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Relationship and Psychological Effects Between Food, Mediterranean Diet and COVID-19

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Abstract

The new pandemic COVID-19, caused by the coronavirus SARS-CoV-2, has already affected millions of people from the majority of world countries, with a mortality rate of 3.1%. We know that the virus does not similarly affect all population groups and the severe or very severe forms of the disease are well-identified among the risk groups. Obesity, type 2 diabetes, chronic kidney disease, or cardiovascular disease are known as risk factors for severe illness for COVID-19 at any age. Society, governments, and several organizations introduced measures to control the pandemic and mitigate health impact and economic recession. Still, they have failed to implement measures to support psychological distress and to encourage the adoption of dietary and nutritional measures aimed to minimize the evolution to more severe forms of COVID-19. The importance of nutritional status, diet, and lifestyle in the prognosis of other serious infections may play an important role in SARS-CoV-2 infection. The Mediterranean diet includes only those that, due to their composition, are beneficial to health and provides a diet with a high content of antioxidants and monounsaturated and polyunsaturated fatty acids and low content of saturated fats. The COVID-19 pandemic related-changes in daily routine boost the coping strategies to deal with psychological distress. The decrease in social support, access to health professionals, and social awareness content, including

advice on food and physical exercise at home, can contribute to increasing variations in eating habits. It´s also essential to include mental and emotional coping strategies, specifically to improve knowledge, awareness, and self-replication to reduce the risk of isolation, anxiety, and depression among the more vulnerable population. Overall, COVID-19 will remain in our lives in a while and it is essential to realize that the world won't be the same again, we will be returning to a "new normal" where our social routines, working environment, and personal behavior will be different.

Introduction

The new pandemic COVID-19, caused by the coronavirus SARS-CoV-2, has already affected more than 31 million people, in 180 countries, with a fatality rate of 3.1%. We know that the virus does not affect all population groups in a similar way and above all, the serious or very serious forms of the disease are in well-identified risk groups. Immunocompromised, elderly, hypertensive, and obese people are particularly vulnerable. Based on this knowledge and the transmission characteristics of the virus, worldwide, Public Health entities and Governments have defined strategies to protect at-risk groups, with the consequence of a progressive reduction in the lethality rate.

In addition to the peculiarities of the cellular penetration of SARS-CoV-2, through the binding of the activated Protein S sub-fraction to the ACE2 receptor, it has also been suggested that the immunodepression associated with the chronic inflammatory state, caused by the co-morbidities, found in the different risk groups, constitutes an aggravating factor for COVID-19. It has been also admitted that this chronic inflammatory state, together with the "cytokine storm", found in serious infections by COVID-19, together, contribute to the high lethality rate associated with the severe forms of COVID-19. For this reason, the use of some anti-inflammatory therapies is under investigation and the benefit associated with the use of corticosteroids, namely Dexamethasone, is understood in the severe forms of the disease.

The importance of nutritional status, diet, and lifestyle in the prognosis of other serious infections is also known, which is why the hypothesis has also been raised that they may play an important role in SARS-CoV-2 infection. Zabetakis I *et al* [1] published a review of the scientific literature on the importance of nutrition as a mitigation strategy to support immune function, amid the COVID-19 Pandemic, having identified some particularly relevant food and nutrient groups.

Iddir M *et al* [2] also analyzed the impact of diet and nutrition on the modulation of immunity and its importance in the control of COVID-19. Scientific evidence has proven the importance of various nutrients in strengthening the immune system, as a consequence of reducing oxidative stress and inflammation. Among these nutrients, we highlight glutamine, arginine and Branched-Chain Amino Acids (BCAA), omega-3 fatty acids, unsaturated fat, fiber, and micronutrients, such as vitamins A, B, C, D and E, zinc, selenium, iron, carotenoids, and polyphenols. Many of these nutrients exert their anti-inflammatory effect through some transcription factors, such as the Kappa B Nuclear Transcription Factor (NF-kB) and the Nuclear Factor Erythroid 2-related Factor 2 (Nrf-2). Phenolic compounds and other nutrients inhibit phosphorylation of Mitogen-Activated Protein kinase (MAP kinases), inhibiting the transcription factor NF-kB and consequently, reducing the synthesis of TNF-alpha and interleukins and the activity of

cyclooxygenase and lipoxygenase. On the other hand, they also activate the transcription factor Nrf2, which increases the expression of the superoxide dismutase and glutathione peroxidase genes that play a relevant role in antioxidant defense.

In the infection sites, it is observed intense activity of cells related to cellular immunity, in particular, of macrophages. This cellular activity results in the production of Reactive Oxygen Species (ROS), triggering oxidative stress. Hence, its close relationship with inflammation and the reason why it strongly modulates the immune response.

It is not necessary to detail here the biochemical processes related to the production of ROS, but it should be noted that they are produced, essentially, by oxidizing enzymes, phagocytic cells, and ionizing radiation. The superoxide anion (O_2-) is probably the first radical to be formed and one of the most important in the inflammatory process, due to its high capacity to cross biological membranes and to be highly reactive with transition metal ions, such as iron and copper. The most potent of the ROS and the most harmful to human health is the hydroxyl radical. OH which can react with biological macromolecules (lipids, proteins, nucleic acids, and carbohydrates).

