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Review Article

Fatty liver disease, risks, strategies, and its relationship with COVID-19 with an emphasis on nutrition and exercise: A narrative review

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Abstract

The COVID-19 epidemic has caused lifestyle changes in people from all walks of life and has become a global threat to the health and well-being of all countries of the world. Considering changes caused by the prevalence of the disease and quarantine conditions, the increased likelihood of the prevalence of overweight and obesity in people is among these threats. On the other hand, patients with overweight and obesity, and consequently, non-alcoholic fatty liver disease (NAFLD) have a weaker immune system than other people with ideal weight, and as a result, are more likely to develop COVID-19. As there is currently no definitive treatment for COVID-19 and NAFLD, and because people with NAFLD are more likely to develop COVID-19 based on the research in this area, paying attention to this important issue is thus necessary. Considering a regular physical activity program and having a balanced diet are among the essential strategies and may help prevent NAFLD, and consequently, COVID-19. However, given the novelty of COVID-19 pathogen and the ambiguity of the exact cause of why people get NAFLD, further research is needed to be done on the type of effective diet, as well as the type, intensity, and volume of exercise for these people. This study aimed to summarize the available evidence on the pathology and epidemiology of NAFLDs and COVID-19, as well as the effect of NAFLD on COVID-19 in people. Given the existing risks, the nutrition and exercise strategies were investigated in this regard.

Key Words: **COVID-19, NAFLD, Lifestyle, Exercise, Nutrition**

Introduction

Corona virus became prevalent in December 2019. The disease originated at Wuhan city of China, the capital of Hubei Province, and soon spread rapidly and engaged individuals and health organizations. Then the novel coronavirus, COVID-19, spread all around the world. At the beginning of the disease outbreak, the China's government decided to quarantine Wuhan city to prevent the disease from becoming epidemic, and this decision led to the cancellation of all flights to and from Wuhan and the evacuation of non-native individuals. The fear of the disease and the disease transmission then raised among the people because some people initially thought that this virus would stay in the air for a long time. Naturally, rumors spread so quickly in such an atmosphere, and this caused more anxiety and concern per se. Here we needed a global solidarity and accompaniment of people to overcome and defeat this disease. COVID-19 spread increasingly around the world until finally on 11 March that the head of the World Health Organization described corona as a pandemic disease and the world entered a new phase to fight it (Pakzad & Owlia, 2020). According to the global count statistics of coronavirus, by February 7, 2021, the SARS-CoV-2 virus has infected more than 106 million people worldwide, of which more than 2.3 million have died. In Iran, about 1470 people have been infected and there have been about 58500 deaths registered and this number is increasing every moment. This is while these figures and numbers are probably higher due to lack of testing, test errors and other factors. Currently, there is no approved therapeutic method for COVID-19, however, very simple but practical preventative strategies such as quarantine, social distancing, observing public health and using facial masks are the best methods to reduce COVID-19 outbreak.

The World Health Organization (WHO) describes it as worrying that there is lack of regular physical activity and lifestyle changes during quarantine, and considers it as one of the causes of the increased mortality in this period and even in the coming years of life. In the quarantine situation caused by COVID-19, the nutritional balance of the people's diet is disturbed due to less mobility and more access to various foods, and this imbalance will result in the increased risk

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of cardiovascular disease, diabetes, fatty liver, etc. NAFLD may be a risk factor for developing COVID-19. Moreover, obese people are among groups at high risk of getting this disease. Evidence shows that people with body mass index (BMI) above 30 are more likely to develop COVID-19 than people with ideal weight and scale. Therefore, by losing weight and boosting the immune system through regular physical activity and a healthy diet, as a useful solution, an effective step can be taken to prevent people from getting COVID-19 and NASLD. Recent evidence has shown that a healthy lifestyle can play a supportive and preventive role for COVID-19 patients (Barikani & Pashaeypoor, 2019; Shakoor et al., 2021; Shirvani & Rostamkhani, 2020).

COVID-19 disease

In late December 2019, a novel pneumonia case was reported in Wuhan city of China in Hubei Province whose clinical characteristics were very similar to those of viral pneumonia. The WHO and the International Committee for the Classification of Viruses (ICTV) named the virus COVID-19 and SARS CoV-2, respectively. This virus belongs to the β-coronavirus family that are prevalent in nature and like other viruses have many potential natural hosts, which act as intermediate hosts or final hosts. This issue poses major challenges for the prevention and treatment of COVID-19. The initial genome analysis of this virus confirmed that it shares the closest homology to bat SARS coronavirus (SARSr-CoV-RaTG13). Therefore, it was hypothesized that COVID-19 may have been transmitted from bats to humans (L. Wang et al., 2020; Xu et al., 2020). Coronaviruses are among single-stranded, enveloped RNA viruses with a 120–80 nm diameter. They are classified into four groups: Alpha, Beta, Delta, and Gamma coronaviruses. Prior to the identification of COVID-19, only six types of coronaviruses could infect humans, and COVID-19, a member of the beta-coronavirus family, is the seventh type. Among these viruses, four coronaviruses: HCoV- 299 E, HCoV OC43, HCoV-NL63, and HCoVHKU1 are less pathogenic and cause only mild respiratory illness, but two coronaviruses: severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), which have been respectively transmitted from cats and camels to humans, led to two fatal epidemics. Meanwhile, the homology and pathogenesis mechanism of SARS-CoV is very similar to that of COVID-19 (Figure 1). Due to COVID-19 virus adaptation to bat body, which has a higher temperature than human's, this virus is more resistant to temperature than SARS- CoV (Chan et al., 2013; He et al., 2020 Chan et al., 2013; He et al., 2020). COVID-19 uses the human angiotensin-converting enzyme 2 (ACE2) receptor and infects the cells with ACE2 (Figure 2). The ACE2 receptor is abundant in the lung, heart, kidney, intestine, and blood vessels cells. Because of the high affinity between ACE and COVID-19, the number of viruses infecting cells is more than other coronaviruses. ACE 2 protein also affects the physiology and pathology of the reproductive system, including the testicles and ovaries. This way COVID-19 affects sperm production, lowers the sperm count, affects the production of sex hormones, and can lead to decreased libido (Ding et al., 2017; Ganji et al., 2020; Segars et al., 2020).

What is Angiotensin-converting enzyme 2 or ACE2?

It is an enzyme attached to the cells' outer surface in the lungs, blood vessels, heart, kidneys and intestines. This enzyme lowers blood pressure by breaking down angiotensin 2 (a vasoconstrictor peptide) into angiotensin 7-1 (a vasodilator). ACE2 is the entry point of some types of coronaviruses to hook into the body cell. The human ACE2 is called hACE2. ACE2 function is the opposite and counter point of angiotensin-converting enzyme (ACE), and because it reduces angiotensin 2 and increases angiotensin 1-7, it is one of the future promising therapies for cardiovascular diseases. ACE2 is a transmembrane protein and the main point of entry to host cells for some types of coronavirus, such as human coronavirus SARS-CoV (the cause of SARS), and SARS-CoV-2 (cause of COVID-19). Decreased levels of the ACE2 enzyme in the cell are thought to be helpful in fighting this infection. But on the other hand, the presence of ACE2 enzyme protects the lung cells from damage caused by the virus by increasing the level of the vasodilator "angiotensin 1-7". In addition, based on studies on mice, viral spike/ACE2 interaction decreases the amount of this enzyme in the cell and increases damage to lungs (Khanizadeh et al., 2020; Saeidi et al., 2020). The most common clinical symptoms of COVID-19 infection include fever (9.87%), cough (7.67%), and fatigue (1.38%), while diarrhea (7.3%) and vomiting (5.0%) are rare. From this perspective, it is similar to other coronaviruses of animal origin.

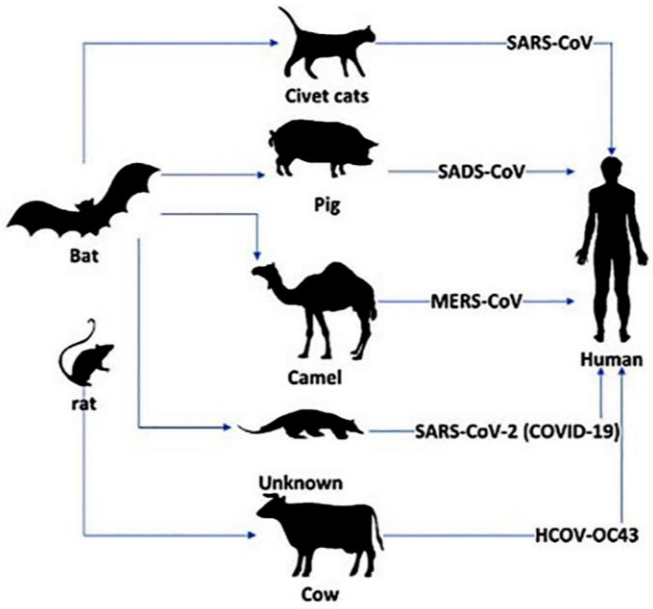

Figure 1. Animal origin of human coronavirus (Ganji et al., 2020)

Acute respiratory distress syndrome (ARDS) occurs about 9 days after the onset of infection. In addition to the lungs, the virus damages other tissues, including the heart, kidneys, liver, eyes, and nervous system (Yang et al., 2020). Dizziness, forgetfulness, weakening and disappearance of smell and taste power, and nerve pain to seizures and strokes are among the neurological symptoms of this virus, which are related to hypoxia and brain inflammation. Brain inflammation can be indirectly caused by a cytokine storm (autoimmune encephalitis) or directly by a broken blood-brain barrier (BBB) by a virus (viral encephalitis) (Filatov et al., 2020; Ye et al., 2020). Extensive genetic diversity and frequent recombination of the coronavirus has increased its interspecies transmission. Direct contact and respiratory droplets are the most common virus transmission method in society. The average incubation period is 3 days (with a range of 0 to 24 days) and the average time from symptom onset until death is 14 days (Xu et al., 2020; Zhou et al., 2020). High temperature, low or high pH and sunlight reduce the virus count. The survival rate of the virus varies on different surfaces from 2 hours to 9 days. Factors affecting the survival of the virus include surface type, temperature and relative humidity. Common disinfectants, such as ethanol 70% and hypochlorite 0.1% kill the virus in one minute. Asymptomatic carriers play a key role in the person-to-person transmission of the disease. There is limited information on the asymptomatic carriers. People younger than 15 years constitute a significant percentage of these carriers. Clinical signs and CT scans do not help much in diagnosing asymptomatic carriers, and the best way to diagnose them is Real Time (PCR) test because most of them have no clinical signs and have a normal CT image (Bai et al., 2020; Organization & (UNICEF), 2020).

