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İÇİNDEKİLER

BÖLÜM 1

THE ANNUAL CHANGES IN OCCUPATIONAL DISEASES IN THE MANUFACTURING OF CHEMICALS AND CHEMICAL PRODUCTS IN TURKEY

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INTRODUCTION

Chemical industry is an essential sector that contributes significantly to the economy of many countries. However, it is also a sector that poses significant risks to workers' health and safety due to exposure to hazardous chemicals and other occupational hazards. The chemical industry is a sector that involves the production, handling, and use of chemicals, which can pose significant risks to workers' health and safety. Work accidents and occupational diseases are common in this industry due to the presence of various risk factors. Occupational diseases and work accidents are common in the chemical industry, and their relationships have been the subject of scientific research for many years.

Chemicals are essential substances used in all areas of life. The use of chemicals improves the quality of life, but without proper regulation and effective recycling processes, it can have serious harmful consequences for the environment and organisms. Controlling and managing the use of chemicals, complying with legislation, taking environmental protection measures and managing waste are extremely important for living organisms and the environment (Baydemir, 2020; Ayık, 2023).

Considering the joint definition of Occupational Safety and Health (OSH) by the World Health Organization (WHO) and the International Labour Organization (ILO), it can be stated that it is a set of practices aimed at protecting and improving the physical, mental and social well-being of workers in all occupations at the highest level; at preventing workers from suffering damage to their health as a result of working conditions; at protecting workers from risks arising from factors at the workplace that are detrimental to health; at ensuring that workers work in a job that is appropriate to their physical and mental capabilities; and, in summary, at adapting work to people and adapting each person to his or her work (WHO, 2005). OSH practices are an important building block of working life and it is important to establish and continuously improve OSH policies to cover all employees in national and international areas (ÇASGEM, 2018). In order to ensure this harmony and the necessary legal basis, the Occupational Health and Safety Law No. 6331 came into force in Turkey in 2012 (Occupational Health and Safety Law, 2012).

According to the WHO, workers account for half of the global population and play an important role in economic and social growth. Their health is influenced not just by workplace dangers, but also by societal and individual variables, as well as access to health care (WHO, 2007). On average, economically engaged persons devote one-third of their daily life to work. Employment and working circumstances have a significant influence on healthcare equality. Good working circumstances may give

social security and prestige, as well as possibilities for personal growth and protection from physical and emotional risks. They can also boost workers' self-esteem and enhance their health (WHO, 2017).

Workers' health is critical to household income, productivity, and economic growth. Improving and sustaining functioning capacity is thus an essential role of health care. Heat, noise, dust, dangerous chemicals, unsafe machinery, and psychological stress all have the potential to induce occupational illnesses and exacerbate pre-existing health issues. Working circumstances, occupation, and position in the working hierarchy all influence health. People who work under stressful or unstable situations are more likely to smoke, exercise less, and consume an unhealthy diet (WHO, 2017).

Workplace risk factors can be analysed in five groups: biological (bacteria, viruses, etc.), physical (noise, vibrations, etc.), chemical (solvents, mines, etc.), psychosocial (stress, harassment, etc.) and ergonomic (poor posture, working hours, etc.). Solvents such as mercury and ammonia, metals such as arsenic, chromium and nickel, non-metals such as phosphorus, and gases such as carbon dioxide, hydrogen sulphide, formaldehyde and nitric oxide are chemical risk factors (Tavman, 2016). If the necessary precautions are not taken, they can negatively affect the health of employees and cause a number of situations such as suffocation, irritation, burning, fire, explosion, poisoning and cancer (Yakut, 2019).

OSH is a multidisciplinary field that involves many disciplines, such as medicine, economics, law, chemistry, technology, biology and physics. One of the main reasons for the occurrence of occupational accidents and diseases is the deficiencies in this field (Duran, 2022). Considering the high number of occupational accidents and occupational diseases, this situation is a major problem not only in human terms but also in economic terms (Kılkış & Demir, 2012). Effective practices can be implemented to prevent occupational diseases and accidents. For example, many hazards and risks can be prevented by practices such as encapsulation of pollution sources, ventilation, noise control, substitution of hazardous chemicals, improvement of devices, equipment and work organisation. The role of the OSH professional is to assess these risks and make recommendations for the prevention of occupational accidents and occupational and work-related diseases (WHO, 2017).

The aim of this study is to analyse the annual changes in occupational diseases in the chemical and chemical products manufacturing sector.

OCCUPATIONAL DISEASES

Occupational disease is caused solely by the nature of work or the working circumstances. In other words, it is a disease that results from the employee's labor, and different occupational diseases develop depending on the person's job (Spurgeon et al, 1997; İlhan et al, 2006; Koçali; 2023). The ILO defines occupational disease as a disease that occurs as a result of exposure to risk factors arising from work activities (ILO, 1996). It is also defined in the Occupational Health and Safety Act No. 6331 as "a disease resulting from exposure to occupational risks" (Occupational Health and Safety Act, 2012).

The main characteristic of occupational diseases is that they can be prevented through risk analysis and proper implementation of inspection and control, if the necessary precautions are taken. The methods of preventing occupational diseases are source-oriented methods, worker-oriented methods and medical protection methods (Ayık, 2023). Occupational diseases that are accepted as forensic cases are temporary or permanent illnesses and physical and mental damages that occur due to this work while the employee is performing the work assigned by the employer (Ilıman, 2015). According to the World Health Organization (WHO), around 11 million cases of occupational diseases are reported worldwide each year, with approximately 700,000 of them resulting in fatalities (Soyaslan Banbal, 2019).

In Turkey, the classification, list and liability periods for occupational diseases are specified in the Regulation on Health Procedures of the Social Insurance Law (Table 1) (Social Insurance Health Procedures Regulation, 1972). Occupational diseases caused by chemical risk factors are generally included in the group of occupational diseases caused by chemical substances (Group A). In Turkey, the number of insured persons with occupational diseases in 2022 is 955 and the number of insured persons who died as a result of occupational diseases is 8 (SGK, 2022).

Table 1. Classification of occupational diseases in Turkey

Groups	Name	Subgroups	Diseases
Group A	Occupational diseases caused by the chemicals	25	67
Group B	Occupational skin diseases	2	-
Group C	Pneumoconioses and other occupational respiratory tract diseases	6	9
Group D	Occupational infectious diseases	4	30
Group E	Occupational diseases caused by physical factors	7	12

DEFINITION AND SCOPE OF CHEMICALS AND CHEMICAL PRODUCTS MANUFACTURING INDUSTRY

The chemicals and chemical products industry, which plays an important role in the economy, supplies raw materials and intermediate products to almost all sectors of industry, as well as the final products it manufactures in many fields, from plastics to cosmetics, from pharmaceuticals to paints. Due to the broad scope of the sector, our report analyses "Chemicals and chemical products", one of the four sub-sectors of the chemical industry. The chemicals and chemical products manufacturing industry has almost 4,000 companies, more than 60,000 employees, exports of almost USD 6 billion and accounts for 4.5 per cent of total manufacturing value added. It makes a significant contribution to the economy (ICI, 2015).

The products manufactured by the chemical industry are very diverse and are used today in almost every sector as intermediate or final products. Chemicals with a wide range of products sector for almost all branches of industry production of raw materials and intermediate products and therefore both the chemical industry and the also contribute to the development of other industries are available. About 30 per cent of chemical industry products are consumed by final consumers, while about 70 per cent is used by other industries (ICI, 2015).

RISK AND RISK FACTORS

The working environment includes not only various safety hazards, but also health hazards. Knowing what these are and what to expect in which profession is very important in order to take precautions against occupational diseases and to be protected (Ayık, 2023). The possibility of loss, injury or other harmful consequences arising from the hazard is known as the risk (Occupational Health and Safety Law, 2012). The possibility of harm arising as a result of a hazard can also be expressed as hazard activation (Yakut, 2019). Hazard also includes risk. Hazard and risk situations also vary depending on the industry. One of the important steps in occupational safety and health practice is risk assessment (Yakut, 2019).

Workplace risk factors can be analysed in five groups: biological (bacteria, viruses, etc.), physical (noise, vibrations, etc.), chemical (solvents, mines, etc.), psychosocial (stress, harassment, etc.) and ergonomic (poor posture, working hours, etc.). Solvents such as mercury and ammonia, metals such as arsenic, chromium and nickel, non-metals such as phosphorus, and gases such as carbon dioxide, hydrogen sulphide, formaldehyde and nitric oxide are chemical risk factors (Tavman, 2016). If the necessary precautions are not taken, they can negatively affect the health of employees and cause a number of situations such as suffocation, irritation, burning,

fire, explosion, poisoning and cancer (Yakut, 2019). Psychosocial risk factors in the workplace include the work environment, working hours, compensation, coworkers, management, and their relationships. Stress can cause work discontent, burnout, weariness, and aggression. As motivation and focus decline, the probability of making mistakes and mishaps at work increases. Furthermore, many psychological diseases cause additional disorders in the body, resulting in exponential harm (Yakut, 2019). Ergonomics, or the science of work design, is the organization of the workplace around the needs of the workers. Ergonomic standards have an impact on employee health, safety, and performance. Ergonomic difficulties are a leading source of musculoskeletal illnesses (ÇASGEM, 2016; Yakut, 2019).

Chemical Risk Factors

A chemical is defined as any element, compound or mixture found in nature, produced during a process or as a waste product and used as an additive to improve the quality of a product (Yaylacı, 2010; Ayık, 2023). Chemicals are widely utilized both in business and in our daily lives. Chemicals are used to make a wide range of useful items, including plastics, paints, medications, and detergents. Some substances may look innocuous, yet they can cause damage upon contact. Long-term exposure and latent periods may lead to serious health consequences (Lim & Koh, 2014). The effects of hazardous chemicals can be acute or chronic. These effects range from eye infections to lung diseases. There are several ways in which chemicals can enter the human body, including through the skin, digestion and inhalation. Workers can be exposed to chemicals by any of these routes. Therefore, the risk of exposure to chemicals must be eliminated. Eliminating these risks requires replacing hazardous chemicals with non-hazardous or less hazardous chemicals, regular inspections and regular use of personal protective equipment (PPE) provided by the employer to the worker (Ayık, 2023). The employer is required to provide training to the employee to teach the correct use of personal protective equipment. Exposure to chemical risks should be minimised through training (Özdemir et al., 2020). Exposure to chemicals can be controlled through well-planned production processes (Baydemir, 2020).

In the Regulation on health and safety measures when working with chemical substances: “The purpose of the Regulation is to establish the minimum requirements to protect the health of workers from the hazards and harmful effects of chemical substances found, used or processed in any way in the workplace and to provide a safe working environment”. According to this regulation, employers are obliged to prevent workers from coming into contact with chemical substances when working with them, to minimise the risk of exposure if this is not possible, and to protect workers

against hazards (Kimyasal Maddelerle Çalişmalarda Sağlik ve Güvenlik Önlemleri Hakkinda Yönetmelik, 2013).

The chemical industry, which is not only production-oriented but also provides warehousing and logistics services, enables the manufacture of a wide variety of products using large facilities. Risks arising from flammability, corrosion, toxicity, explosion and chemical reactions can be cited as examples of the risks that occur in chemical processes, which present many risks (Tarım, 2017; Ayık, 2023). Temperature and pressure are also recognised as risk factors in chemical reactions. Flammable chemicals used in the chemical industry can explode and cause industrial accidents if the necessary precautions are not taken. In many chemical processes, metal and plastic dust can cause poisoning. Accordingly, inadequate ventilation, improper storage of hazardous gases, liquids or other substances, failure to prevent fires, failure to use appropriate PPE (gloves, boots, masks, helmets, goggles, overalls, earplugs, etc.) are among the main causes of accidents in the chemical industry (Korkmaz, 2011; Ayık, 2023).

