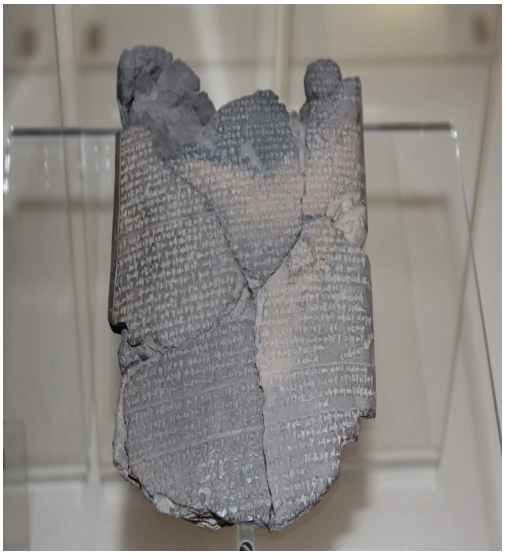


Figure 6: Clay Tablet; II. Mursili's Plague Prayer

Istanbul Archaeological Museum, Env. NO: 2803 ÇBA (KUB XIV 8)
Bogazkoy, Hattusa, the Hittite Imperial Period,
4th century BC, second half (13th century BC Copy), Hittite
Photo: Tuğba Gençer

Figure 7

Figure 7: Bronze Mirror;

Scene of Extispicy by Examining the Liver of Animals Sacrificed by *Haruspex*, Late 5th century BC. Vatican Museum, Cat NO: 12240
Vulci - Painting: It is used from the museum's own catalogue.

Figure 8

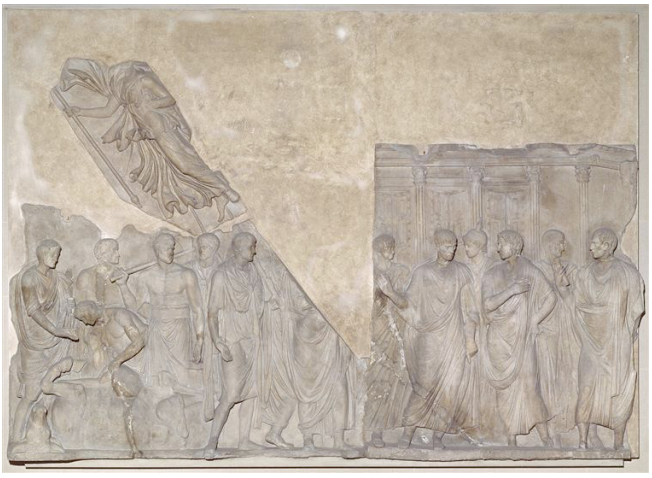


Figure 8: Wall Relief from Trajan's Forum;

Haruspex (Diviner) Maintenance Scene Roman Imperial Period, 2nd-century
LOUVRE Museum, Env. No: MA978,
Photo: Tuğba Gençer

References

1. Florioti HD. Eski Mezopotamya'da Kehanet Olgusuna Genel Bir Bakış. Tarih Okulu Dergisi. 2013(XV):23-42.

2. Böck B. Physiognomy in ancient Mesopotamia and beyond: from practice to handbook. In: Annus A, editor. Divination and Interpretation of Signs in the Ancient World: The Oriental Institute of the University of Chicago; 2010. p. 200-4.

3. Demirci K. Eski Mezopotamya Dinlerine Giriş: Tanrılar, Ritüel, Tapınak. İstanbul: Ayışığı Kitapları; 2013.

4. Oppenheim AL, Reiner E. The Assyrian dictionary of the Oriental Institute of the University of Chicago. Vol. 10. "M" Part II. Chicago: The Oriental Institute; 2004.

5. Kıymet K. Hititler'de Bir Tufan Öyküsü: Atra(M)Haši. The Journal of Academic Social Science Studies. 2013;6(2).

6. Donbaz V. Mezopotamya ve Anadolu'da Eski Tıp. III Türk Tıp Tarihi Kongresi 20-23 Eylül 1993. 1999:319-36.

7. Bottero J. Mezopotamya: Yazı, Akıl ve Tanrılar. Ankara: Dost Kitabevi Yayınları; 2012.

8. Kramer SN. Sümerler. İstanbul: Kabalcı Yayınevi. 2002.

9. Scurlock JA, Andersen BR. Diagnoses in Assyrian and Babylonian medicine: ancient sources, translations, and modern medical analyses. Urbana: University of Illinois Press; 2005. xxiii, 879 p. p.