Liver as an organ

The liver is a large organ in vertebrates which is located in the upper quadrant of the abdomen, below the diaphragm. As most of the com-

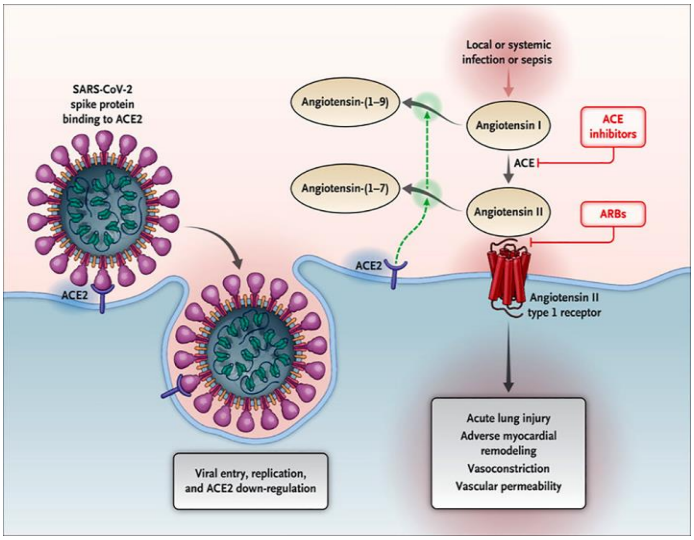

Figure 2. COVID-19-ACE2 receptor interaction (Ganji et al., 2020)

-pounds absorbed by the intestine pass through the liver, this organ acts as the body's control center, which integrates different metabolic processes, as well as regulates the process of receiving and sending fuel molecules (such as carbohydrates, fats, and proteins used in energy metabolism) in the body. Liver cells are called "hepatocytes", making up about 60% of liver tissue. They participate in metabolic and secretory functions. The second group of liver-related cells includes cells called "Kupffer cells," also known as stellate macrophages, which control vascular networks. Their main task is to recycle red blood cells that are no laonger functional. They also play a key role in the hemoglobin degradation process and the separation of heme iron from them. One of the other important functions of the liver gland is bile secretion. Bile is an alkaline compound that helps with fat digestion. The liver is responsible for about 500 functions in the body. Other functions of the liver include the synthesis of blood clotting agents, the excretion of waste products and other cellular toxins, elimination of worn-out red blood cells, metabolism of carbohydrates, fats, and proteins, blood sugar supply, cholesterol synthesis, lipoproteins synthesis, non-essential amino acids synthesis, etc (Ammar, 2018; Hall, 2016).

Liver diseases jaundice, fatty liver disease (alcoholic fatty liver and non-alcoholic fatty liver), hepatitis, fibrosis, liver cirrhosis, Gilbert's syndrome, hemochromatosis, and type II glycogen storage (Hall, 2016).

Non- alcoholic fatty liver disease (NAFLD)

NAFLD refers to the accumulation of fat in the liver (more than 5% of liver weight) in the absence of excessive alcohol consumption. The disease includes a spectrum ranging from steatosis (fat infiltration to the liver) to steatohepatitis (liver cells inflammation and damage) followed by liver fibrosis, and eventually, cirrhosis (Figure 3). Currently, NAFLD is regarded as one of the most common causes of chronic liver disease in the young population both in developing and developed countries. NAFLD and obesity have been estimated to be the most important cause of death from liver disease and NAFLD by 2030. NAFLD prevalence is associated with several factors, such as age, gender, ethnicity, and presence of sleep apnea. Additionally, there is a robust relationship between NAFLD and obesity, insulin resistance, Type II diabetes and metabolic syndrome. Negative changes in lifestyle over recent decades have caused an increase in obesity in the population. NAFLD prevalence is increasing in parallel with obesity. This amount is reported to be 54.4% in Iran. In a study, the prevalence of NAFLD in obese people was 80%, while this rate is reported to be 16% in those with normal BMI. In addition, it is stated that more than two-thirds of people with diabetes developed NAFLD (Ammar, 2018).

One of the simplest and cheapest indicators of liver damage intensity is measuring the levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphate (ALP) enzymes. Level of these enzymes greater than twice its natural rate is a sign

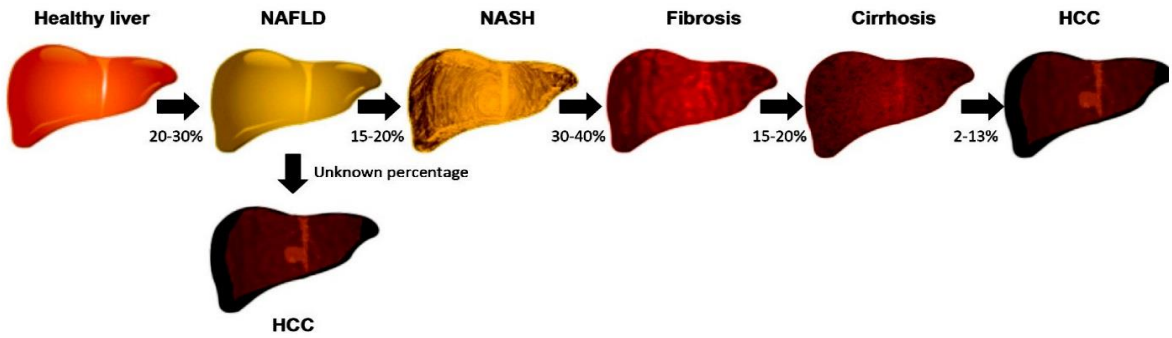

Figure 3. NAFLD stages. The appearance of the liver at different stages of the disease schematically shows the physical changes occurred with the progression of the disease. The percentage of patients progressing from one stage to the next is shown below the arrows. NASH: non-alcoholic steatohepatitis. HCC: Hepatocellular carcinoma (Hanson et al., 2018).

of fatty liver disease. In the acute stages, an ultrasound of the liver is prescribed. In this stage the physician examines the extent of enlargement of the liver occurring as a result of liver inflammation. Weight loss and exercise seem to be the first line of treatment for fatty liver disease and the reduction of these enzymes. The regular exercise has been reported to play a positive role against liver injury, reduction of injury inflammation, and liver fibrosis (Fabbrini et al., 2010). Obesity is on the other hand defined as a disorder in the body's physical composition in the form of a relative or absolute increase in the amount of adipose tissue. This condition is the result of a complex interaction between environmental factors, genetic predisposition, human behavior, and human lifestyle. Obesity is known to be associated with a diverse spectrum of functional and hormonal disorders leading to progression to insulin resistance and dyslipidemia, finally resulting in metabolic syndrome, NAFLD, and increased morbidity and mortality. Different research studies suggest that this obesity-induced mild inflammation may lead to long-term complications such as insulin resistance (and, as a result, metabolic syndrome), endothelial dysfunction, and atherosclerosis. Moreover, it is considered a key mediator of steatohepatitis in animal samples. In other words, the adipose tissue of the human body is not only a place to store excess energy, but also an active endocrine organ that is known to generate a number of active proteins, including CPR, TNFα, IL-6, IL1β, IL-8, leptin, tumor. The hepatic manifestation of metabolic syndrome, in other words, fatty liver, embraces a wide range of clinical and pathological conditions from simple steatosis and steatosis with non-specific inflammation to NASH, and can progress to cirrhosis of the liver. The prevalence of NAFLD in the general population is estimated to be 25% and greater among obese people. Considering the importance of these inflammatory and proinflammatory factors in the pathogenesis of fatty liver, different studies have investigated the possibility of stopping this process, strategies to reduce these factors, and factors affecting them (Somi et al., 2017). The importance of this study is in investigating the nutritional behaviors, physical activity, and smoking as risk factors for fatty liver disease, which can be modified mainly via training interventions. Generally, determining modifiable risk factors for the prevention and treatment of fatty liver is of importance in reducing the outbreak of this disease. Accordingly, a combination of educatio--nal, behavioral and motivational strategies is necessary to change patients' lifestyles. This issue requires the cooperation of a team of psychologists, nutritionists and professionals in sport. Design and implementation of educational programs with the aim of enhancing public awareness about the risk factors for the disease outbreak in infected and non-infected individuals, improving people's attitudes as a facilitating factor for healthy eating behaviors, and empowering people to adopt a healthy lifestyle may lead to the improvement of nutritional habits, and consequently, BMI, and increase the activity level and reduce cigarette consumption, and be effective in preventing or causing new cases of this disease, and canthus to some extent prevent the exacerbation of COVID- 19 disease (Barikani & Pashaeypoor, 2019).