In occupational health and safety, substances that pose chemical hazards are classified as solids, liquids, gases, vapours and dusts. Chemical hazards are among the factors that affect the health and safety of workers. The gaseous state of chemicals is one of the important factors that pose a threat to workers and the environment (Ersoy et al., 2022). In order to minimise the factors that can affect occupational health and safety in the use of all chemicals, chemicals should be stored and used in accordance with the safety data sheets (Ayık, 2023).

THE ANNUAL CHANGES OF DISEASES CAUSED BY CHEMICAL RISK FACTORS

Workers in the chemical industry are at risk of occupational diseases. Harmful chemicals that are inhaled, substances that come into contact with the skin and harmful conditions in the workplace can cause occupational diseases. Health problems such as lung diseases, skin diseases, poisoning and cancer caused by inhaled chemicals are among the most common occupational diseases. The implementation of occupational health and safety measures, regular health checks and the use of protective equipment play an important role in the prevention of occupational diseases.

Changes in the number of insured persons suffering from occupational diseases in the manufacture of chemicals and chemical products in Turkey over the last decade are shown in Figure 1 (SGK, 2022).

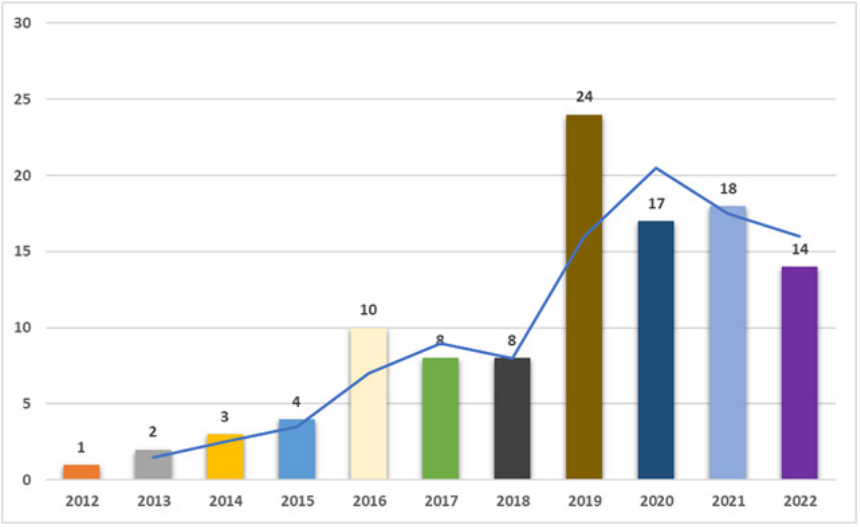

Figure 1. *The number of insured persons suffering from occupational diseases in the manufacture of chemicals and chemical products in Turkey (SGK, 2022).*

The number of insured persons with occupational diseases increases over the years. There is a significant increase in the number of insured persons from 2016 to 2019, with a peak of 24 persons in 2019. The number of insured persons seems to stabilise in 2020 and 2021 with 17 and 18 persons respectively. There is a slight decrease in the number of insured individuals in the year 2022, with 14 individuals.

The number of insured persons with occupational diseases increases steadily over the years, indicating a potential increase in occupational health risks. The peak in the number of insured persons in 2019 suggests a possible outbreak or increase in the prevalence of occupational diseases in that year. The stabilisation of the number of insured persons in 2020 and 2021 may indicate the success of prevention or control measures implemented in those years. The decrease in the number of insured persons in 2022 could be due to various factors, such as improved workplace safety measures or changes in occupational health policy.

The results from this table highlight the importance of monitoring and managing occupational health risks to protect workers from occupational diseases. The increase in the number of insured persons with occupational diseases over the years emphasises the need for effective prevention strategies and interventions at the workplace. The stability and decrease in the number of insured persons in certain years suggest that efforts to improve occupational health and safety measures can have a positive impact on reducing the incidence of occupational diseases.

CONCLUSION

In conclusion, the chemicals and chemical products industry poses enormous risks to workers' health and safety. Occupational disorders are widespread in this sector due to the existence of several risk factors. To avoid occupational disorders, it is critical to apply risk-control measures such as the usage of personal protective equipment and the deployment of engineering controls.

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BÖLÜM 2

THE INTERACTION OF LEPTIN, GHRELIN, AND NESFATIN-1 IN OBESITY AND WEIGHT CONTROL

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ABSTRACT

Obesity is a disease that occurs when fat accumulates as a result of overeating due to multifactorial causes such as genetic, environmental, biological, psychosocial and economic, and when the body mass index is greater than 30 kg/m². Obesity is an increased risk factor for various diseases such as diabetes, heart attack, high blood pressure, cancer and even premature death. There are hormones in our bodies that increase and decrease appetite, regulate food intake and control energy metabolism. Understanding the relationship between hormones, weight gain and hypothalamic function helps to understand obesity. Nesfatin-1, derived from NEFA/nucleobindin2 (NUKB2), is a recently discovered hormone that suppresses food intake via melanocortin in the hypothalamus. Leptin, ghrelin and nesfatin-1 play an important protective role against the development of obesity by regulating energy metabolism. The localisation of nesfatin-1 in the brain and peripheral tissues has advanced significantly in recent years. This study examines the hormone leptin, a protein synthesised in adipose tissue, which plays an important role among the appetite-suppressing hormones associated with obesity; nesfatin-1, a neurohormone expressed in the hypothalamus, adipose tissue, pancreas and brain; and the relationships with the appetite-stimulating peptide hormone 'ghrelin'.

Keywords: Body Mass Index, Ghrelin, Leptin, Obesity, Nesfatin-1

OBEZİTE VE KİLO KONTROLÜNDE LEPTİN, GHRELİN VE NESFATİN-1 ETKİLEŞİMİ

ÖZET

Obezite, genetik, çevresel, biyolojik, psikososyal ve ekonomik gibi çoklu faktörlü nedenlerden kaynaklanan aşırı yeme sonucu oluşan yağ birikimi ve vücut kitle indeksinin 30 kg/m²'nin üzerinde olması durumunda ortaya çıkan bir hastalıktır. Obezite, diyabet, kalp krizi, hipertansiyon, kanser ve hatta erken ölüm gibi çeşitli hastalıklar için artmış bir risk faktörüdür. Vücudumuzda, besin alımını düzenleyen ve enerji metabolizmasını kontrol eden iştahı artıran ve azaltan hormonlar bulunmaktadır. Hormonların kilo alımı ile hipotalamik fonksiyonlar arasındaki ilişkinin anlaşılması, obezitenin daha iyi anlaşılmasına katkı sağlar.

NEFA/nukleobindin2 (NUKB2) kökenli nesfatin-1, son zamanlarda keşfedilen bir hormondur ve hipotalamusta melanokortin aracılığıyla yemek alımını baskılar. Leptin, Ghrelin ve nesfatin-1, enerji metabolizmasını düzenleyici etkileri nedeniyle obezitenin gelişimine karşı önemli bir koruyucu rol oynamaktadırlar. Nesfatin-1'in beyinde ve periferik do-

kularda lokalizasyonu konusundaki bilgi, son yıllarda büyük ilerlemeler kaydetmiştir.

Bu çalışma, obezite ile ilişkili olan iştahı azaltıcı hormonlar arasında önemli bir rol oynayan leptin hormonu, adipoz dokudan sentezlenen bir protein; nesfatin-1, hipotalamus, yağ dokusu, pankreas ve beyinde ifade edilen bir nörohormon; ve aynı zamanda iştah artırıcı 'ghrelin' adlı peptit hormonunun ilişkilerini incelemiştir.

Anahtar Kelimeler: Obezite, Beden Kitle İndeksi, Leptin, Ghrelin, Nesfatin-1

INTRODUCTION

Over the past decade, obesity has become more prevalent in many developed countries. As a result, researchers are focusing more than ever before on understanding the molecular mechanisms underlying energy balance. The accumulation of excess body fat is a hallmark of obesity, a multifactorial disease. Using the body mass index, a person is classified as overweight if their weight is between 25 and 29.9 kg/m², obese if their weight is 30 kg/m² and morbidly obese if their weight is more than 30 kg/m². A sophisticated network of central and peripheral signals regulates appetite. Peripheral regulation includes things like fat signals and satiety, while central control involves a variety of systems including neuropeptinergic, monoaminergic and endocannabinoid systems. Satiety signals include peptide YY (PYY), glucagon-like peptide 1 (GLP-1) and cholecystokinin (CCK). When food is consumed, these signals originate in the gastrointestinal tract and proceed to the brainstem's nucleus tractus salitarius (NTS) via the vagus nerve. The arcuate nucleus (ARC) is reached by afferent fibers from the NTS project. Here, adipose signals (amylin, insulin, and leptin) and a variety of hypothalamic and suprahypothalamic signals are combined with satiety signals. The brain circuit then forms intricate connections as a result (Valassi et al. 2007). A wide range of endogenous mediators control hunger and metabolism, which in turn govern the short- and long-term energy balance. The pharmaceutical industry has focused on gut, pancreatic, and adipose neuropeptides as mediators in the development of drug therapies for obesity. The goal of these interventions is to either enhance anorexigenic and lipolytic signals or block orexigenic and lipogenic signals (Mendez MA., et al., 2005).

OBESITY-CAUSING FACTORS

Obesity appears to be related to biological, psychosocial, behavioral, genetic, socioeconomic, and cultural factors, though its precise cause is unknown (Mendez MA., et al., 2005). Overeating causes a person to gain

weight and develop adiposity, which is the storing of extra energy as fat. These two factors combine to cause obesity. Neurogenic disorders are primarily responsible for obesity. Studies have demonstrated that obesity in animals is brought on by overeating due to lesions in the ventromedial hypothalamic nuclei. A pituitary tumor that invades and destroys the hypothalamus can lead to obesity. Youngsters whose parents make them overeat exhibit higher levels of fat storage and newly formed fat cells. According to Skelton JA et al. (2011), children who are obese have three times more fat cells than children of normal weight.

Genetics is another factor that contributes to obesity. Genes, nutritional gateways, and metabolic pathways that control energy expenditure and fat storage are the main causes of obesity. Obesity is single-gene (monogenic) for three reasons. The last factors contributing to obesity are congenital leptin gene deficiency, MCR-4 mutation, and leptin receptor mutation in conjunction with environmental factors (Farooqi IS, et.al, 2004). Obesity has been linked to genetic disorders like Prader-Willi and Bardet-Biedl syndromes (Farooqi IS, et.al, 2004; Guyton AC, Hall JE, 2013).

THE ROLE OF THE HYPOTHALAMUS IN NUTRIENT INTAKE

The hypothalamus is the area of the central brain that receives signals from peripheral organs to control energy metabolism, eating behaviour and food intake (enjoyment, quality and taste). It keeps the body in balance by integrating central information to regulate energy balance. The regulation of energy metabolism is largely influenced by the lateral hypothalamic area (LHA), paraventricular area (PVH), ventromedial area (VMH), dorsomedial area (DMH), arcuate nucleus (ARC) and Hall JE (2013) of the hypothalamus. Neurons in the ventromedial and dorsomedial areas act as glucoreceptors, which are sensitive to changes in venous and arterial glucose, helping to regulate food intake. Food stimulates neurons in the ventromedial region, blocking α-adrenergic receptors and resulting in satiety when consumed. Excessive food cravings and insatiability brought on by a lesion in the ventromedial region lead to obesity. Neurons in the lateral region stimulate dopaminergic and β-adrenergic receptors, which results in hunger. Ventral and lateral neurons control the amount of food consumed and preserve equilibrium by mutually inhibiting one another (Ganong WF, 1995).