10. Orhun M. Hititler'de karaciğer falı, kuş uçuşu falı ve bunların etrüskler'deki uzantısı. Gazi Akademik Bakış. 2009;3(5):231-50.

11. Bottero J. Eski Yakındoğu-Sümer'den Kutsal Kitap'a. Ankara: Dost Yayınları; 2005.

12. Uncu M. Eski Mezopotamya'da Tıp. History Studies International Journal Of History. 2013;5(5):110.

13. Black JA, Green A, Rickards T, British Museum. Gods, demons, and symbols of ancient Mesopotamia: an illustrated dictionary. London: Published by British Museum Press for the Trustees of the British Museum; 1992. 192 p. p.

14. Erbaşı FS. Hititlerde öteki kurban ve büyü: cenaze/diğer ritüeller: Arkeoloji ve Sanat Yayınları; 2013.

15. Biggs RD, Sasson JM, Baines J. Medicine, surgery, and public health in ancient Mesopotamia. Civilizations of the ancient Near East; 3. 1995;3:1911-24.

16. Stol M. " To be ill" in Akkadian: The Verb Salā'u and the Substantive Sili'tu. Advances in Mesopotamian Medicine from Hammurabi to Hippocrates: Brill; 2010. p. 29-46.

17. Reiner E, Biggs RD. The Assyrian dictionary of the Oriental Institute of the University of Chicago. Vol. 2. “B”. Chicago1998.

18. Oppenheim AL, Reiner E. The Assyrian dictionary of the Oriental Institute of the University of Chicago. Vol. 1. part II. Chicago: The Oriental Institute; 1968.

19. Maul SM. Divination Culture and the Handling of the Future. The Babylonian World2007. p. 361-72.

20. Rochberg F. The Heavenly Writing: Divination, Horoscopy, and Astronomy in Mesopotamian Culture. Cambridge: Cambridge University Press; 2004.

21. Halloran JA. Sumerian lexicon: Logogram publishing Los Angeles; 2006.

22. Zorzi ND. The Omen Series Šumma Izbu: Internal Structure and Hermeneutic Strategies. KASKAL-Rivista di storia, ambienti e culture del Vicino Oriente Antico. 2011(8):43-75.

23. Jacobs J. Traces of the omen series Åumma izbu in cicero, De Divinatione. In: Annus A, editor. Divination and Interpretation of Signs in the Ancient World: The Oriental Institute of the University of Chicago; 2010. p. 317-39.

24. Heimpel W. Letters to the king of Mari : a new translation, with historical introduction, notes, and commentary. Winona Lake, Ind.: Eisenbrauns; 2003. xxv, 657 p. p.

25. Oppenheim AL, Reiner E. The Assyrian dictionary of the Oriental Institute of the University of Chicago. Vol. 17. “Š” Part III. Chicago: The Oriental Institute; 2008.

26. Stol M. Epilepsy in Babylonia (Cuneiform Monographs, 2): Brill; 1993.

27. Richardson SF. On seeing and Believing: Liver Divination and the Era of Warring states (II). In: Annus A, editor. Divination and Interpretation of Signs in the Ancient World: The Oriental Institute of the University of Chicago; 2010.

28. Bayat AH. Tıp Tarihi. İstanbul: Merkez Efendi Geleneksel Tıp Derneği; 2010.

29. Rutz MT, Kersel M. Archaeologies of text: archaeology, technology, and ethics: Oxbow Books; 2014.

30. Fincke JC. The Babylonian Texts of Nineveh: Report on the British Museum’s “Ashurbanipal Library Project”. Archiv für Orientforschung. 2003:111-49.

31. Spar I, Lambert WG. Cuneiform Texts in the Metropolitan Museum of Art II: Literary and Scholastic Texts of the First Millennium BC: Brepols; 2005.

32. Collins D. Mapping the entrails: The practice of Greek hepatoscopy. American Journal of Philology. 2008:319-45.

33. Ünal A. Hitit Tıbbının Ana Hatları. Belleten. 1980;44(175):475-96.