COVID-19 and its relationship with fatty liver

The liver can be a target of COVID-19 infection. Though major liver damage is not common, this virus may directly affect the liver (e.g., virus transmission from the gut to the liver) or indirectly (e.g., systemic inflammation, liver ischemia and hypoxia, effects on previous liver diseases, drug-related liver injury) and poses a new challenge for hepatologists. It should be noted that NAFLD is a chronic metabolic pandemic which has reached its highest rate of outbreak (Marhl et al., 2020; Portincasa et al., 2020). The common liver diseases in the world are prevalent in the Western population with a prevalence rate of 30%. Additionally, NAFLD does not exist by its own but it is usually associated as "satanic fellow traveler" with a set of risk factors, metabolic syndrome and illnesses (Figure. 4). In addition to this perspective, the acronym NAFLD has been recently revisited by the acronym MAFLD "metabolic dysfunction-associated fatty liver disease". NAFLD/MAFLD can thus influence the final result in COVID-19-infected patients. Moreover, the liver itself has increased sensitivity to drugs in case of chronic damage. In this setting, the existence of inflammatory pathways (especially those that involve cytokines) in patients with NAFLD and COVID-19 may

increase liver inflammation or be a sign of metabolic risk factors worsening the clinical outcome. Due to the pandemic characteristics and high mortality rate of COVID-19 infection, accurate knowledge about the behavior of the virus and risk factors predisposing to the onset and progression of this disease plays an important role in the near future to predict virus-related events all around the world. In the analysis conducted by Wang et al, hypertension, diabetes, chronic obstructive pulmonary diseases (COPD), cardiovascular diseases and cerebrovascular diseases were independent risk factors related to patients with COVID-19. Ji et al. conducted a study on 202 COVID-19 infected patients and NAFLD status. They reported liver abnormalities in 50% and 75% of patients upon admission and within hospitalization period, respectively and manifested as hepatocellular pattern. From admission to the last follow-up, 33% of patients had abnormal liver function. The COVID-19 progression was associated with the male gender, age more than 60, high BMI, obesity, and NAFLD. Most studies have reported the increased level of liver enzymes in COVID-19 infected patients. It can be said that patients with NAFLD show a different risk of disease progression when they are infected by COVID-19 because they are at significant excessive metabolic risk. There are several injury mechanisms that can link COVID-19 to the liver and need to be considered (Figure 5).

1. Direct viral injury (virus transmission from the gut to the liver through Port blood flow). 2.Hypoxia in chronic liver diseases in patients with COVID-19 may cause an increase in expression of ACE2 receptors and hypoxia-inducible factors. Such changes may exacerbate metabolic diseases such as NAFLD. 3. Patients with severe COVID-19 showed increased inflammatory biomarkers such as C-reactive protein (CRP), serum ferritin, LDH, D-dimer, interleukin-6 and interleukin-2. Interleukin-6 in particular seems to be a key factor in the onset and progression of "cytokine storm" described in patients infected with COVID-19. Increased levels of this factor have been reported in patients with NAFLD. Cytokine MCP -1 often increases in patients infected with COVID-19 and acts as the further hit for steatohepatitis. Generally, it can be said that inflammation is a common neighbor of COVID- 19 and fatty liver. 4. Liver damage caused by various antiviral drugs as initial clinical guidelines suggested for COVID-19 infected patients; the presence of underlying metabolic abnormalities and NAFLD may exacerbate drug-induced liver injury. 5. Reactivation of pre-existing liver disease: patients who already have chronic liver disease may be more prone to liver injury caused by COVID-19. 6. Hepatic lipid metabolism: The production and degradation of lipid in the liver provide lipid species which worsen the status of chronic metabolic inflammation (Portincasa et al., 2020).

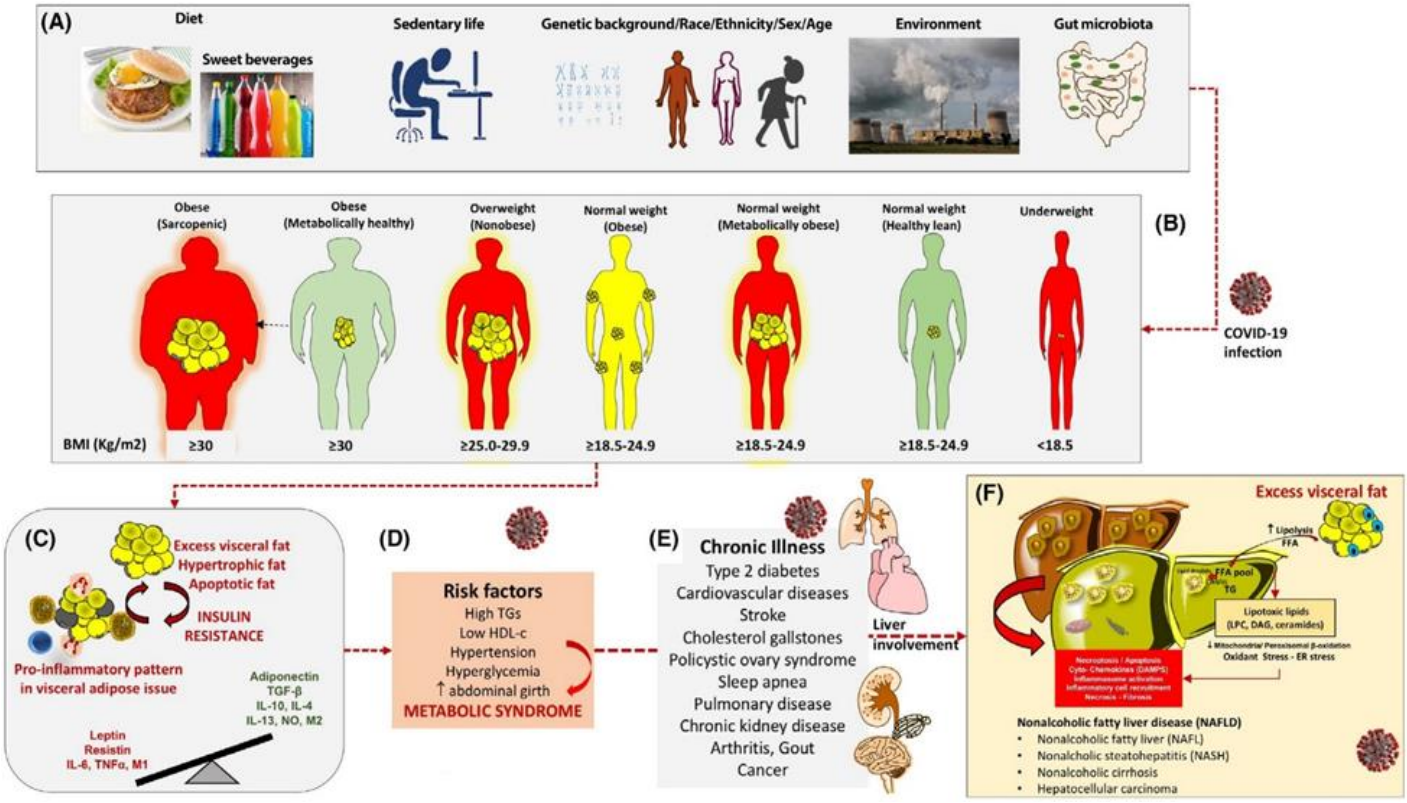

Figure 4. Sequences of pathophysiological mechanisms that are prone to metabolic diseases and hepatic steatosis. Possible description of multi-organ and liver injury during COVID-19 infection (Portincasa et al., 2020).

Despite lack of direct evidence indicating that in the acute phase of the disease, further liver injury happens in COVID-19-infected patients with pre-existing NAFLD, the common pathogenic mechanisms involved in COVID-19 and NAFLD can develop an increased risk of NAFLD progression to hepatitis in the long run in patients with COVID-19. In these patients, a follow-up with the aim of investigating the long-term outcomes of liver injury is thus needed. In fact, despite hopes for more specific therapies for COVID- 19 infection, namely vaccines, a rational approach toward future disease prevalence must embrace preventive measures like e.g., lifestyle changes to decrease the burden of chronic metabolic disorders, obesity, and proinflammatory conditions, and to preserve a healthy immune response. This result is supported by the emergence of the relationships between COVID-19 results and recurrent metabolic abnormalities (diabetes, hypertension, dyslipidemia, obesity) coexisting with NAFLD.

Finally, consider the following table 1, which shows the possible association between coronavirus and some underlying diseases.

Healthy lifestyle for NAFLD treatment

From the distant past, when Hippocrates announced interesting points in his treatise, the secrets of a physician's success, about paying attention to people's lifestyles, including physical activity, good nutrition, and clean water, until later when physicians found a relationship between infectious diseases and lifestyle, and now that the relationship between lifestyle and non-communicable and chronic diseases has been investigated and confirmed, all indicate the importance of lifestyle in health. WHO defines lifestyle as a combination of behavioral patterns and personal habits throughout

Table 1- Effect of different conditions and diseases on determining the probability of injury following infection with SARS CoV 2 virus, 2- High risk factors and diseases are shown in red, medium risk factors and diseases in orange, and Low risk factors and diseases in yellow (Khanizadeh et al., 2020).