The two types of nerve cells that control appetite and energy expenditure in the arcuate nucleus of the hypothalamus are the proopiomelanocortin (POMC) neurons, which produce alpha-melanocyte-stimulating hormone (alpha-MSH), cocaine and amphetamine-regulated transcript (CART), and the neurons that produce neuropeptide Y (NPY) and agouti-related protein

(AGRP), which are appetite stimulants. Alpha-MSH secreted by POMC neurons stimulates melanocortin receptors on paraventricular nucleus neurons, resulting in a decrease in food intake and an increase in energy expenditure. There are at least five types of melanocortin receptor (MCR). MCR-3 and MCR-4 are crucial in regulating food intake and energy balance. When MCR-3 and MCR-4 are active, both food intake and energy expenditure decrease. When MCR-3 and MCR-4 are suppressed, activation of AGRP neurons increases food intake and energy expenditure. When the body is low on energy, the appetite stimulant NPY is released, which blocks MCR-4 and causes an increase in food intake. Y. Zhang and associates (1994).

Numerous protein and peptide hormones affect appetite directly or via the hypothalamus. These hormones fall into one of two categories based on how long- or short-term an impact they produce. Preventing overindulgence during mealtimes is the goal of temporary regulation. The three short-term regulators are ghrelin, which increases appetite, nesfatin-1, which increases appetite, and cholecystokinin, which reduces appetite and energy intake. Maintaining the body's normal energy reserves is the goal of long-term regulation. Long-term regulators include insulin, leptin, obestatin POMC, and MCR-4 as appetite suppressors and NPY and AGRP as appetite stimulators (Chen X, et.al., 2012).

LEPTIN

The polypeptide leptin, encoded by the obesity gene, commonly referred to as the 'ob gene', was first discovered in mice (Dubern and Clement, 2012). The leptin gene is located on human chromosome 7q31, while the leptin receptor gene is located on chromosome 1q31, according to Friedman (1997). Research suggests that the placenta, pituitary gland, skeletal muscle and mammary gland all secrete leptin, which is mainly synthesised in adipose tissue (Myers MG, et al, 2010). There are two different forms of leptin in the blood: free and protein-bound. The free form is thought to be responsible for the effects of leptin. Studies have shown that the majority of leptin is present in its free form in the serum of obese individuals (Friedman JM, 1997). Therefore, the observation that there is an increase in the free form of leptin in obese individuals supports the finding that leptin resistance, rather than leptin deficiency, is the primary factor contributing to the development of obesity. The main source of leptin, which is involved in energy hemostasis and body weight regulation in the neuroendocrine system, is adipose tissue (Licinio J, et al., 2010; Jimerson DC, et al., 2015). It is closely linked to a number of reproductive processes in both humans and animals, according to Jimerson DC et al. (2015).

Leptin controls energy metabolism and body weight by acting on the brain's satiety centres, telling the brain where the body's main energy stores are. It also increases energy expenditure and restricts food intake (Jimerson DC, et al, 2015). Leptin is thought to be crucial in this process. Indeed, the finding that intrauterine fetal development is associated with fetal cord blood leptin levels independently of other factors has prompted further investigation into the function and importance of leptin in pregnancy (Jimerson DC, et al, 2015). 1.4.1. Leptin functions In the body, leptin primarily regulates energy metabolism and food intake, which has a negative feedback loop on the brain, especially the hypothalamus, and delays the onset of obesity, according to Auwerx and Staels (1998). It is also essential for immune regulation, gastrointestinal function, angiogenesis, osteogenesis, sexual development, metabolism, haematopoiesis and sympathetic activation, according to research by Oswal and Yeo (2010). Leptin is present in the blood in proportion to body fat mass and moves to the central nervous system in proportion to plasma levels.

According to body fat mass, leptin is present in the blood and moves to the central nervous system in proportion to plasma levels. Leptin's main mechanism of action is to stop neuropeptide-Y from being expressed and released from the arcuate nucleus. This neuropeptide-Y mainly increases appetite and is involved in the regulation of many pituitary hormones (Martins CM, et al., 2012).Studies have demonstrated that leptin interacts with multiple other mediators and possesses a complex communication network.These mediators fall into one of two general categories: anabolic or catabolic. Anabolic mediators, such as neuropeptide Y, increase daily food intake and decrease daily energy expenditure to create a positive energy balance. The most important and first identified catabolic mediator is alpha- melanocyte stimulating hormone (alpha-MSH), a member of the melanocortin family. The melanocortin receptor family, which includes the precursor proopiomelanocortin (POMC), ligandises many different members. The two most important members of this family are the melanocortin 3 receptor (MC3R) and the melanocortin 4 receptor (MC4R), which are mainly synthesised in the brain. There is evidence that MC4R mice lacking a gene are obese and that giving them a synthetic agonist of this receptor makes them less hungry. MC4R signalling has been shown to limit food intake and the growth of adipose tissue. Although genetic deficiency of MC3R results in the storage of excess body fat, this effect is mild and does not lead to an increase in food intake. In the arcuate nucleus, leptin controls POMC neurons that are close to neuropeptide Y (Martins CM, et al., 2012). Arcuate nucleus neurons also have a variety of functions in energy homeostasis. For example, lesions in the paraventricular nucleus (PVN) lead to obesity, while lesions in the lateral hypothalamic

area (LHA) lead to anorexia in order to maintain a low body weight. So not only do these two neurons receive leptin signals from neurons in the arcuate nucleus, they also communicate with each other. Anorexigenic signals from PVN neurons are less frequently transmitted when a person is losing weight because their LHA neurons fire when they should, increasing food intake and decreasing energy expenditure. Filling up fat stores should therefore lead to weight gain. Conversely, food intake decreases (loss of appetite), energy expenditure increases and fat stores decrease in response to increased signalling from PVN neurons (Seufert J, et.al, 1999). Thus, leptin increases energy expenditure and blocks the anabolic signalling in the brain that causes weight gain, while activating the catabolic signalling that prevents excessive weight gain. The gastrointestinal tract sends signals to the brain to control meal frequency and size in addition to leptin. In addition to leptin, the gastrointestinal tract communicates with the brain to regulate the frequency and size of meals. Some of these signals are sent directly to the brain by mechanical impulses caused by stretching of the gastrointestinal tract, but most are carried to the brain by afferent branches of the vagus nerve. The first and most important hormonal satiety signal to reach the vagus nerve is cholecystokinin. Cholecystokinin and leptin also work together. In addition, leptin reduces meal size by increasing cholecystokinin sensitivity (Banks WA, et al, 2004). The nucleus of the solitary tract (NTS) serves as the primary hub for integration and communication between the ventral hypothalamus and vagal afferent fibres from the gastrointestinal tract. These neurons express POMC neurons in addition to MC4R and leptin receptors. It follows that the NTS is essential for leptin function (Seufert J, et al, 1999).

LEPTIN DEFICIENCY AND RESISTANCE

There are two types of leptin deficiency: acquired and congenital. Congenital leptin deficiency, caused by leptin mutations leading to obesity and dysregulation of the hypothalamic axis, can be treated with leptin hormone replacement therapy (Bluher S, et al, 2009). Acquired leptin deficiency is associated with low body weight, especially in cases of hypothalamic amenorrhoea (HA) caused by exercise, stress or prolonged fasting, which disrupts the hypothalamic-pituitary-gonadal axis (Martins CM, et al., 2012).

Sáinz N, et al. (2012) state that leptin resistance can be caused by either impaired leptin receptor function or impaired leptin passage across the blood-brain barrier. Leptin is a hormone that crosses the blood-brain barrier with the help of transporters. Impairment of these transporter functions results in leptin resistance (McConway MG, et al, 2000).

THE LINK BETWEEN OBESITY AND LIPID

The hypothalamus receives information about the amount of energy stored in adipose tissue from serum levels of the hormone leptin, which causes an increase in energy expenditure and a decrease in appetite. Consequently, when leptin levels rise, appetite decreases and energy expenditure increases; conversely, when leptin levels fall, appetite increases and energy expenditure decreases (Sáinz N, et.al, 2012). It has been found that obese individuals have higher serum leptin levels than normal individuals (Friedman JM, 2010). Leptin resistance, caused by hypothalamic receptors that are insensitive to leptin hormone and therefore have high levels of leptin, is the reason why obese people are unable to control their body weight (Myers MG, et.al, 2010; Oswal A, Yeo G, 2010).

Serum leptin levels in obese people have been found to differ by gender. Serum leptin levels and body mass index are positively correlated, and leptin levels are higher in obese women than in obese men (Oswal A, Yeo G, 2010). Not only is leptin deficiency the cause of human obesity, but leptin resistance is also present in obese individuals. Leptin resistance is caused by transporters in the blood-brain barrier or problems with receptors in the central nervous system (Banks WA, et al, 2004). The results of the study suggest that the primary cause of obesity is abnormalities in the ability of serum to cross the blood-brain barrier (Farr OM, et.al, 2010).

GHRELIN

Growth hormone secretagogues (BHSMs) are defined by Banks et al. (1976) as opioid peptide derivatives that exhibit a weak growth hormone secretagogue effect rather than opioid activity (Al Massadi O, et.al., 2017). In 1984, BHSM-6, a strong growth hormone secretagogue (BHSM), was developed (Banks WA, et al., 2004). An unsuccessful attempt was made to extract the endogenous BHSM receptor ligand from tissues where growth hormone secretagogue receptor synthesis occurs, including the brain, pituitary and hypothalamus (Al Massadi O, et.al., 2017). Kojima et al (1999) isolated the endogenous BHSM receptor ligand from the stomach. The term “ghre” is derived from the root of the word “grow”, meaning development, and “relin”, meaning secretion (Kojima M, et.al., 1999). Ghrelin has a half-life of 15 to 20 minutes and exists in the body in two forms: acyl and deacyl. Serine, the third amino acid from the N-terminal end of ghrelin, is bound to an eight-carbon fatty acid. The octanyl group, a bound fatty acid, is what makes up the active acyl portion of ghrelin. The majority of ghrelin in circulation is deacylated ghrelin, which is not attached to the octanyl group. The only hormone that is triggered by a fatty acid is ghrelin. The hydrophobic property of deacylated ghrelin is acquired upon binding with a fatty acid molecule. This characteristic makes it simple for it to reach the

pituitary and hypothalamus. Proghrelin, the ghrelin precursor molecule, is made up of 117 amino acids (Sakata I, et al., 2002; Date Y, et.al., 2002).

The auxin glands in the stomach's submucosal layer contain X/A-like cells that are the primary producers of ghrelin (Gnanapavan S, et al., 2002). According to Date Y, et al. (2002), Gnanapavan S, et al. (2002), Sato T, et al. (2012), among other tissues, it is expelled from the hypothalamus, pituitary gland, salivary gland, thyroid gland, small intestine, kidney, heart, pancreas, lung, placenta, gonads, immune system, and breast.

The ghrelin hormone increases serum levels of cortisol, catecholamines, ACTH, prolactin, and aldosterone in adipose tissue, increasing appetite, and energy consumption. It also plays a role in the synthesis of growth hormone and controls food intake and satiety. In contrast to leptin hormone, ghrelin hormone increases appetite, increases food intake, throws off the energy balance, and results in an excessive increase in body weight (Sato T, et.al., 2012).

THE MECHANISM BY WHICH GRENADE WORKS

With seven transmembrane domains, the GH secretor receptor (GHS-R) is a G protein- coupled receptor. The hippocampal, ventromedial, and arcuate nuclei are the sites of GHS-R mRNA synthesis. Numerous tissues and organs, including the pituitary, heart, lung, liver, kidney, pancreas, stomach, small and large intestine, adipose tissue, immune cells, and hypothalamic nuclei, contain GHS-R mRNA (Nakazato M, et.al., 2001; Kola B, et.al., 2002). Two distinct mRNAs code for GHS-R. GHS-R1a is present in the hypothalamic nuclei, dorsal vagal complex, and mesolimbic dopaminergic system of the central nervous system, which regulates appetite and energy balance. Due to the absence of certain transmembrane domains, GHS-R1b is inactive (Kola B, et.al., 2002). We have said that the functional form of acyl- ghrelin is acyl-ghrelin by binding a serine eight-carbon fatty acid to the third amino acid, which is necessary for ghrelin to be active. The enzyme that enables the binding of this fatty acid is GOAT (Ghrelin O-acyl transferase) Ghrelin is activated in part by GOAT (Ohgusu H, et al., 2009).

THE CONNECTION BETWEEN GLUTIN AND OBESITY

Ghrelin affects appetite in three different ways. First, the hormone ghrelin, which is produced in the stomach, stimulates the appetite center by actively transporting itself to the hypothalamic ARC through blood circulation. Second, by inducing GHS-R expression, the hormone ghrelin, which is produced in the periphery, stimulates vagal afferent nerve endings and the hypothalamus. Thirdly, the ARC produces more NPY and AGRP

and less POMC (appetite suppressor) when the hypothalamus synthesizes ghrelin hormone. As the energy store is emptied, the blood serum level of the hormone ghrelin increases, stimulating appetite (Gutierrez-Grobe Y, et al., 2010; Hagemann D, et al., 2003). Thin people have higher ghrelin levels than obese people do, and obese people who lose weight through diet and exercise have been shown to have higher ghrelin levels. Individuals suffering from anorexia nervosa had higher plasma leptin levels than obese individuals when comparing their plasma ghrelin levels (Gutierrez-Grobe Y, et.al., 2010).

GHRELIN EXPRESSION AND SECRETION REGULATION

Eating is the primary factor that regulates ghrelin secretion. Ghrelin levels in plasma are highest during fasting and fall after eating. It's unclear, though, if these elements have any effect on controlling ghrelin secretion. Plasma ghrelin levels are lowered by oral and intravenous glucose administration (Ohgusu H, et al., 2009; Hagemann D, et al., 2003). The levels of ghrelin in human plasma rise at night and peak at approximately 02.00. One hour after the meal, it returns to its starting value after increasing twice before (Ohgusu H, et.al., 2009). Water intake does not cause a change in the concentration of ghrelin in plasma when the stomach is filled. When given a low-protein diet, ghrelin levels rise, and when given a high-fat diet, they fall (Hagemann D, et.al., 2003). Following gastric bypass surgery, it has been demonstrated to decrease (Gale SM, et.al., 2003; Cowley MA, et.al., 2003). Ghrelin and Obestatin's Physiological and Biochemical Impacts GHS-R, a cell surface receptor, interacts with ghrelin to largely mediate its biological effects (Ohgusu H, et.al., 2009). When mice with the GHS-R gene are injected with ghrelin, they do not exhibit any GH release or appetite induction response. This clarifies why GHS-R is referred to as the ghrelin receptor and why it is believed that ghrelin acts through it (Kola B, et.al., 2002). It was unknown that ghrelin was the endogenous ligand of GHS-R prior to its discovery.

GHRELIN'S PHYSIOLOGICAL AND BIOCHEMICAL IMPACT

Ghrelin's interactions with the cell surface receptor GHS-R are primarily responsible for its biological effects (Kola B, et.al., 2002). In response to ghrelin injection, mice devoid of the GHS-R gene do not exhibit GH release or increased appetite. This clarifies why GHS-R is referred to as the ghrelin receptor and why it is believed that ghrelin acts through it (Ohgusu H, et.al., 2009). It was unknown that ghrelin was the endogenous ligand of GHS-R prior to its discovery. Thirteen While hypothalamic GHRH is known to stimulate pituitary GH release, exogenous GHS is thought to

induce pituitary GH release through an alternative pathway. Strong stimulation of GH release occurs from ghrelin (Kola B, et al., 2002). Strong and dose- dependent GH secretory activity is exhibited by ghrelin and GHSs (Nakazato M, et al., 2001). Intravenous ghrelin administration strongly releases growth hormone in healthy individuals (Kola B, et al., 2002). Rats' GH secretion is unaffected by the intravenous and intracerebrovascular administration of obestatin (Gutierrez-Grobe Y, et al., 2010). Adrenocorticotropic hormone and cortisol levels were elevated in healthy subjects receiving systemic administration of ghrelin (Nakazato M, et al., 2001). In pituitary cell cultures, the prolactin secretory effect of ghrelin has been directly demonstrated (Kola B, et.al., 20025). Ghrelin, when administered centrally or peripherally, raises body temperature in a dose- dependent manner; however, the mechanism of administration affects the rate of rise in body temperature.

For instance, when ghrelin is injected intraperitoneally, the temperature rises in 5–20 minutes, but when it is injected intracerebroventricularly, the temperature rises in 10–60 minutes. It is acknowledged that ghrelin has an impact on energy expenditure and conservation, even though the exact cause of this temperature shift is unknown (Hagemann D, et.al., 2003). It has been demonstrated that the placenta synthesizes and expresses ghrelin. It is believed that ghrelin may be involved in fetal growth because larger offspring of rats given ghrelin were observed (Gale SM, et.al., 2003; Cowley MA, et.al., 2003). The possibility that ghrelin and GHSs play endocrine and paracrine roles in embryonic implantation is also emphasized (Inui A, et al., 2001). Nutrition is the primary factor influencing the regulation of ghrelin secretion. According to Gale SM et al. (2003), ghrelin is also known to be effective in the use of nutrients and the secretion of hormones connected to metabolism. Ghrelin, desachylated ghrelin, and C-ghrelin levels are lowered by nutrition (Cowley MA, et.al., 2003). Nevertheless, compared to total ghrelin levels, postprandial acylated ghrelin levels drop more quickly. Changes in acylated ghrelin secretion and/or acylated ghrelin desacylation could be the cause of this (Nakazato M, et al., 2001). There are conflicting findings in publications about how diet affects obestatin levels. According to some publications, diet both negatively and not at all affects obestatin levels (Ohgusu H, et.al., 2009). Fasting does not change obestatin levels, but it does raise ghrelin, desacylated ghrelin, and C-ghrelin levels at the same rate. Ghrelin levels in plasma rise during fasting and fall following meal consumption (Kola B, et al., 2002; Ohgusu H, et al., 2009). adiposity and weight gain (Gutierrez-Grobe Y, et al., 2010). Rats given intracerebroventricular injections consumed more food in a manner that was dose-dependent. Giving ghrelin intracerebroventricularly to rats lacking in growth hormone causes them to eat more. These findings imply

that ghrelin's orexigenic action occurs independently of the GH signaling pathway. Ghrelin administered continuously intracerebroventricularly stimulates food intake and increases fat mass, which results in weight gain (Gutierrez-Grobe Y, et al., 2010). The obestatin ratio can change due to chronic positive balance ghrelin.

Obese people have higher preprandial ghrelin and obestatin ratios than people of normal weight who are the same age and sex. According to Gale SM et al. (2002), body mass index (BMI) is a significant independent factor that is positively correlated with pre-prandial ghrelin and obestatin ratios. The heart and aorta have also been shown to contain ghrelin mRNA (Kola B, et al., 2002). Human volunteers who received ghrelin experienced a reduction in heart rate but no change in arterial pressure (Cowley MA, et.al., 2003). Ghrelin was injected intracerebroventricularly into the nucleus tractus solitarii of rats, resulting in a suppression of sympathetic activity and a lowering of blood pressure and heart rate (Cowley MA, et al., 2003). In arteries, ghrelin eliminates endothelin-1's vasoconstrictor effect (Cowley MA, et al., 2003). In arteries, ghrelin eliminates endothelin-1's vasoconstrictor effect (Cowley MA, et al., 2003). Theoretically, obestatin, the twin of ghrelin, should have the opposite effect. Nevertheless, no research has been done on this topic yet. By preventing sympathetic activity and inducing vasodilatation, ghrelin lowers blood pressure. According to studies (Ohgusu H, et al., 2002; Kola B, et al., 2002), it has been discovered to have an accelerating effect on gastrointestinal parasympathetic activity and an inhibiting effect on ejaculation. Adenocorticotropic hormone, prolactin, follicle stimulating hormone, luteinizing hormone, and thyroid stimulating hormone (TSH) released from the pituitary gland were all unaffected by ghrelin administration in experimental animal studies, but GH secretion was increased (Gutierrez-Grobe Y, et.al., 2010). Administering ghrelin to volunteers in experimental studies increases cortisol, GH, adenocorticotropic hormone, and appetite. It has been demonstrated that ghrelin increases the release of prolactin, the expression of GHRH, GH, adenocorticotropic hormone, aldosterone, glucagon, and gastric acid; it also positively affects gastric motility and inhibits the secretion of insulin and somatostatin; furthermore, it has an impact on numerous systems, including nutrition and cell proliferation (Cowley MA, et.al., 2003). 16 In the liver, adipose tissue, and skeletal muscle, ghrelin regulates lipid metabolism in a significant way. In addition to increasing triglyceride content and lipogenic pattern gene expression, it inhibits the liver's ability to oxidize fatty acids. Ghrelin raises the activity of mitochondrial oxidative enzymes and lowers the triglyceride content of the gastrocnemius muscle. When in an active state, it reduces the amount of fat in skeletal muscles by specifically increasing skeletal muscle peroxisome proliferator activator receptor

γ (Gale SM, et al., 2003). Ghrelin guarantees the accumulation of liver triglycerides in skeletal muscles in this manner. There is little information available about how desacylated ghrelin affects lipid metabolism.Desacylated ghrelin, like acylated ghrelin, inhibits isoproterenol-induced lipolysis in rat adipocytes and directly increases lipogenesis in vivo (Hagemann D, et al., 2003).It is unknown how obestatin affects the lipid mechanism.

GHRELLINE'S IMPACT ON GLUCOSE METABOLISM

It has been proposed that ghrelin is crucial for the metabolism of both glucose and insulin (Gnanapavan S, et al., 2002). By controlling hepatic glycogenesis, insulin secretion and activity, and neuronal sensitivity to glucose, ghrelin plays a role in maintaining glucose homeostasis in the brain (Gale SM, et al., 2003). By releasing growth hormone, raising insulin resistance, and promoting gluconeogenesis, it controls blood glucose levels (Cowley MA, et al., 2003). Human plasma glucose levels rise when ghrelin is administered systemically acutely, inhibiting insulin secretion (Gnanapavan S, et al., 2002). There have also been some contradicting findings published about how ghrelin affects insulin secretion (Sato T, et al., 2002). In a study, it was discovered that ghrelin increased the pancreatic secretion of insulin in both normal and diabetic subjects. Additionally, it was noted that the islets of Langerhans of diabetic rats had a higher quantity of ghrelin immunoreactive cells (Hosoda H, et al., 2000). Insulin release was inhibited by ghrelin injection administered in situ perfusion in isolated rat pancreas (Gnanapavan S, et.al., 2002). Moreover, desacylated ghrelin might control how glucose is metabolized. According to reports, desacylated ghrelin eliminates the effects of acylated ghrelin on insulin secretion and is found in pancreatic islet cells isolated from mice and rats at a concentration 10 times higher than acylated ghrelin in accordance with plasma concentration (Kola B, et.al., 2002). 17 It is also said to eliminate insulin's ability to suppress endogenous glucose synthesis while having no effect on glucose intake. Both peptides are administered simultaneously to produce these effects (Ohgusu H, et al., 2009). Desacylated ghrelin suppresses the effect of ghrelin on the release of glucose and inhibits the glucose output from primary hepatocytes. Nonetheless, there is ongoing debate regarding ghrelin's function in insulin secretion (Sato T, et al., 2012). Studies on the effects of intravenous ghrelin administration on glucose levels in normal and obese individuals have been reported (Gnanapavan S, et.al., 2002; Sato T, et.al., 2012; Hosoda H, et.al., 2003; Nakazato M, et.al., 2001). Co-administration of GH receptor antagonist was found to dramatically increase insulin resistance in humans (Gale SM, et.al., 2003). ral glucose administration in humans has been demonstrated to lower ghrelin levels independently of insulin, while intravenous glucose administration suppresses ghrelin levels in both humans and rodents (Cummings DE et.al., 2006).