Heart failure, such as cardiomyopathy	Asthma	*Bone marrow transplant*
Chronic kidney diseases	Cerebrovascular disease	AIDS
COPD	*Hypertension*	*Nervous system diseases*
(BMI≥30) Obesity	*Pregnancy*	*Liver diseases*
Sickle cell disease	*Smoking*	Thalassemia
Type 2 diabetes	Using drugs that weaken the immune system	*Hereditary metabolic disorders*

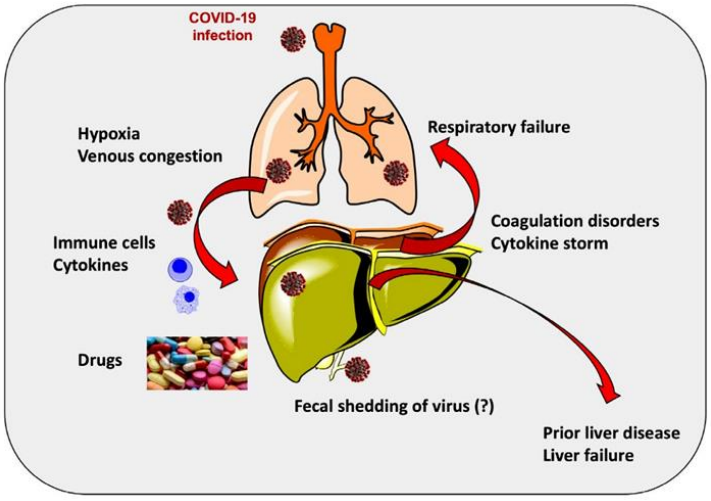

Figure 5. Factors include the involvement of the lung that leads to hypoxia and venous congestion caused by stasis of blood within the liver, contribution of immune cells and cytokines, drug-induced liver injury, and addition of coagulation disorders and cytokine storm. A pre-existing liver disease may exaggerate the injury caused by progressive COVID-19 infection (Portincasa et al., 2020).

life, including nutrition, exercise, smoking, sleep and rest, which have been formed following the process of socialization (Barikani & Pashaeypoor, 2019). Foods necessary for the body include: proteins, carbohydrates, fats, vitamins and minerals. This necessary and sufficient amount or nutritional requirements in different people differ from each other. Age, gender, the level of activity of the person, environmental conditions, and health or illness are among factors leading to these differences. Nowadays, industrial and urban life has caused overweight and obesity in many people of the society following changes made in lifestyle, such as reduced activity and consumption of high-fat ready-to-eat foods such that according to the WHO in 2014, 39 % of people aged 18 years and over were overweight and 13% obese. The other important component of a healthy lifestyle is having regular physical activity and exercise. Nevertheless, in spite of the many benefits of physical activity, most people of the world are sedentary. The estimated global adult physical inactivity is 17% and the average activity levels vary from 31% to 51% for less than 2.5 hours per week and its global average is 41%. Therefore, it can be said that only 1 in 4 people in the world have regular and desirable physical activity. Smoking cigarettes is one of the most important and preventable causes of premature death and disability worldwide. Of them, 4 million people, half of whom are below 70, lose their life annually due to smoking-related diseases, such as cancer, cardiovascular diseases, and respiratory diseases. According to the WHO predictions, this number will reach 10 million deaths each year by 2020. Considering the growing trend of chronic diseases in the world and the high prevalence of NAFLD in developed and developing countries and its devastating effects on the individual and society and the lifestyle importance in preventing

this disease and lack of systematic coherent studies on the dimensions of lifestyle based on the latest evidence, researchers decided to conduct studies aimed at determining the lifestyle associated with NAFLD to take a step to pay special attention to and plan for changing the lifestyle of high-risk groups and reducing the exorbitant costs of this disease in the future. In the treatment of NAFLD, it is important to note that no pharmacological drug has been so far discovered to treat these patients (Barikani & Pashaeypoor, 2019). As there is a long way to discover the best treatment for NAFLD, and extensive studies have not been done yet in this area (Jamali & Jamali, 2010), moreover, as there are limitations of drug treatments, such as increasing insulin sensitivity drugs, fat reducers, and antioxidants for fatty liver whose continued use is not recommended due to their high cost and side effects, lifestyle changes, including diet modification and physical activity thus play an important role for patients with NAFLD. In other words, losing weight and changing lifestyle together with diet and increased physical activity are often mentioned as the first strategy in the treatment of NAFLD, and in the meantime, sport exercises are one of the most important therapeutic factors for NAFLD such that American Gastroenterological Association has emphasized them (Keymasi et al., 2017; Nabizadeh Haghighi, 2016). Numerous studies have been done on lifestyle modification and its positive effect on fatty liver, and in all these studies, regardless of the type of exercise (aerobic, anaerobic, high-intensity interval training, resistance, strength) the main emphasis has been put on performing minimal-based-physical activities. The WHO recommends 60 minutes of regular physical activity each day for children and 150 minutes of regular physical activity per week for adults. They have also suggested calorie intake be limited and the right types of carbohydrates, fats, and vitamins be consumed (Dyson & Day, 2014; Morgan, 2016; Nseir et al., 2014). Numerous studies have suggested the benefits of a training program, but the type, intensity, and volume of exercise recommended for patients with NFLD has not yet been developed (Galedari & Kaki, 2017). Aerobic exercise violates this cycle by improving glucose control, fat oxidation via increasing glucose transport with glucose transporter 4 in the striated muscle, expression and activity of glycogen synthase enzyme in insulin receptors, glycogen storage in muscle and liver, increasing triglyceride synthesis in muscle cells, reducing the accumulation of fatty acid metabolites, and suppressing inflammatory state associated with insulin resistance. Moreover, resistance training reduces fat (body fat, visceral fat, and subcutaneous fat), and increases strength and muscle mass, insulin sensitivity, consumption potential for FFAs, basal metabolism, and consequently, the burning of body fat, and overall, lead to weight loss. On the other hand, another type of exercise, including combined exercises (aerobic and resistance) can help inhibit liver fat by increasing energy intake, improving fat oxidation, reducing subcutaneous fat and FFA flow to the liver (Aliniya et al., 2020). Considering the importance of sport exercises for the treatment of NAFLD, Kaki and Galedari (2017) stated in study that both resistance training and high-intensity interval training are appropriate training strategies to reduce ALT plasma concentration, lipid profile, insulin resistance and liver fat content (Galedari & Kaki, 2017). Moreover, in a study, interval and continuous sports activities were found to be accompanied by a significant increase in superoxide dismutase (SOD) and catalase enzymes performance, as well as the level of anti-inflammatory mediator interleukin 10 (IL-10) in liver tissue. On the other hand, the level of inflammatory mediator necrosis factor-α, lipid peroxidation rate and the number of liver apoptosis cells were significantly reduced (Mahdian et al., 2018). According to the evidence presented, it can be said that exercise is considered a robust stimulant for lipolysis of adipose tissue. In other words, performing high-intensity interval training (such as high-intensity interval exercises) and continuous training (such as aerobic exercise) can dynamically regulate the profile of immune cells in adipose tissue and activate the accumulation of M2 macrophages. This may present an important mechanism independent of the weight loss by which the exercise activates a desirable profile of immune cells in adipose tissue (Shirvani et al., 2018). In the following we present the physical activity guidelines provided by the American Association for the Study of Liver Disease (AASLD), The European Foundation for the Study of Diabetes (EFSD), and Korean Association for the Study of the Liver (KASL) as a solution to the severity, duration, and type of physical activity for patients with NAFLD (Table 2). Moreover, other studies conducted in this area are presented. But before that, we must mention the pivotal role of skeletal muscle in getting liver diseases and must state the role of regular physical activity in helping skeletal muscle.

Muscle-liver crosstalk in treating NAFLD

Multiple organ systems are involved in the pathophysiology of NAFLD, but so far, the role of skeletal muscles has not received extensive attention. The growing evidence has investigated the effect of skeletal muscles on insulin resistance and systemic inflammation, which has caused the muscle–liver axis to be in the center of NAFLD pathogenesis waterfall. Population-based studies show that sarcopenia is an effect moderator throughout the NAFLD spectrum that is extremely associated with the increased risk for NAFLD, NASH, and advanced liver fibrosis-which are independent of obesity and insulin resistance. Additionally, longitudinal studies indicate that an increase in skeletal muscle weight may both reduce the risk of NAFLD and improve pre-existing NAFLD over time. Unfavorable muscle composition, including low muscle mass and high muscle fat infiltration (myosteatosis) is highly prevalent in patients with NAFLD. The risk of functional impairment in NAFLD patients caused by low muscle mass is exacerbated with myosteatosis whose prevalence in NAFLD patients is two times high-

-er than that of liver chronic diseases. Studies show that sarcopenia is prevalent in people with cirrhosis and in obese people with an estimated prevalence of 40% and 70%, respectively. In a national research in Korea, more than 12% of all patients with NAFLD had obesity-independent sarcopenia and insulin resistance. On the other hand, up to 30% of sarcopenic individuals without metabolic syndrome and obesity had NAFLD. Therefore, the two-way muscle-liver axis seems to be capable of playing a significant pathological role in the entire spectrum of liver chronic diseases. Based on the conducted studies, the muscle–liver crosstalk is affected by several factors, such as obesity, lack of regular physical activity, vitamin D deficiency, ectopic fat deposition, oxidative stress, and proinflammatory mediators. For instance, lipotoxicity caused by excessive consumption of fatty acids (FA) can lead to ectopic fat deposition in various organs, namely the liver (hepatic steatosis) and skeletal muscles (myosteatosis). This condition is probably mediated by hepatokin and myokines. In this case, the skeletal muscle can play a causative role in NAFLD via the irregular secretion of different myokines against sarcopenia. In light of the above and based on the results of previous research, paying attention to regular exercise and physical activity is necessary, especially for skeletal muscles health and efficiency throughout life. Given the obtained evidence, aerobic exercise causes an increase in the insulin sensitivity of skeletal muscle and thus modulates insulin resistance. Moreover, like aerobic exercise, proper resistance training can increase insulin sensitivity and energy expenditure, and can improve quality of life. Additionally, these exercises can decrease basal levels of cytokines in the long term (Chakravarthy et al., 2020; Kazemi et al., 2017).