NESFATİN

NUCB2 (nucleobindin2) is the recently discovered precursor molecule of nesfatin, an 82 amino acid protein. When a person is fasting, the hypothalamic paraventricular nucleus's NUCB2 expression decreases, indicating that endogenous nesfatin may regulate appetite physiologically. It is a derivative of the NUCB2 peptide with 82 amino acids that prohormone convertase changes into Nesfatin 1. It has been found that intracerebroventricular injection reduces body weight by inhibiting food intake in a dose-time dependent manner (Oh-I S, et.al., 2006). According to a study by Shimizu et al. (Shimizu H & Mori M, 2012), the prohormone convertase enzyme converts the nesfatin/NUCB2 molecule to nesfatin-1, which is linked to appetite regulation. Nesfatin-1 has been found to suppress food intake in rats in a dose-dependent manner when injected intraperitoneally; however, the longer-lasting effect of subcutaneous administration occurs when food intake is suppressed. These results led to the conclusion that peripheral nesfatin administration might represent a novel approach to the management of obesity. Shimizu & Co. Nesfatin-1 intravenous injection dramatically lowered blood glucose levels in hyperglycemic rats, according to a different study by Shimizu H. et al. (2009). This antihyperglycemic effect was found to be time, dose, and insulin dependent, and it also had a peripheral effect. Although the exact mechanism of nesfatin's antihyperglycemic effect is still unknown, it is thought to involve interactions with insulin signaling. Zhang Ai- Qing et al. Nesfatin-1 levels in fasting plasma were compared in groups with type 1 diabetes, type 2 diabetes, and control (Ai-Qing Zhang et al., 2010). Type 1 diabetes had higher levels than the control group, while type 2 diabetes had lower levels than the type 1 and control groups. In order to assess the potential benefits of nesfatin1 in the treatment of metabolic diseases, particularly type 2 diabetes, more research is required. Fasting plasma nesfatin levels may be involved in the pathophysiology of diabetic hyperphagia. It was over.

MECHANISM OF NESFATIN-1 ACTION

In the arcuate nucleus of the hypothalamus, which is home to the regions responsible for hunger and satiety, or in the tractus solitarius nucleus of the brainstem, the hormone known as nesfatin-1 activates transcript neurons regulated by POMC (pro-opiomelanocortin), the precursor of ACTH (adrenocorticotropic hormone), cocaine, and amphetamine. This hormone also crosses the blood-brain barrier through neural network interaction. It comes from both exogenous (external) and endogenous (internal) sources to the brain's centers (Stengel A, et al., 2013; Chen X, et al., 2012). The satiety hormone α-MSH (alpha-melanocyte stimulating hormone) is linked to the expression of nesfatin-1. NUCB2 gene expression and

nesfatin-1 expression are both elevated in the paraventricular nucleus by α-MSH (Stengel A., 2015). In conclusion, NUCB2/nesfatin-1 in the brain suppresses appetite by acting as a secretory mediator via the receptors for histamine, oxytocin, POMC/MSH, CRF, serotonin, and TRH (Ai-Qing Zhang, et al., 2010; Stengel A, et al., 2013; Chen X, et al., 2012; Stengel A., 2015).

THE LINK BETWEEN NESFATIN-1 AND OBESITY

There is inconsistent research on the connection between plasma nesfatin-1 level and obesity. The level of nesfatin-1 and total body fat are inversely correlated (Van BK, et al., 2011; Mirzaei K, et al., 2015; Ogiso K, et al., 2011). It has been noted that in obese people with low nesfatin-1 levels, there is an increase in energy, protein, and carbohydrate intake; in obese people with high nesfatin-1 levels, the percentage of body fat decreases (Ogiso K, et.al., 2011; Çatli G, et.al., 2013; Zegers D, et.al., 2013). Children who are obese have lower serum levels of nesfatin-1 than children who are of normal weight (Zegers D, et al., 2013; Pan W, et al., 2007).

According to Çatli G, et al. (2013), congenital nesfatin-1 deficiency is characterized by early obesity and obesity-associated congenital prohormone convertase 1 deficiency, which results in the conversion of NUCB2 into nesfatin-1, 2, and 3. Seven distinct regions of the NUCB2 gene were discovered as a result of the research, along with the first genetic variation of nesfatin-1 in obese individuals. The possibility that these different nesfatin-1 variations could cause obesity in the brain was revealed, but these changes had no effect on the level that was circulating. Scientific research is necessary for this (Zegers D, et al., 2013). More research is anticipated to determine whether variations in body weight, age, gender, and assessment techniques are relevant factors (Tsuchiya T, et.al., 2012). Long-term studies with conclusive data are required to determine the impact of nesfatin-1, which is known to decrease food intake and can cross the blood-brain barrier, on obese people (Çatli G, et al., 2013; Zegers D, et al., 2012).

CONCLUTION

A number of factors contribute to obesity, including an excessive build-up of body fat, a body mass index (BMI) of greater than 30 kg/m2, and an energy intake that exceeds expenditure. There are numerous factors that contribute to obesity, including genetic, environmental, psychosocial, and economic factors. Lesions in the hypothalamic ventromedial nuclei cause obesity by inducing an excessive desire for food, and decreased physical activity and overnutrition, particularly in childhood, lead to excessive fat storage. Genetics is the other factor that contributes to obesity. Obesity is caused by a combination of MCR-4 mutation, environmental factors resul-

ting from leptin gene deficiency, and leptin receptor mutation. The causes of obesity are numerous. The area of the brain responsible for regulating nutrient intake and energy metabolism is called the hypothalamus. Hormones that stimulate and suppress appetite are known to act directly on nutritional intake or on the hypothalamus. Among these hormones, ghrelin, one of the hormones that stimulate appetite, and obesity were studied individually. Among these, leptin and nesfatin-1 are hormones that suppress appetite. Leptin hormone acts on the hypothalamus to negatively feedback loop, restricting food intake and regulating food intake and energy metabolism. Leptin levels are higher in obese people than in normal people. Transporter or receptor defects in the blood-brain barrier lead to leptin resistance. The peptide hormone known as ghrelin secretes growth hormone, which works in opposition to leptin hormone to increase appetite. Ghrelin increases hunger in three different ways: The ghrelin hormone synthesized in the periphery causes the expression of the ghrelin hormone receptor and stimulates the hypothalamus; the ghrelin hormone synthesized in the hypothalamus suppresses the production of POMC (an appetite suppressant). The ghrelin hormone synthesized in the stomach stimulates appetite by active transport with the blood. There is conflicting research on the appetite suppressant hormone nesfatin-1 and its connection to obesity. Thus, further investigation into the connection between hormones and obesity is warranted.

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BÖLÜM 3

THE RELATIONSHIP BETWEEN QUALITY HEALTH AND COVID-19 DEATHS[1]

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1 This work is derived from a medical specialization thesis. Author: Rıdvan OT, Thesis Advisor: Assoc. Prof. Dr. Akın DAYAN, Publication Year: 2023 T.C. Health Sciences University Haydarpaşa Numune Training and Research Hospital Family Medicine Clinic Relationship Between COVID-19 Fatality and Satisfaction with Quality Health Services in OECD Countries

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1. INTRODUCTION

COVID-19, a viral respiratory disease caused by the novel coronavirus, dubbed SARS-CoV-2, began as a pandemic with the first cases in Wuhan, People's Republic of China ("Basics of COVID-19 | CDC," n.d.). As COVID-19 has turned into a pandemic, there have been many new cases and deaths. In this context, the importance of adequate and quality health care has increased.

Quality health is one of the most frequently emphasized health policy principles. In this context, the World Health Organization has put forward a health system strengthening strategy under the framework of "building blocks". The building blocks are service delivery, health workforce, knowledge, medical products-vaccines-medical technologies, finance, leadership/management. Intermediate strategies have been identified to improve health and achieve the ultimate goals of the health system, and these intermediate strategies can be listed as quality, safety, accessibility, and inclusion. The ultimate goals of the health system are health improvement (level and equity), responsiveness to needs, financial protection/financial justice, increased efficiency (Eu, Busse, Klazinga, Panteli, & Quentin, n.d.).

The United States Institute of Medicine has defined quality as the satisfaction of individuals and communities with health outcomes and consistency with current medical knowledge (Schuster, McGLYNN, & Brook, 2005). The six dimensions of a quality health service are listed as safe, timely, effective, efficient, effective, patient-centered, and fair service. Preventable hospital admissions due to chronic diseases such as asthma and COPD can be given as an example as a determinant of the quality of primary health care services and death due to acute myocardial infarction 30 days after hospital admission can be given as an example as a determinant of the quality of emergency health care services (Eu et al., n.d.).

Investigating patients' satisfaction with health care services is an important indicator of health quality (Grol, Wensing, & Kersnik, 2000). Patient satisfaction studies, which are used as an indicator of the health services provided, are conducted through satisfaction surveys developed for this purpose. The EUROPEP scale (European Patients Evaluate General/Family Practice), developed in 1999 by the European Working Party on Quality in Family Practice (EQuiP), a sub-unit of the European organization of the World Association of Family Physicians (WONCA), which has international standards and is currently used in 25 European countries, is an example of this (Republic of Turkey Ministry of Health, Mollahaliloğlu, Kosdak, & Eryılmaz, 2011).

The OECD (Organization for Economic Cooperation and Development) reports that between 2000 and 2010, health expenditures in approx-

imately 34 countries increased by more than 70% (Stabile et al., 2017). However, high costs are not always associated with high quality care. In this context, there is the "Closing the Quality Gap" report published by the United States of America (USA) Institute of Medicine in 2001 (Avcı, 2018).

In studies evaluating the impact of socioeconomic factors on mortality (Backer, Rezene, Kahar, & Khanna, 2022; Chang, Chang, He, & Jui Keng Tan, 123 C.E.; Kim, Jeung, Choi, & Park, 2022a), increased mortality was found in people with limited access to health services, in low-income groups and in social isolation. Increased mortality was observed as per capita income from gross domestic product decreased. Increased COVID-19 mortality was found as the number of doctors and health personnel per capita decreased.

When the relationship between air pollution and COVID-19 was analyzed; it was found that air pollution and smoking are important causes of morbidity and mortality by increasing respiratory diseases in humans, and there is a relationship between exposure to atmospheric pollutants and the spread of SARS-CoV-2 virus (Gallo, Street, Guerra, Fanos, & Marcialis, 2020).

In order to ensure social welfare, continuous improvements in the health status of individuals in society are important. Ensuring equality in health, improving quality of life and prolonging life span are essential for a healthy society. As stated in the framework of the "building blocks" put forward by the World Health Organization, the correct, effective, and timely use of the resources necessary for health, and the use of the power of modern science in the use of these resources are the key to improvement in health (Tezi, Sectors, Coordination, & Directorate, 1994). Health services and quality in the provision of health services are important for the economic and social dynamism of countries. The main goals in health services are to increase the quality of health services provided, to provide equal, effective, quality services for every individual in every part of the society, to increase patient satisfaction and thus to increase the efficiency and effectiveness of health services (Assoc, Şanli, Branch, Undergraduate, & Antalya, 2006). According to the United States Institute of Medicine, quality is defined as the satisfaction of individuals and societies with health outcomes and consistency with current medical knowledge, and the human factor comes to the fore in the quality of health care. Therefore, the health services provided vary in terms of quality, scope, and capacity. The fact that the service provider is an expert in his/her field, the physical characteristics of the environment where the service is provided, the accuracy, effectiveness, timeliness, and continuity of the service are the factors that determine the quality of service. Patients are the consumers of this service,

which is decisive in terms of health service quality. The opinions and satisfaction of patients about the health service provided are the main criterion of health service quality. Patient satisfaction studies enable the evaluation of the quality of healthcare services received by patients. It is also a stimulus for health planning and helps to analyze outputs (Republic of Turkey Ministry of Health et al., 2011).