Paying attention to the stage of the disease is of paramount importance to modify the lifestyle aimed at losing weight and increasing physical activity to treat NAFLD. About 70 - 90% of patients have simple steatosis, which is a liver-associated benign prognosis and can potentially be managed in a primary care setting. However, approximately one-third of patients have NASH, which can progress to fibrosis and cirrhosis, putting them at risk for liver-related complications and mortality, or the patients may recover from the disease if it is diagnosed early and managed (Figure 6). There are two strategies in the management of patients with NAFLD: first, direct treatment regarding the management of obesity and metabolic syndrome complications with potential secondary "liver effects"; Second, specific " liver directed (non-mediated)" treatments for patients with advanced diseases for whom there are no other treatments. Lifestyle modification with the aim to lose weight and increase physical activity is vital for all patients with NAFLD. Patients must be urged to lose 10% of their body weight. Losing weight (by making changes in diet and exercise) improves steatosis and may reduce liver inflammation and injury (only with a weight loss of 7–9%), but to date, there is no evidence indicating liver fibrosis improvement. Promrat et al. found that patients who received dietary

Table 2. Guidelines for physical activity The American Association for the Study of Liver Diseases(AASLD): NASH, non-alcoholic steatohepatitis; The European Foundation for the Study of Liver (EFSL)- European Association for the Study of Diabetes (EASD), The European Association for the Study of Obesity (EASO), and Korean Association for the Study of the Liver (KASL) (Kwak & Kim, 2018)

Study	Physical activity
AASLD	Moderate-intensity exercise is good for fatty liver, but its effects on other aspects of liver histology are not known. Optimal training intensity and duration are uncertain. The main effects on NASH or fibrosis are less clear.
EASL - EASD - EASO	Three to 5 sessions of moderate-intensity aerobic exercise for 150-200 minutes per week is generally preferred. Resistance training is also effective. Physical activity has a dose-response relationship, and using vigorous activity instead of moderate activity has the full benefit for NASH and fibrosis.
K ASL	Exercising more than 2 times a week and for more than 30 min has *beneficial* effects on hepatic steatosis.

recommendations for weight loss and performed 200 min moderate physical activity every week for 48 weeks lost body weight by about 3.9%. Insulin resistance is one of the key pathophysiological mechanisms leading to NAFLD. Research studies on moderate-intensity exercises, high-intensity exercises, and resistance training have shown that the improved liver enzymes and reduced steatosis are independent of weight loss. Scientists have shown that 8 weeks of resistance training in sedentary adults with NAFLD lead to a relative reduction of 13% in liver fat and insulin resistance. All patients with NAFLD should be suggested to increase their physical activity and exercise regularly. The easiest way is to exercise 30 minutes on average 5 times a week. Most patients with NAFLD find it difficult to adapt to these recommendations, and using pedometers (10,000 steps/day target) may be helpful. People with NAFLD are less active than healthy people, and there is evidence showing that they lack the confidence to exercise and are not ready to make lifestyle changes. This shows that behavioral counseling may also have an important place in the management of this disease (Dyson & Day, 2014).

Considering the above mentioned materials with regard to changing lifestyle to treat NAFLD, the importance of healthy nutrition is such that it is considered the main root of NAFLD prevention and treatment. A significant improvement in the treatment of fatty liver is achieved only by losing weight through dietary changes. Therefore, the right diet selection and weight control can be a protective factor against this disease (Barikani & Pashaeypoor, 2019). An increase in

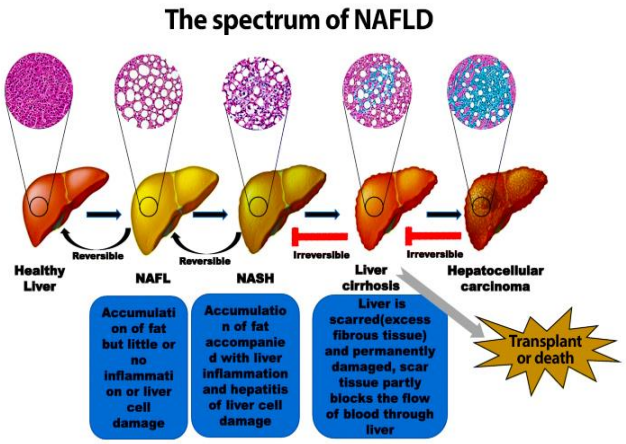

Figure 6. Stages of fatty liver disease progress and whether it is reversible or not (J. Wang et al., 2020).

food intake, as well as diets rich in fat or carbohydrates can lead to a reduction in insulin sensitivity; and/or an increase in serum free fatty acid levels will lead to NAFLD (Nabizadeh Haghighi, 2016). Moreover, research on diets has shown that the consumption of fast foods containing high amounts of energy, fat, saturated fatty acids, glycemic index, and on the other hand, low in fiber, vitamin C, A, and calcium causes weight gain, obesity, increased insulin resistance, hyperglycemia, type 2 diabetes, hyperlipidemia and metabolic syndrome, which in turn put a person at risk for NAFLD (Tavakoli et al., 2018). The most appropriate way to achieve the desirable weight is limiting the calorie intake or calorie restriction. Considering the amount of weight loss and proper use of vitamins and proteins in food diets, adopting a low-calorie diet is very useful and should be continued until the desired weight is achieved. What patients should consider is that after reaching the desirable weight, they should keep it off using proper exercise and diet because in case of lack of attention to this issue and increasing calories intake (overeating), they will develop the complications of fatty liver disease again because exercising helps maintain an ideal weight by controlling appetite. In other words, the role of exercise is insignificant in losing weight and it plays a main role in maintaining the ideal weight. After achieving the ideal weight through a proper diet, exercise seems to be able to keep weight off (Jamali & Jamali, 2010). For example, studies show that people with a BMI>25 kg/m2 are about 30 times more likely to develop NAFLD than those with a BMI< 25 kg/m2. On the other hand, it has been stated that lifestyle intervention with the aim of losing weight via reduction of daily calories and energy intake (without further intervention) leads to a reduction of 42-81% in NALFD; and the greater the weight loss, the lower the risk of developing NALFD (Barikani & Pashaeypoor, 2019). In a prospective study by Vilar et al. the effect of lifestyle modification through a low-calorie diet with exercise on the histological features of NASH was evaluated in a large group of patients. They studied these patients during routine clinical work for 12 months. This research investigated the relationship between the degree of weight loss and the improvement of general histological parameters. A significant dose-response relationship was reported between the percentage of weight loss and overall histological changes. Moreover, the highest reduction was observed in patients who had the greatest weight lost. A 10% of weight loss to induce NASH improvement (90% of patients have achieved this weight loss) or the improvement of fibrosis up to at least one stage (81%) is required. However, the average weight loss (7%-10%) creates important advantages for NAS (88%) and its components (steatosis 100%, lobular inflammation 100%, and ballooning 90% of patients who achieved this weight loss). In a post hoc analysis of this study, patients with weight loss of 7%-10% and "undesirable" risk factors, such as female gender, the existence of diabetes, BMI>35, or a large number of ballooned cells at the baseline showed a lower rate of NASH improvement. However, higher rates of improvement in NASH were observed in individuals with significant weight loss (≤10%) regardless of the presence of "undesirable" risk factors. The obtained results show that the weight loss of >10% is required in the high risk patients group (Figure 7).