2. THE RELATIONSHIP BETWEEN QUALITY IN HEALTH AND MORTALITY

Primary prevention is of great importance in improving community health outcomes. This includes reducing mortality through early interventions for common chronic diseases (Bellamy & Smith, 2007; Hung et al., 2007). Effective primary prevention is associated with reduced mortality, increased life expectancy, and more equitable health outcomes (Engström, Foldevi, & Borgquist, 2009; Starfield, Shi, & Macinko, 2005). The quality of primary healthcare services varies depending on the service providers (Republic of Turkey Ministry of Health et al., 2011). The study conducted in England contradicts this issue and emphasized that the traditional physician payment system does not lead to high quality care and investments in quality improvement; the relationship between the National Primary Care Performance-Based System, the UK Quality and Outcomes Framework (QOF), a quality indicator associated with this system, and premature death due to all causes or specific causes associated with this framework was examined. No association was found between mortality rates and healthcare quality as measured by the quality indicators in the QOF. The quality markers in the QOF consist of the structure of the healthcare organization, patient experience and management of more chronic diseases. Examples include chronic ischemic heart disease, cancer, chronic obstructive pulmonary disease, hypertension, stroke and diabetes (Kontopantelis et al., 2015).

3. THE RELATIONSHIP BETWEEN SOCIOECONOMIC FACTORS AND MORTALITY

Social determinants of health are defined by the World Health Organization as a set of structural, political, and socioeconomic factors that combine in a given society. Determinants of susceptibility or resistance to diseases and access to quality health care lead to different levels of health outcomes. In the current COVID-19 pandemic, the health system has taken on a major burden in the fight against the pandemic. The emphasis is on providing inclusive health care to all people in need of health care, overcoming illness and preventing death. Barriers such as social isolation, poverty and limited access to health services are obstacles in the fight

against the pandemic. The impacts of the pandemic shed light on the constraints and basic needs of society. For example, nutritional needs, income justice, general well-being and housing conditions... A society living in poverty has more severe pathologies than those living in better economic conditions. From this perspective, poverty and poor health conditions are interrelated, i.e., as long as poverty exists, poorer health outcomes will be detected and, in a vicious circle, poor health conditions will further trigger poverty (Chávez-Almazán, Díaz-González, & Rosales-Rivera, 2022).

In the study conducted in Mexico, which evaluated the impact of socioeconomic determinants on COVID-19 mortality, it was emphasized that approximately 41.9% of the Mexican society, i.e., 52.4 million people, are in poverty, and it was emphasized that such a large population is likely to have limited access to acceptable levels of services and the risk of contracting diseases more than others. In addition, Mexican society is characterized by conditions that negatively affect health. For example, high prevalence of obesity, diabetes and cardiovascular diseases, unsafe work, problems in access to clean water, overcrowding. These factors limit access to preventive services and create problems in accessing basic rights such as health, food, education, housing and social security. As a result, in developing countries like Mexico, widespread poverty and inequality are exacerbating the COVID-19 pandemic and worsening its negative consequences. During the COVID-19 pandemic, the need to take decisions to improve the quality of life of poor and socially isolated populations in need of protection against coronavirus is emphasized (Chávez-Almazán et al., 2022).

In the study conducted in the state of Florida in the United States of America, it was emphasized that there are social determinants of health associated with risk factors that have an impact on quality of life. These were listed as poverty, lack of insurance coverage, household size and social sensitivity. The relationship between these factors and COVID-19 cases and deaths was tried to be determined. The analysis revealed that mortality rates were higher in poverty regions. The importance of lack of insurance coverage in mortality was emphasized (Backer et al., 2022).

4. THE RELATIONSHIP BETWEEN THE NUMBER OF HEALTH WORKERS AND MORTALITY

Increased hospital admissions are leading to increased workloads for health professionals at all levels (Williams, Rondeau, Xiao, & Francescutti, 2007). In the United Kingdom in 2018, 43% of consultations were unmet, indicating a shortage of providers, and recent research suggests that the mid-level physician workforce will be unsustainable with current staffing levels (Chaudhuri, Mason, Logan, Newbery, & Goddard, 2013; Focus

on Physicians Census of Consultant Physicians and Higher Specialty Trainees 2018, n.d.). Hospital healthcare quality is influenced by the number of healthcare workers (Bell, Lambourne, Percival, Laverty, & Ward, 2013; Mueller et al., 2012). Hospital doctors are a group that has an impact on mortality, but available data show that the impact is different according to the working diversity of doctors. The population of the community and the number of hospital doctors per head of population also contribute to this marked difference (Griffiths, Ball, Murrells, Jones, & Rafferty, n.d.; Jarman et al., n.d.). Low nurse staffing levels have been shown to be associated with increased inpatient mortality (Bray et al., n.d.; Needleman et al., 2011; Peter Griffiths et al., 2019). Various social and political determinants affect the incidence, mortality and fatalities of COVID-19. When considered within the healthcare system, the number of doctors and nurses is recognized as an important factor (Kim, Jeung, Choi, & Park, 2022b). In a study conducted in 23 countries, the social and political determinants of COVID-19 were investigated, and it was found that the number of doctors per capita and the number of health personnel per capita were associated with COVID-19 mortality and fatalities, while the elderly population, income constraints and low number of health workers were associated with high morbidity and mortality. In this context, it is emphasized that various social and political determinants should be taken into consideration when determining COVID-19 policies (Kim et al., 2022a).

5. THE RELATIONSHIP BETWEEN NUMBER OF PATIENT BEDS, MEDIAN AGE AND MORTALITY

As a part of service delivery, hospitals play a key role in strengthening the health system. In this context, the number of patient beds and the number of intensive care beds are important. According to a study in China, strong government initiatives have driven improvements in maternal health. Maternal mortality rates in China fell staggeringly in every region between 2004 and 2016. Adequate investment in health system reform, including increasing the number of hospital beds, was a driving force behind such progress. China significantly increased the number of hospital beds at the national level between 2004 and 2016. The increased number of hospital beds has contributed to a steady reduction in inequalities in the distribution of hospital beds. The increased number of hospital beds and the elimination of inequitable geographical distribution of hospital beds have contributed to reducing maternal mortality rates. At the same time, increased resources and equity in their distribution have led to improvements in the health system (Tian & Pan, n.d.).

According to a study conducted in three countries, intensive care admissions over the age of eighty years had a prolonged survival in hospital

compared to hospital admissions, but survival beyond two years was similar (Abuhasira et al., 2022). An increase in the number of older people requiring intensive care admission has been associated with increased costs and resource utilization (Bagshaw et al., 2009; Lerolle et al., 2010).

With the aging of the world population, an acceleration in the increase in costs and use of health income is expected (Nations, of Economic, Affairs, & Division, n.d.). Age is a significant independent risk factor for ICU mortality, but it is not clear whether ICU admissions in the elderly population benefit patients in the short or long term (Berwick & Hackbarth, 2012; Fuchs et al., 2012; Halpern, Pastores, & Greenstein, 2004; Sprung et al., 2012a). However, low levels of intensive care and non-intensive care beds have been associated with higher mortality in older people (Robert et al., 2012; Simchen et al., 2004). Increased ICU capacity was associated with increased ICU admissions in the older population, but no increase in 1-year survival (Fuchs et al., 2012). Conversely, some benefits have been observed in ICU admissions of older people. Half of older patients admitted to the ICU survived for more than 2 years (Roch et al., 2011). Contrary to the assumption that older people are more likely than younger people to refuse ICU admission and have higher mortality on admission, mortality reduction in ICU admissions has been observed at a higher rate in older people than in younger people (Sprung et al., 2012b).

In a study based on worldwide databases, the relationship between COVID-19 fatalities and recovery times and determinants such as hospital capacity, age distribution and the number of tests performed was examined, and no significant relationship was found between fatalities and the number of patient beds per capita. The proportion of the population aged 65 years and over and the number of computed tomography scans performed were not significantly associated with fatalities. In contrast, there was a significant difference between hospital capacity, age distribution and number of tests performed and COVID-19 fatalities. In high-income countries, hospital capacity, age distribution, number of tests performed, and number of mechanical ventilators were significantly associated with COVID-19 mortality. As a result, countries' COVID-19 preparedness levels, testing and health capacity were listed as significant determinants of COVID-19-related mortality and recovery rates (Khafaie, Malehi, & Rahim, 2021).

6. THE RELATIONSHIP BETWEEN EDUCATION AND MORTALITY

Education is highly associated with subsequent health outcomes, including late-life mortality. In 2007, age-standardized mortality rates for high school graduates aged 25-64 years were more than twice as high as those

with higher levels of education (Xu, Kochanek, Murphy, & Tejada-Vera, 2010).

According to many studies, completion of compulsory education is highly associated with health well-being. These findings are independent of whether the health level measurement is based on mortality rates, morbidity rates and health awareness, and whether the observation is made on an individual or a group. Evidence is weak on whether this association reflects a causal link that more schooling leads to better health. This relationship should be seen as reverse causality. This is because longer life expectancy increases investment in schooling. Healthy students can stay in school longer (Grossman, 2010).

The study of 21 country-level factors affecting COVID-19 investigated factors commonly associated with infectious diseases (such as population and tourism activities), as well as country-specific factors that shape COVID-19 outcomes. Among these factors; female-to-male ratio, population density, urbanization increase the severity of COVID-19, while conversely, education, temperature and religious diversity mitigate the impact of the pandemic on morbidity and mortality (Chang et al., 123 C.E.).

7. SUMMARY OF REFERENCE RESEARCH

OBJECTIVES: To examine the relationship between COVID-19 mortality and satisfaction with quality health care in OECD countries, taking into account the effectiveness of primary and secondary health care services.

MATERIALS AND METHODS: Data from 27 OECD countries were collected from open access websites to assess the relationship between dependent and independent variables. The dependent variable was COVID-19 mortality, and the independent variables were primary health care effectiveness, secondary health care effectiveness, gross domestic product, median age, number of inpatient beds, number of intensive care beds, number of doctors and nurses, number of computerized tomography devices, educational status and air pollution. Countries with available data on all variables were included in the study. Spearman Rho correlation and partial correlation were used to analyze the data and linear regression analysis was performed.

FINDINGS: There was a statistically significant correlation between case fatality rates and the effectiveness of secondary health care services ($p<0.05$). The relationships between the effectiveness of primary health care services, gross domestic product, median age, number of intensive care beds, number of doctors and nurses, number of computerized tomography devices, educational status, air pollution and case fatality rates were

not statistically significant. Satisfaction with quality healthcare services was negatively correlated with the efficiency of primary healthcare services ($p<0.05$) and positively correlated with the number of nurses ($p<0.01$) and the number of computerized tomography devices ($p<0.01$). However, there was no statistically significant correlation between satisfaction with quality healthcare services and COVID-19 fatalities ($p>0.05$). The efficiency of secondary health care services and gross domestic product were positively associated ($p<0.05$). In addition, Generalized Linear Model (GLM-Logit Model) regression analysis was performed to evaluate the effect of independent variables on fatalities and only the effect of secondary health care services ($p<0.01$) and number of inpatient beds ($p<0.05$) on fatalities were statistically significant.