Effect of different diets on NAFLD

Changing a patient's diet, with or without weight loss, is a key component of an effective life program. The composition of the diet as a dietary intervention depends on whether the diet is isocaloric or hypocaloric. In particular, saturated fats seem to preferably increase de novo lipogenesis and the amount of liver fat through calorie intake compared to unsaturated fats and carbohydrates. A short-run study (conducted within 2-4 weeks) on isocaloric diet showed that a high-fat (43%-56%) / low-carbohydrate (30%-38%) diet increases hepatic triglyceride content compared to a low-fat (16%-23%) / high-carbohydrate (57%-65%) diet. An extreme isocaloric very low carbo-

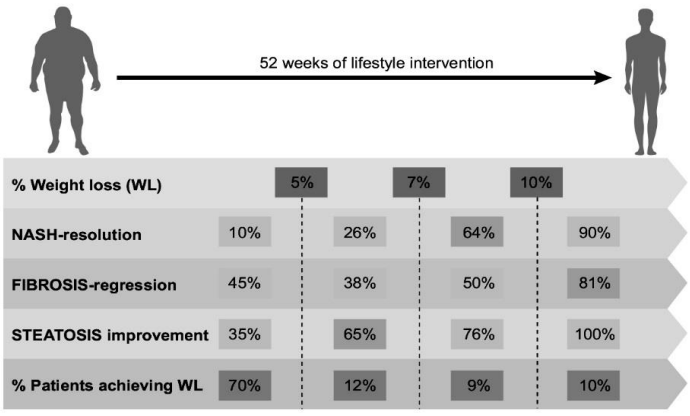

Figure 7. Likelihood of achieving NASH resolution and fibrosis regression (at least one stage) and improvement of steatosis in patients with NASH under lifestyle intervention given the percentage of weight loss (Romero-Gómez et al., 2017)

-hyderate (4%) together with high-fat (72%) and protein (24% of energy) was found to decrease hepatic de novo lipogenesis, increase fatty acid oxidation, and decrease significantly (43%) liver fat within two weeks. Interestingly, this diet changed the composition and function of gut microbiota, indicating that it may mediate changes caused by diet in liver fat in the absence of significant weight loss. In this short-run study, diet was used, which may not be desirable in the long-run. However, it provides proof for the concept of the role of diet and modulation of gut microbiome in the NAFLD lifestyle treatment. Finally, the role of diet protein is unknown. Cross-sectional studies reveal a relationship between high protein intake and NAFLD in the elderly. However, short-run interventional studies showed that increasing animal or plant protein in diet by 30% of the required energy (with carbohydrates 40% and fat 30%) decreases liver fat by 36% within 6 weeks, probably by changing peripheral adipose metabolism. Likewise, in T2DM patients with stable weight, a high protein (30%) diet with 30% carbohydrate and 40% fat reduces hepatic steatosis within 6 weeks, indicating that replacing carbohydrate or fat with protein intake can act as a successful strategy to decrease hepatic steatosis. It should be noted that longer duration (3-6 months) low-calorie diets that lead to weight loss, cause the same reduction in the hepatic triglyceride content regardless of whether they are low-carbohydrate (10%-30%) or low fat (20%) diets. In the customers who always consume drinks containing sugar, decreasing intake from 10% to ≤1% of daily calorie might be an important component of nutritional therapy because it reduces hepatic triglyceride content independently of weight loss. This may happen partly due to the reduction of fructose. Fructose is a type of sugar which leads to de novo liver lipogenesis. In this vein, short-term isocaloric fructose restriction lowers liver fat content in children with obesity. However, a research on overweight men showed the same increase in hepatic triglyceride content with high fructose or high glucose diet, indicating the need to minimize the excessive amount of fructose and glucose in patients with NAFLD. In addition to describing diets in terms of their fat or carbohydrate content, it should be said that the Mediterranean diet is rich in monounsaturated fatty acids with high intake of olive oil, nuts, vegetables, fruits, beans, whole grains and fish. This diet is associated with reduced mortality and cardiovascular disability. Therefore, it is an attractive supplementary lifestyle for patients with NAFLD who die mainly due to CVD. Two randomized controlled studies have shown that the Mediterranean diet decreases hepatic triglyceride more than a low-fat diet (30%), while the third study conducted using ad libitum diet revealed equivalence. Notably, the recent experiment which focused on changing the composition of macronutrients rather than losing weight, showed that using this method can bring a 25%-30% relative reduction in hepatic steatosis. The Mediterranean diet is easier than a low fat diet (88% versus 64%). Moreover, improving CVD risk factors, such as lipid and glycated hemoglobin to a great extent support its inclusion in the rec-ommendations of European Guidelines (Hallsworth & Adams, 2019).

Vitamins and antioxidants

A diet rich in antioxidants to treat NALFD is one of the latest findings which have received attention over the last five years. The imbalance in the prooxidant/antioxidant system is defined as oxidative damage or oxidative stress. Antioxidants intake can inhibit reactive oxygen species (ROS) or toxic effects that cause liver fibrosis. This feature of antioxidants distinguishes them from other therapeutic methods for NAFLD. Additionally, a study on patients with blood cholesterol greater than 130 mg/dL found that daily consumption of 750 ml of orange juice can help significantly reduce low-density lipoprotein (LDL) cholesterol concentration in the intervention group compared to the control. As the level of antioxidants in patients with NAFLD is low, today the use of antioxidants along with other therapeutic methods has been considered in these patients and further studies in this field are necessary (Barikani & Pashaeypoor, 2019). Micronutrients, such as vitamin D and vitamin E, have antioxidant and immune-modulatory effects and are involved in the pathogenesis of NAFLD and NASH. Though observational studies have shown low levels of vitamin D in developing liver injury, fibrosis, and NAFLD, small clinical trials have not revealed any effect on liver histology. In contrast, vitamin E, which contains robust antioxidant characteristics, has been found to cause NASH resolution in respectively 36%–58% of adults and children, although not any improvement in fibrosis. EASL and AASLD guidelines suggest considering vitamin E (800 IU/day) to treat non-diabetic non-cirrhotic patients with NASH, although the efficacy in patients with T2DM was also shown in a recent trial. However, a meta-analysis of clinical trials, which has not specifically targeted patients with NAFLD, has shown an increase in the risk of mortality with vitamin E supplementation. This raises concern over long-term use of this vitamin. Coffee and tea have antioxidant effects partly due to polyphenol compounds. Green tea and coffee have the same and slightly greater antioxidant content compared to black tea. Cross sectional studies in selected populations of biopsy-proven NAFLD patients show that coffee is related to less liver fibrosis, especially in patients with lower degrees of resistance to insulin. Population studies have been inconsistent with regard to whether tea or coffee consumption has to do with fatty liver or not, though other studies have shown the reduced rate of chronic liver disease (all-cause) and HCC. However, there are no clinical trial data, and recommending coffee as an effective therapy for NASH is thus premature, although coffee ingestion seems not to be harmful. Interestingly, a small human cross-over trial of NASH patients demonstrated that consuming 40 g of dark chocolate (cocoa>85%) per day enhanced serum markers of oxidative stress and apoptosis, indicating its probable benefits (Figure 8) (Hallsworth & Adams, 2019).

Effect of probiotics on liver and liver diseases

Since probiotics have been used as a therapeutic method for over a century, their goal is to prevent and treat a wide range of diseases, and there is robust evidence for their effectiveness in some clinical diseases. Additionally, having a proper understanding of their risks and benefits is necessary. Probiotics are non-pathogenic microorganisms. The majority of these microorganism's form part of the human gut normal flora and have a symbiotic relationship with the gastrointestinal flora. By reducing bacterial urease activity, probiotics reduce the amount of ammonia in the portal system, and decrease ammonia absorption by reducing the pH and intestinal permeability. Probiotics prevent the absorption of toxins and cause a reduction in inflammation and oxidative stress by reducing the absorption of ammonia and toxins. Overall, probiotics can help treat liver diseases and also prevent them from happening (Hamidi Hesari & Bani torfi, 2019).

In this section, the guidelines for weight loss and dietary restriction provided by the AASLD, EASL, EASD, EASO, and the KASL are represented as a strategy for diet and weight loss in patients with NAFLD (Table 3).

According to the materials mentioned above, it can be said that the design and implementation of educational programs, as well as planning with regard to empowering people to achieve a healthy lifestyle can be effective in preventing fatty liver and even help treat it (Barikani & Pashaeypoor, 2019).

Healthy lifestyle for COVID-19 infected people

The novel pandemic of the 2019 coronavirus (COVID-19) is a global threat, and how widely it finally affects the world has remained unknown. But like the flu pandemic of 1918, COVID-19 is likely to remain an endemic epidemic and occurs in recurrent waves. In addition to serious pathology to the respiratory tract, COVID-19 seems to cause extrapulmonary manifestations that affect the cardiovascular, gastrointestinal, urinary, and nervous systems. Now, the most effective measure to stop COVID-19 transmission and prevent its relevant chronic complications is to avoid exposure to the virus through physical distance, face masks, and eye protection, but the effects of pandemic COVID-19 on physical and mental health is significant. Pandemic-associated mental health problems include depression, anxiety, fatigue, and post-traumatic stress disorder (PTSD) (Lange & Nakamura, 2020). These psychological effects are mostly caused by quarantine / hospitalization, which are essential to prevent the spread of the disease. On the other hand, in response to this stressful situation, people trapped in their homes may change their daily eating behaviors (Haddad et al., 2020). Extensive, long-term lockdown of schools and businesses leads to significant changes in daily program and lifestyle behaviors. Detrimental health behaviors, such as overeating, smoking, and alcohol overdose, may likely be initiated by people affected by economic shutdowns, quarantine, and regulation. Mental distress caused by SARS-CoV-2 may be associated with increased energy intake and decreased physical activity, leading to weight gain, overweight, and obesity (Lange & Nakamura, 2020). A large study on the Italian population reported that during COVID-19 quarantine, 35.8% of subjects under study consumed less healthy food, while 48.6% had overweight (Angelidi et al., 2021). Adequate nutrition is of paramount importance to the optimal functioning of the immune system, and both malnutrit-

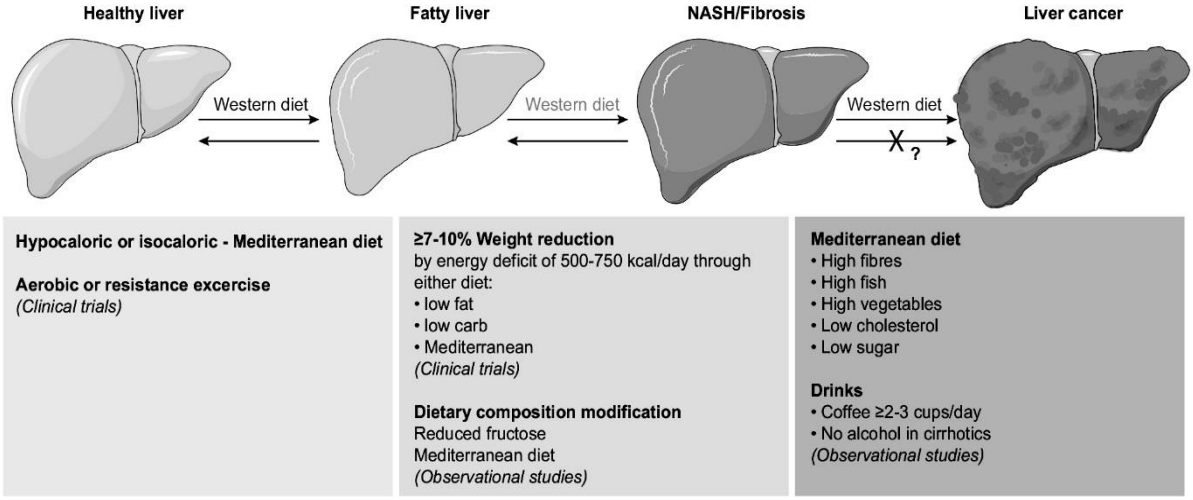

Figure 8. Summary of the nutritional treatment options (based on clinical trials or objective studies) through the course of NAFLD. As shown by clinical trials, elimination of steatosis may occur with weight loss from several types of diets or Mediterranean isocaloric diets (which induce metabolic and anti-inflammatory benefits). There is no evidence from clinical trials to improve diet composition for resolution of NASH or fibrosis, while there is evidence that at least 7% weight loss is required. To prevent the progression to liver cancer, evidence related to specific foods and nutrients can only be obtained from large-scale observational studies and further confirmation is needed (Romero-Gómez et al., 2017).

-ion and overeating may have a negative effect on immune responses. Lack of nutrients, energy, protein, and micronutrients from malnutrition and starvation can disrupt the immune system and resistance to infection. On the other hand, certain nutrients may affect immune function by changing the composition of the gut microbiota, activating cells, modifying gene expression, and producing signaling molecules. While home quarantine can be a safe measure in the face of the coronavirus spread, it reduces the people's physical activity and changes their exercise patterns. In fact, the coronavirus pandemic exacerbates the pandemic caused by sedentary behavior. A national cross-sectional study conducted in China during home quarantine in the initial stage of COVID-19 outbreak reported that approximately 60% of adults temporarily lead a sedentary lifestyle. This amount of inadequate physical activity is more than twice its global prevalence (Lange & Nakamura, 2020). The human immune system is a quite complicated network that keeps the host away from disease, viral infections, and tissue infections. Sport activity has a significant effect on the normal function of the immune system, and it has been shown that having greater cardio-respiratory and physical fitness than same-gender peers, as well as, performing moderate to severe exercise based on the scientific guidelines lead to less chronic inflammation, improve immune system response to vaccine, and improve safety indicators in chronic diseases such as cancer, AIDS, cardiovascular disease, obesity, and mental illnesses. As coronavirus is a new virus, no scientific coherent research has been so far conducted on corona disease, especially in the area of the effect of sport exercise and activity on its different aspects. However, based on physiological characteristics of the corona disease and the effect of the disease on the patient's immune system, and using the existing sport recommendations and the research literature on the effect of exercise on immune system and other viral diseases, such as the flu, attempts were made in this research to review these issues and propose sports instructions for certain groups to provide sports professionals, coaches, and the general public with scientific information during home quarantine and social distancing. Exercising is beneficial for all patients, especially those with underlying diseases and the elderly who are generally more susceptible to infection and groups identified vulnerable during the spread of COVID-19. Therefore, it is of considerable importance to try to maintain levels of physical activity within the range of the recommended guidelines (Barikani & Pashaeypoor, 2019).

Exercise training guidelines

There is likely to be very limited opportunity for practicing outdoor physical activity during this period, and a majority of people should stay at home or adopt social distancing protocols to prevent the virus transmission. People are thus recommended to stay active by exercising at home. For this purpose, various exercise states can be used, namely aerobic exercise via stationary bikes or rowing ergom-

Table 3. Guidelines for weight loss and dietary restriction. AASLD: NASH, EASL - EASD – EASO, K ASL (Kwak & Kim, 2018).

Dietary restriction	Weight loss	Study
Low calorie diet (daily reduction up to 500 to 1000 kcal)	*Improves steatosis* = 3%-5% reduction	**AASLD**
Special macronutrient composition: The need to them has been proven **Mediterranean Diet: Seems beneficial**	7%-10% = reduction. Improves most histopathological features of NASH, including fibrosis.	
Reduction of 500 to 1000 kcal of energy to induce weight loss of 500 to 1000 g per week **Low to moderate fat and moderate to high carbohydrates intake** **Avoid fructose-containing drinks and foods**	7%-10% reduction	**EASL - EASD - EASO**
Energy reduction by 400 to 500 kcal **Low carbohydrates diet and low fructose diet**	7%-10% reduction	**K ASL**

-eters, bodyweight strength training, dance-based exercise and active gaming. Aerobic exercise is defined as an exercise resulting in a low, moderate, or high cardiovascular pressure. As aforementioned such training sessions can be performed on stationary bikes or rowing ergometers, treadmills, or through various types of dancing and gymnastics. Additionally, this type of sport devices and other sports facilities for efficient aerobic training at home can be used to achieve cardiovascular and metabolic health effects because this type of training ensures moderate to vigorous aerobic training, which is capable of being controlled via heart rate monitors or power output loading program (Hammami et al., 2020). A review of studies on physical exercise and viral infections shows that the regular, moderate-intensity aerobic exercise (65-80% VO2max) increases antibody levels, lymphocyte growth rate, interferon-gamma (IFNγ) production rate, NK cell count, and G and M immunoglobulin levels. On the other hand, it will modulate the levels of inflammatory cytokines and chemokines, and this process will lead to stronger and longer-lasting responses in influenza-vaccinated adults (Shirvani & Rostamkhani, 2020). Moderate-intensity exercise seems to be accompanied by a reduction in the

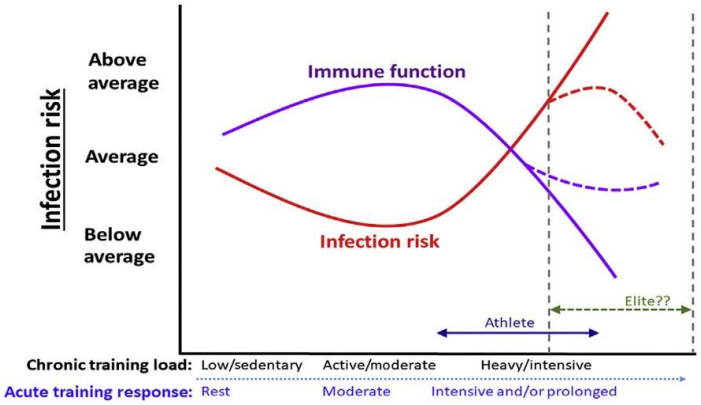

Figure 9. "J" curve model shows the relationship between exercise workload and risk of upper respiratory tract infection (URTI). However, other factors can also affect this mutual relationship, including travel conditions, exposure to pathogens, irregular sleeping patterns, psychological pressures, and diet. On the other hand, new studies have shown that there is a difference between professional (elite) and non-professional athletes and normal people (Jones & Davison, 2018; Shirvani & Rostamkhani, 2020).

incidence, duration, and severity of infections, especially the upper respiratory tract viral infections. For example, epidemiological data show that regular physical activity is associated with reduced incidence and mortality rate of influenza and pneumonia. However, physical activity may affect, either positively or negatively, safety depending on the nature, duration and intensity of exercise. This relationship has been described in terms of a "J-shaped curve", which is the graphical representation of the disease risk depicted versus the characteristics of exercise (Lange & Nakamura, 2020).

Some animal studies that have investigated the effect of exercise on susceptibility to infectious factors have reported the protective effect of moderate-intensity exercise done prior to infection. On the other hand, vigorous and stressful exercise prior to infection increases the mortality rate. Epidemiological studies in humans have shown that vigorous and competitive exercise (such as running a marathon) increases the sensitivity to URTI. However, further research is needed on the interactions between exercise and infectious diseases, such as the influenza in human societies (Shirvani & Rostamkhani, 2020). While people involved in moderate physical activity show a lower susceptibility to URTI compared to sedentary people, vigorous endurance training may suppress immune function and increase the risk of disease. Research has suggested short-term moderate-intensity exercise (up to 45 minutes) to strengthen the immune system, while long-term vigorous strenuous exercise (more than 1.5 hours) can weaken the immune system. In other words, low to moderate exercise-induced immunity may increase immune responses that play a role in the spread of COVID-19 infection (Lange & Nakamura, 2020). Weight bearing exercise, in simple terms, is any exercise that involves using the bod-y as a means to resist gravity. Examples of weight bearing exercises for upper body and lower body include push-up, pull-up stretch, squats, lunges, box jump, skipping rope, and burpee. The advantages of weight bearing exercise for musculoskeletal health and functional capacity for adults, the elderly, and a wide range of non-athlete patients are well documented. For example, research has shown that plyometric exercise, as well as resistance exercise with slow movements can improve physical function in the elderly. Moreover, 10 weeks of weight bearing exercise strengthened the selected body composition elements and fitness components, including strength, flexibility and aerobic capacity in sedentary women aged 21-23 years (Hammami et al., 2020). In the following, we will refer to the different aerobic exercise intensities and types of weight bearing exercises (Tables 4 and 5).