CONCLUSIONS: Satisfaction with quality health care is not associated with COVID-19 fatalities. Satisfaction with quality healthcare services was affected by primary healthcare services, number of nurses and number of computerized tomography devices. As the efficiency, i.e. quality, of secondary healthcare services increases, COVID-19 fatalities decrease. In addition, the number of patient beds has a negative effect on COVID-19 fatalities. Primary healthcare services have no effect on COVID-19 fatalities. The effectiveness of secondary healthcare services and the level of pandemic preparedness of countries play a decisive role in COVID-19 fatalities.

8. THE RELATIONSHIP BETWEEN HEALTH SERVICE QUALITY AND COVID-19 FATALITY

A 2015 study by Kontopantelis et al. in England highlighted that the traditional physician payment system does not lead to high quality care and quality improvement, and examined the relationship between the National Primary Care Performance-Based System, the UK Quality and Outcomes Framework (QOF), a quality indicator associated with this system, and all-cause or specific-cause premature mortality associated with this framework. High mortality rates were seen in areas of deprivation, urban areas and areas with high non-white populations. Incentivized - observed - performance improvements within the National Primary Care Performance-Based System were not associated with subsequent reductions in premature mortality. The lack of a large effect on mortality in the medium term suggests that the QOF is not an ideal investment in the use of health system resources, but that mortality rates should be further investigated within the primary care system, taking into account the quality of local secondary care. There was no association between mortality rates and the quality of health care measured by the quality markers in the QOF. The quality markers in the QOF consist of the structure of the healthcare or-

ganization, patient experience and management of more chronic diseases. Examples include chronic ischemic heart disease, cancer, chronic obstructive pulmonary disease, hypertension, stroke and diabetes (Kontopantelis et al., 2015).

Considering the findings of our study, similar to Kontopantelis' study, it was observed that there was no relationship between COVID-19 fatalities and satisfaction with quality healthcare services. Investigating satisfaction with health services is a way to measure quality in health (Grol et al., 2000) and satisfaction surveys are used for this purpose (Republic of Turkey Ministry of Health et al., 2011). Unlike the EUROPEP scale, the satisfaction survey used in OECD health statistics uses a method that assumes that each question has the same weight and calculates satisfaction with each dimension as the average value obtained from the questions that make up that dimension. The lack of a relationship between satisfaction with quality health services and COVID-19 fatalities may be due to this difference in measurement method. There was no correlation between the effectiveness of primary health care services and COVID-19 mortality, while the effectiveness of secondary health care services was negatively correlated with COVID-19 mortality. Similar to the Kontopantelis study, the fact that the increase in the effectiveness of secondary health care services has a decreasing effect on COVID-19 mortality, and the lack of a relationship between the effectiveness of primary health care services and COVID-19 mortality may make it necessary to investigate COVID-19 mortality within primary health care services, considering the quality of secondary health care services. Because satisfaction with quality healthcare services is affected by the effectiveness of primary healthcare services and was found to be negatively correlated. No statistically significant relationship was found between the efficiency of secondary health care services and satisfaction with quality health care. It is seen that primary care is effective in the measurement of satisfaction with quality health care.

9. THE RELATIONSHIP BETWEEN THE EFFECTIVENESS OF PRIMARY HEALTH CARE SERVICES AND COVID-19 FATALITY

In a study by Rasella et al. to assess the impact of Brazil's Family Health Program (the largest primary health care program in the world) on mortality from heart disease and cerebrovascular disease between 2000 and 2009, coverage of the Family Health Program was found to be negatively associated with mortality from heart disease and cerebrovascular disease with and without accompanying demographic, social and economic components. As a control, the Family Health Program had no effect on mortality rates from accidents. Family Health Program coverage was

associated with increased health education activities, home visits and medical consultations, and a reduction in hospitalizations for heart disease and cerebrovascular disease (Rasella Postdoctoral Researcher, Harhay Phd Student, Pamponet Researcher, Aquino Associate Professor 1 2, & Barreto, n.d.). The study by Rasella et al. differs from our study in that the characteristics investigated were non-communicable diseases. In our study, there was no statistically significant difference between the effectiveness of primary health care services and COVID-19 fatalities. The effectiveness of primary health care services is negatively associated with the effectiveness of secondary health care services. This is similar to the findings in the study by Rasella et al. In Brazil, primary health care services reduced hospitalizations for heart disease and cerebrovascular diseases thanks to the Family Health Program.

In Macinko and colleagues' study of 30 years of data from 18 rich OECD countries, the impact of primary health care on variation in health outcomes was examined, and strong primary health care was found to be negatively associated with all-cause mortality, all-cause premature mortality, cause-specific asthma, bronchitis, emphysema, pneumonia, cardiovascular disease, and heart disease-related mortality (Macinko, Starfield, & Shi, 2003). In Macinko et al. study, unlike our study, 30-year data of 18 rich OECD countries were analyzed and strong primary health care services were found to be negatively associated with mortality and premature mortality. This difference may be due to the fact that the data were collected from 18 rich OECD countries and it is remarkable in terms of primary health care services.

10. RELATIONSHIP BETWEEN SOCIOECONOMIC FACTORS AND COVID-19 FATALITY

In 2020, Chaudhry et al. evaluated the impact of socioecenomic factors, country preparedness level and country health policies on COVID-19 mortality and related health outcomes, and found that increased COVID-19 caseload was associated with high obesity prevalence, age, long-term close contact. Increased mortality is significantly associated with high obesity prevalence, GDP. Reduced income inequality reduced COVID-19 cases and mortality. The association of prevention of close contact, full quarantine practices and prevalence of COVID-19 testing with COVID-19 mortality is not statistically significant. However, full quarantine and decreased country susceptibility to biological threats are associated with increased patient recovery rates (Chaudhry, Dranitsaris, Mubashir, Bartoszko, & Riazi, 2020).

In a study conducted by Hashim et al. in 93 countries in 2020, 8 diseases (asthma, lung cancer, chronic obstructive pulmonary disease, Alzhei-

mer's disease, hypertension, ischaemic heart disease) affecting COVID-19 mortality; 6 sociodemographic factors (GDP, unemployment, population over 65 years of age, urbanisation, population density and sociodemographic index). In bivariate analysis, COVID-19 mortality was found to be associated with Alzheimer's disease, lung cancer, asthma and COPD (chronic obstructive pulmonary disease). In multivariate modelling, COVID-19 mortality is associated with Alzheimer's disease, COPD, depression and high GDP (Hashim, Alsuwaidi, & Khan, 2020).

In our research findings, there is no statistically significant relationship between GDP figures and COVID-19 fatality rates. These findings support the notion, articulated in the "closing the quality gap" report published in the United States, that the high costs are not always associated with high-quality care. While wealthy countries allocate a greater share of GDP to healthcare services, this does not necessarily correlate with high-quality health outcomes or reduced fatality rates. The increased use of resources and the high number of tests conducted have led to increased costs.

In studies conducted by Chaudhry and Hashim, unlike our research, a high GDP has been associated with high COVID-19 mortality rates. The main reasons for this include widespread testing in high GDP countries, widespread infectivity, robust surveillance and reporting systems, air transportation, and increased travel opportunities to wealthy countries ("Coronavirus Disease (COVID-19) Situation Reports," n.d.).

Studies by Almazan and Backer have identified poverty, limited access to healthcare, and social vulnerability as determinants of COVID-19 mortality. Increased income inequality exacerbates COVID-19 mortality. While COVID-19 mortality appears higher in countries with high GDP, this may be attributed to the difficulty of detecting COVID-19 cases due to inadequate testing in poor countries.

In our research findings, as GDP increases, the effectiveness of secondary healthcare services and the number of computed tomography devices increase. It can be said, based on these findings, that investment is made in quality improvement in high GDP wealthy countries. However, the positive correlation between the number of computed tomography devices and GDP suggests that the high allocation of GDP to healthcare spending in high GDP wealthy countries can be evidence. The insignificant relationship between the number of computed tomography devices and the quality of secondary healthcare services indicates that the resources spent do not contribute to the quality of secondary healthcare services but rather increase satisfaction with healthcare services.

11. HEALTHCARE WORKFORCE AND COVID-19 FATALITY RELATIONSHIP

A study conducted in the UK by Griffiths and colleagues examined the relationship between nurse numbers and mortality, considering doctor numbers and other healthcare personnel. It was found that an excess of patients per nurse and doctor was associated with increased mortality. While significance persisted for doctors and other healthcare personnel in the multivariable model, significance for nurse numbers was lost (Griffiths et al., n.d.).

In another study in the UK by Bray and colleagues, the relationship between healthcare worker working hours and mortality of patients admitted to stroke centers was investigated. No significant difference was observed in stroke risk between periods when stroke specialists worked throughout the week and when they worked only on weekdays. The highest death rates were observed with the lowest nurse-to-patient bed ratios. In multivariable analysis, mortality was higher in patients admitted to stroke centers on weekends with a nurse-to-patient bed ratio of 1.5 compared to patients admitted when the ratio was 3 (Bray et al., n.d.).

In another study conducted by Griffiths and colleagues in the UK, they examined the relationship between the number of daily nurses and nurse assistants and hospital mortality. It was found that mortality increased by 3% on days when the number of nurses was below average. For every extra hour of nursing care above average, a 3% decrease in mortality was observed. Increased mortality was observed on days when admissions per nurse exceeded the average by 125%. Decrease or increase in the number of nurse assistants is associated with increased mortality [36].

In a study conducted by Kim and colleagues in 23 countries, the social and political determinants of COVID-19 were investigated. It was observed that an increased number of doctors and healthcare personnel per capita were associated with a decrease in COVID-19 mortality and fatality. Restrictive policy measures, such as preventing people from gathering, led to a decrease in COVID-19 mortality. The elderly population, income limitation, and a shortage of healthcare workers were associated with high morbidity and mortality. In this context, it is emphasized that various social and political determinants should be considered when determining COVID-19 policies (Kim et al., 2022a).

In our research findings, the relationship between the number of doctors and nurses per capita and COVID-19 fatality is not statistically significant. As GDP increases, the number of nurses also increases. This may provide evidence for increased healthcare spending in wealthy countries and expenditures aimed at increasing satisfaction with healthcare services.

The number of computed tomography devices can also be considered in this context. In the study by Griffiths and colleagues, the impact of hospital doctors on inpatient mortality was discussed, and an increased number of doctors was found to be associated with decreased mortality. A shortage of nurses was found to be associated with high mortality. However, in our research, since primary healthcare services and secondary healthcare services were evaluated as a whole, it may not have been statistically significant. Additionally, median age and the number of computed tomography devices were positively correlated with the number of doctors. The allocation of healthcare spending from GDP is in this regard for doctor numbers.

12. HOSPITAL BED COUNT, MEDIAN AGE, AND COVID-19 FATALITY RELATIONSHIP

In a study conducted in China by Tian and Pan, it was found that strong government initiatives directed improvements in maternal health. Between 2004 and 2016, the maternal mortality rate decreased from 48.3 per 100,000 live births to 19.9 per 100,000 live births. The number of hospital beds per 1000 people, which was 2.28 in 2004, increased to 4.54 in 2016. Regression modeling revealed a negative relationship between the number of hospital beds and maternal mortality rates. Sufficient investment in healthcare system reforms, including increasing the number of hospital beds, played a driving role in achieving such progress. Increasing the number of hospital beds contributed to a steady reduction in inequalities in the distribution of hospital beds. It was emphasized that addressing the inequality in the geographic distribution of hospital beds contributed to reducing maternal mortality rates (Tian & Pan, n.d.).

In a retrospective study conducted in the USA by Castagna and colleagues, the clinical characteristics, treatments, and outcomes of patients admitted due to COVID-19 between March 2020 and February 2021 were analyzed. The inpatient mortality rate decreased from 25% in March 2020 to approximately 10.8% towards the end of the year. During this period, the use of remdesivir, steroids, and anticoagulants increased, while the use of hydroxychloroquine and other antibiotics decreased. The daily hospital bed occupancy rate ranged from 62% to 118%. In a multivariable model, an increased hospital bed occupancy rate was found to be associated with increased 30-day inpatient mortality among COVID-19 patients after controlling for demographic characteristics, comorbidities, and acute illnesses (Castagna et al., 2022).

In our research findings, like studies conducted in China and the USA, it is observed that the number of hospital beds has a negative impact on fatality. As the availability of hospital beds and hospital capacity increases, COVID-19 deaths decrease. Considering the positive correlation be-

tween the number of hospital beds and intensive care unit (ICU) beds, an increased number of hospital beds in secondary healthcare services may lead to increased ICU demand alongside prolonged survival times. When considering the positive correlation between median age and the number of hospital beds, the picture becomes clearer, as an increase in age may lead to an increased disease burden and thus an increased need for hospital beds.

In a retrospective cohort study conducted by Abuhasira and colleagues in 2022 in the USA, Australia, and Israel, an increase in ICU admissions among elderly individuals was noted, but the benefits of this were uncertain. It was analyzed whether non-restrictive ICU admissions were associated with increased survival times. Individuals aged 80 and above who were admitted to ICUs were included in the study, and data were collected from three countries independently of ICU capacity and admission indication from 2006 to 2015. In-hospital mortality and discharge were referenced at 6, 12, 18, and 24 months. ICU admission rates were recalculated in the model relative to the USA, with rates determined as 67.6% in the USA, 22.1% in Australia, and 6% in Israel. In-hospital mortality rates were found to be 52.3% in Israel, 29.8% in Australia, and 22.1% in the USA. The two-year post-discharge survival rates were 52% in the USA and Australia, and 48% in Israel. As a result, in the study, it was found that ICU admissions among individuals aged 80 and above increased relative to in-hospital survival rates, but similar two-year post-discharge survival rates were observed (Abuhasira et al., 2022).

According to a study conducted by Fuchs and colleagues in Israel, increased ICU capacity was associated with an increased ICU admission rate in the elderly population, but no increase was observed in one-year survival (Fuchs et al., 2012).

The relationship between intensive care unit (ICU) capacity surpassing and mortality was investigated in a cohort-type research modeling conducted by Bagshaw and colleagues in Canada, focusing on patients applying to the intensive care unit. Surpassing capacity was defined as having an intensity of over 95% and less than one available bed. The relationship between intensity and disease severity was examined taking into account ICU length of stay and mortality rates. The intensity percentage was found to be 22.3%, with 17% of admissions identified. Low ICU bed availability (surpassing capacity) was found to be associated with high disease severity (high APACHE II score). When the number of beds was found to be below one, mortality was 11.6%. ICU unit intensity is associated with shortened ICU stays. The primary driver of this is disease severity (Bagshaw et al., 2018).

In our study findings, the relationship between intensive care bed numbers and COVID-19 fatality is not statistically significant. In a retrospective cohort study conducted by Abuhasira and colleagues, increased ICU admissions in individuals over 80 years old did not affect 2-year post-discharge mortality but only increased in-hospital survival. This result is similar to our study. Increased ICU bed numbers do not reduce COVID-19 mortality. The positive correlation between ICU bed numbers and hospital survival can be attributed to increased in-hospital survival. In a study by Fuchs in Israel, increased ICU capacity was shown to be associated with increased ICU admissions but did not result in increased one-year survival. In the study by Bagshaw and colleagues conducted in Canada, low ICU bed availability was found to be associated with high disease severity. Additionally, ICU unit intensity is associated with shortened ICU stays due to disease severity. Considering all these findings, an increase in ICU capacity leads to increased ICU admissions but a decrease in capacity leads to increased disease severity. Increased mortality associated with disease severity is correlated with increased ICU intensity. As our research also found, an increase in ICU unit capacity is not associated with decreased COVID-19 mortality.

13. EDUCATION AND COVID-19 FATALITY RELATIONSHIP

In a study conducted by Buckles and colleagues in the United States, behaviors of attending college to avoid military service during the Vietnam War were investigated to examine the impact of higher education on adult mortality rates. The results indicated that increasing college enrollment from 25% at the state level to 75% would decrease the cumulative death rate for subjects in the sample by 8% to 10% compared to the average mortality rate. The decrease in mortality is primarily attributed to deaths related to cancer and heart disease. Differential gains and health insurance were seen as potential mechanisms influencing this relationship. Mortality decreases by a factor of 2.21 with increased education (Buckles, Hagemann, Malamud, Morrill, & Wozniak, 2016).

Lacroix and colleagues investigated how attending university in Canada would affect death, healthcare consumption, and life expectancy. They found a 39% decrease in mortality rate for ages 51-96, a 10-15% decrease in diabetes, and a 5% decrease in stroke. Additionally, they found a 27.3% decrease in lifelong hospital stays and a 19.7% decrease in consultations with specialists. It was found that education primarily affects mortality by delaying the onset of diseases and managing them effectively (Lacroix, Laliberté-Auger, Michaud, & Parent, 2021).

A cohort study representing the US population from the National Longitudinal Mortality Study (NLMS), consisting of over 400,000 men and

women aged 25-64, was followed for mortality rates between 1979 and 1989. Education and income were compared with mortality. The results from the study, while showing the relationship for both variables is not linear, indicated that education is significantly better defined, both for men (according to a simple linear function) and for women. To explain the relationship between income and mortality rate, it was found that the decrease in mortality rate associated with a $1000 increase in income is much larger in incomes below $22,500 compared to incomes above $22,500, suggesting a two-sloped function rather than a linear one. This is valid for both men and women. Different shapes for the two functional forms suggest that differences in mortality rates may primarily be a function of income at the lower end of socioeconomic continuity, but primarily a function of education at the upper end (Backlund, Sorlie, & Johnson, 1999).

In our study findings, the relationship between the percentage of education (rate of college graduates) and COVID-19 fatality is not statistically significant. Contrary to studies conducted in the US and Canada, education has been found to reduce mortality. However, COVID-19, due to its contagious nature, may differ. The lack of significance of education on COVID-19 fatality could be attributed to this. Considering occupational differences and income status, and the lack of significance in the relationship between GDP and COVID-19 fatality, the absence of an education-related effect on COVID-19 fatality can be explained. Additionally, in our research, educational status was found to be statistically negatively correlated with median age. Given that a younger and more dynamic population may engage more in educational activities, while the median age is higher, the negative correlation is clear, reflecting limited educational opportunities for an aging society. Educational status is positively correlated with GDP.

14. AIR POLLUTION AND COVID-19 FATALITY RELATIONSHIP

Dockery and colleagues investigated the relationship between air pollution and mortality in six US cities, and controlled analysis was conducted for individual risk factors in the study. A prospective cohort study of mortality over 14-16 years was conducted in 8111 adults. Mortality was found to be most strongly associated with smoking. In controlled analysis for smoking and other risks, a statistically significant and strong relationship was found between air pollution and death rates. The adjusted mortality ratio for the most polluted cities compared to the least polluted cities was 1.26 (1.08 to 1.47). Air pollution was found to be positively associated with death from lung cancer and cardiopulmonary disease, but not identified as associated with death due to other presumed causes. The death rate

was found to be most strongly associated with fine particulate air pollution, including sulfates (Nejm199312093292401, n.d.).

In a study conducted by Travaglio and colleagues in the UK, it was emphasized that connections between air pollution and mortality rates have been identified in recent COVID-19 studies, and potential links between major air pollutants related to fossil fuels and SARS-CoV-2 mortality rates in the UK were investigated. Publicly available databases of SARS-CoV-2 cases and deaths were compared with regional and subregional air pollution data monitored at various sites in the UK. Controlled analysis was conducted for population density, age, and median income, revealing positive relationships between air pollutant concentrations, particularly nitrogen oxides, and both COVID-19 mortality rates and transmissibility. Using detailed UK Biobank data, it was shown that a 1 μg/m3 increase in PM2.5 in long-term average is associated with a 12% increase in COVID-19, and PM2.5 was also shown to make a significant contribution to COVID-19 cases in the UK. The relationship between air pollution and COVID-19 was found to depend on temporal evaluation scales (annual and 5-year averages) and remained significant in controlled analysis for socioeconomic, demographic, and health-related variables. A small increase in air pollution was concluded to lead to a significant increase in COVID-19 transmission and mortality rates in the UK. It was emphasized that this study provides a framework to guide both health and emission policies in countries affected by the pandemic (Travaglio et al., 2021).

In our findings, the relationship between air pollution (deaths attributable to air pollution per 100,000 population) and COVID-19 fatality is not statistically significant. In contrast to studies conducted in the US and the UK, it has been found that air pollution increases mortality. When interpreting these data, the effect of air pollution on the transmissibility and disease burden of COVID-19 should also be considered. It can be predicted that air pollution exacerbates disease transmission and symptoms in terms of COVID-19 fatality. Among our findings, there is a statistically significant negative relationship between GDP and air pollution. Low levels of air pollution-related deaths are observed in high-income countries with high GDP. The statistical significance of this situation could be considered masked.

15. CONCLUSION

In our study, as the effectiveness of secondary healthcare services and the number of hospital beds for patients increase, COVID-19 fatality decreases. There is no relationship between other health indicators, demographic indicators, and COVID-19 fatality. Additionally, GDP is positively correlated with the effectiveness, i.e., quality, of secondary healthcare ser-

vices. However, no relationship was found between satisfaction with quality healthcare and COVID-19 fatality. This is because satisfaction with quality healthcare is associated not with the effectiveness of secondary healthcare services but with the effectiveness of primary healthcare services. There is no relationship between the number of doctors and satisfaction with quality healthcare, whereas as the number of nurses and computed tomography devices increases, satisfaction with quality healthcare also increases.

16. COMMENTS AND RECOMMENDATIONS

In pandemics such as COVID-19 that impose a burden on the healthcare system, second-level healthcare services have been found to be effective and play an important role in reducing fatality rates in terms of quality. The importance of primary healthcare services in the spread and prevention of epidemics is significant, and the lack of determination of its impact on fatality in this pandemic suggests the necessity for adjustments in primary care. Additionally, as outlined within the framework of building blocks proposed by the World Health Organization, interim strategies aimed at improving health and achieving ultimate goals for the healthcare system can be listed as quality, safety, accessibility, and inclusiveness. Quality, among these interim strategies, is evaluated through satisfaction surveys and is often seen to have an effect on satisfaction with healthcare services when primary healthcare services are effective. However, in our study, due to the lack of statistical significance in the relationship between COVID-19 fatality and satisfaction with quality healthcare services, a model that considers local second-level healthcare systems and acknowledges the effective role of inpatient treatment services in measuring satisfaction with quality healthcare services in relation to COVID-19 fatality can be developed.

When the effectiveness of second-level healthcare services is evaluated, the number of hospital beds has a negative impact on COVID-19 fatality. Increasing hospital capacity for current and future potential COVID-19-like pandemics and conducting advanced studies in this regard are necessary.

The relationship between GDP and COVID-19 fatality was not statistically significant. GDP growth does not lead to a decrease in COVID-19 fatality, and in some studies, an increase in GDP has been found to increase COVID-19 fatality. However, in our study, a positive relationship was found between GDP and the effectiveness of second-level healthcare services. This underscores the importance of resource allocation in enhancing healthcare quality and achieving the ultimate goals of the healthcare system.

Considering that the relationship between the number of doctors and nurses and COVID-19 fatality is not statistically significant, the distribution of healthcare workers may be more important than the number of doctors and nurses. The importance of healthcare workers, especially within inpatient treatment services, in enhancing healthcare quality is noteworthy. Increasing the number of nurses rather than doctors may be more important for enhancing healthcare quality. Therefore, these studies are also important for the development of effective models for healthcare workforce planning and cost-effectiveness.

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