Therefore, by reviewing the existing research background and the similarity of some complications of COVID-19 disease to H1N1 flu, sports guidelines can be presented to exercise during the outbreak of this virus: 1. Considering the open window hypothesis, strenuous and overwhelming sports activities will probably predispose a person to infection and increase its risk, so people in these conditions had better reduce this type of sports activities. 2. Healthy people without symptoms of the disease can perform moderate-intensity exercises by observing health protocols and can strengthen their immune system based on the J-shaped curve. 3. People who have symptoms of the disease in the upper respiratory tract (such as: runny nose, sinus obstruction, sore throat) can perform light exercise activities by observing health protocols. 4. People who have more symptoms of the disease (such as fever, dry cough, severe sore throat, body aches, shortness of breath, general fatigue) may be infected with COVID-19 and should be prevented from exercising until they completely recover (Shirvani & Rostamkhani, 2020).

Nutritional guidelines

On the other hand, nutritional recommendations beside sports activities can be effective in preventing or facilitating the recovery process of COVID-19. Recent evidence has shown that dietary supplements may play a supportive role in COVID-19-infected patients (Shakoor et al., 2021). Administration of doses higher than what dietary instructions state for e.., vitamins D, C, E, zinc, and omega-3 fatty acids, may have beneficial effects and potentially reduce the SARS-CoV-2 viral load and shorten hospitalization duration (Amrein et al., 2014; Gombart et al., 2020). These nutrients are very well known due to their antioxidant properties and immune-regulating effects. Deficiency of these nutrients may lead to the immune system dysfunction and increase susceptibility to pathological infections. In fact, deficiencies in vitamins and minerals have been observed in diets of groups at high-risk for COVID-19, such as the elderly, which causes an increase in morbidity and mortality (Grant et al., 2020). Current evidence and expert's opinions

Table 4. Classification of exercise intensity types of home-based aerobic exercise training for different groups

Higher intensity symptoms	Patients/elderly		Sedentary		Trained / active		
	RPE (0– 1)	% of HRmax	RPE (0– 1)	% of HRmax	RPE (0– 1)	% of HRmax	Intensity
Comfortable, mild breathing problems	2 (1-3)	60 (50-70%)	2 (1-3)	60 (50-75%)	2 (1–3)	65 (50–80%)	Low
A little difficult *breath*, shortness of breath, talking is possible, but singing .is not possible	3 (2-4)	70 (65-80%)	4 (3-5)	75 (70-85%)	4 (3-5)	80 (70-90%)	Moderate
Difficult, breathing is deep and fast, only a few words can be said without pausing to breathe	5 (3–7)	80 (70–90%)	5 (4–8)	85 (80–95%)	6 (5–10)	90 (85-100%)	High

Note: Heart rate is a percentage of maximum heart rate (HRmax) and rate of perceived exertion (RPE) during low, moderate, and high-intensity aerobic exercises for trained / active people as well as sedentary individuals and patients/ elderly. Session RPE scale 0-10 is related to providing the following intensity feeling: 0: rest, 2: easy, 3: moderate, 5: hard, 7: very hard, 10: maximal. Please note that intensity classifications are described as average values as well as range. HRmax can be estimated as 220 minus age or 208 minus 0.7 multiplied by age (Hammami et al., 2020).

the consumption of fresh and unprocessed plant foods such as vegetables, fruits and whole grains. On the other hand, they recommend consuming fat moderately, preferring unsaturated fats, and avoiding sugar and salt consumption. The Mediterranean diet is one of the healthiest dietary patterns all over the world, which gained reputation due to its effect in preventing cardiovascular diseases and type-2 diabetes in several experiments. This diet is characterized by the inclusion of nutrients derived from plants i.e., fruits, vegetables, beans. nuts. and olive oil. all of which are considerable sources of b--ioactive polyphenols. Due to their antioxidant, anti-inflammatory, and antithrombotic characteristics, polyphenols, especially flavonoids and their metabolites, show multilateral health-promoting effects, particularly in cardiovascular and metabolic disorders. These characteristics become even more important given the inflammatory and prothrombotic medium that is highly related to COVID-19 severe disease. Polyphenols decrease the immune response, they cause an increase in antioxidant defense, lead to the improvement of vascular reactivity, and reduce histological inflammation and cellular

Table 5. Examples of weight-bearing exercises at home (Hammami et al., 2020)

Exercise	Repetitions (reps)	Advantages
Active dynamic warm-up **High-knee Skips** **High Kicks** **Butt Kicks** **Lateral Shuffle**		
Bodyweight squat	Beginner -1–2 sets of 10 reps	*lower body power and strength*
	Advanced-2–3 sets of 20 reps	Performance outcomes
Push-up	*Beginner -1–2 sets of 10 reps*	*Upper body power and strength*
	Advanced-2–3 sets of 20 reps	
Walking lunge	*Beginner -1–2 sets of 5 reps*	*Running speed and hamstring strength*
	Advanced-2–3 sets of 10 reps	
plank	*Beginner -1–2 sets of 20 reps*	Isometric strength of upper and lower body and body posture
	Advanced-2–3 sets of 40 reps	
Jumping jack	Beginner -1–2 sets of 15 reps	*Core strength and endurance*
	Advanced-2–3 sets of 20 reps	
Sit-ups	*Beginner -1–2 sets of 15 reps*	*Core and abdominal strength*
	Advanced-2–3 sets of 20 reps	
Cooling down **Flexibility and static stretching exercises**		

infiltration, and consequently promote metabolic and cardiovascular health. These beneficial effects seem to be applied by preventing the activation of the nuclear factor-κB (NF-κB) signaling pathway and nicotinamide dinucleotide phosphate (NAPDH) enzyme and by decreasing the levels of proinflammatory cytokines such as interleukin-6 and tumor necrosis factor-alpha. Consuming nuts and dried fruits such as raisins that are an integral part of the Mediterranean diet improves cardiometabolic health via their rich composition in nutrients and bioactive phytochemicals. Of them, polyphenols, as antioxidant and anti-inflammatory molecules, play a key role. Continuous research on potential antimicrobial features of some Mediterranean foods, such as raisins and olive products, must be regarded in the context of current research efforts to clarify the flavonoids and other polyphenols' protective effects in the face of the coronavirus infection. In short, following the Mediterranean diet has a desirable effect on cardiovascular diseases and other cardiometabolic disorders e.g., diabetes, which is susceptible to COVID-19 infection, and relevant outcomes. Having high antioxidant, anti-inflammatory, antimicrobial, and immunomodulatory characteristics, the Mediterranean diet can be considered a promising and relatively easy method to decrease the severity of COVID-19 infection. Therefore, the Mediterranean diet may propose a potential strategic therapeutic method to address short-run and long-run circumstances related to the infection and severity of COVID-19 and improve mortality and the whole well-being of the influenced population (Angelidi et al., 2021). On the other hand, based on the conducted studies, probiotics can activate multiple safety mechanisms, affect the host's immune systems, as well as increase the immune response, and reduce, on average, the incidence and duration of viral respiratory infections. Research studies have reported microbial bioavailability with a reduction in lactobacillus and Bifidobacterium in some COVID19-infected people. Therefore, probiotics have been recommended in COVID19 management guidelines. However, the true efficacy of conventional probiotics in the prevention or treatment of COVID19 is unknown (Lange & Nakamura, 2020).

Conclusion

As many of our daily routines have been limited during the outbreak of coronavirus, staying in home quarantine for a long time can be a major challenge to reducing physical activity of the community members. Therefore, sedentary behavior and low level of physical activity may negatively affect the individuals' health, well-being, and quality of life and can be considered as a threat to their health. Finally, we should know that although the corona epidemic is fatal and dangerous, having underlying diseases and neglecting other health aspects and having overweight and obesity further threatens health rather than corona over time and dealing with its long-term consequences, such as NAFLD, doubles this risk. Considering rese--arch studies, improving the quality of life, proper nutrition, and exercise are the best ways to prevent NAFLD, and consequently, COVID-19 disease. Of them, performing aerobic exercises, moderate-intensity exercises, and weight-bearing exercises; using the Mediterranean diet; and consuming antioxidants and probiotics may be beneficial.

What is already known on this subject?

Previous studies have separately examined the effective role of nutrition and exercise training on Covid-19 and non-alcoholic fatty liver disease, and the role of exercise has been less evaluated in these two diseases.

What this study adds?

In the present study, the controlling and preventing effective role of diet and regular physical activity on fatty liver and COVID-19 have been confirmed based on previous studies.

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Compliance with ethical standards

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Author contributions

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