At the beginning of an infectious process, exposure to pathogens generates a defense cellular response, which is physiological, triggering the activation of inflammatory mediating cellular receptors, such as toll-like receptors (TLRs), Interleukin 1 (IL- 1), Interleukin 6 (IL-6) and TNF-α. Thus, both TLRs and Interleukins participate in the regulation of the immune system. TLRs are transmembrane proteins. Interleukins are also proteins, produced by several cells, but, in particular, by activated T lymphocytes that stimulate intracellular signaling pathways and trigger the inflammatory process. We know that chronic diseases are always associated with a systemic inflammation state and that this situation conditions a deregulated immune system, with the consequent increased risk of infection.

We do not know precisely the function of oxidative stress as a response to infection, but it is believed that it is to provide increased protection against invading microorganisms. Perhaps for this reason, in chronic viral infections, we find chronically increased oxidative stress. The relationship between inflammation, ROS, and endothelial injury has also been demonstrated, which seems to play a key role in COVID-19. In severe forms of the disease, we find increased plasma levels of cytokines, suggesting the presence of a "cytokine storm", resulting in an exacerbated state of the inflammatory response. The consequence is the worsening of the immune status, which in the presence of malnutrition or dietary and nutritional imbalance is already deficient, making individuals even more vulnerable to infection. The severe forms of COVID-19, of which the maximum expression is the Severe Acute Respiratory Syndrome (SARS), are directly related to the increase in viral load. This is a consequence of viral replication, which is facilitated by the inflammatory state and immune depression.

The authors [2] drew attention to the fact that the benefit of the anti-inflammatory diet is particularly relevant in the period of "COVID-19 cytokine storm", that is, in the period of hyper inflammation of the disease.

Society, governments, and various institutions have introduced measures to control the pandemic to mitigate its impact on health and the economic recession. However, they have failed in measures to support psychological distress and to encourage the adoption of dietary and nutritional measures aimed to minimize the evolution to more severe forms of COVID-19. Nutritional care should be mandatory and carefully integrated into the assessment and treatment of patients with COVID-19.

Careful analysis of the risk factors associated with the evolution to severe forms of COVID-19 has demonstrated, unequivocally, that obesity, together with Arterial Hypertension, are the main risk factors. Obese patients infected with SARS-CoV-2 are 6 times more likely to develop a severe form of the disease than non-obese patients and of those hospitalized with COVID-19, 48% are obese and this prevalence is higher in younger patients, reaching 59% in the 18-49 age group.

According to Scheen [3], multiple causes may justify the relationship between obesity and severe forms of COVID-19, such as the chronic inflammatory state associated with obesity; the excessive immune response associated with the pro-inflammatory state; the changes in respiratory performance; the presence of comorbidities (high blood pressure, diabetes or obstructive sleep apnea).

SARS-CoV-2 can infect any individual, in any age group. However, it is those included in some specific groups that are at the greatest risk of developing severe forms of COVID-19. Among these, those who consume diets rich in saturated fats and sugars are at an increased risk, as they are more obese and have a higher prevalence of diabetes and high blood pressure. Its risk is further increased because diets rich in saturated fats and sugars are associated with a state of chronic inflammation and immunodepression that is secondary to the poor adaptive capacity caused by those diets, resulting in the deficient host response to viral aggression. It is also questioned if this systemic pro-inflammatory state, aggravated by unhealthy diets, could be related to the development of chronic neurodegenerative diseases.

The relationship between dementia and Vitamin B12 deficiency is known and has been scientifically demonstrated. Tangney CC [4] published in 2009 in "Neurology" that serum concentrations of methylmalonic acid and vitamin B12 may be one of the most important risk factors for cognitive decline, particularly in older people. According to Sophie Lefèvre-Arbogast [5], in a sample of 1321 participants followed for 7.4 years, it was found that in individuals with higher serum folate levels, the risk of progressing to dementia was 50% lower (HR = 0, 47; 95% CI 0.28; 0.81), concluding that a higher intake of folate was associated with a lower risk of dementia. In this study, no relationship was found between dementia and vitamin B6 or B12 intake.

So now, more than ever, the priority should be to focus on widespread access to healthy food and a nutrient-balanced diet so that we can reduce the long-term susceptibility to complications of COVID-19.

Obesity and COVID-19

When our society reached a modern age were the infective diseases from the past were no longer the cause of morbimortality and the main focus of interest, investigation, and investment were directed to chronic illness, things took a radical unexpected turn. The world that we used to know changed and no one could predict the extension or the way those changes were going to affect all our lives. COVID-19 presented itself to us…

The memories of the Black Plague (XIV century), Spanish Flu (1918 - 1920), American Polio (1916), Asian Flu (1957 - 1958), Swine Flu (2009 - 2010), West African Ebola (2014 - 2016), and even, Zica virus (2015), were starting to fade [6]. COVID-19 reminded us all that most things in nature are cyclic, and again, the world faced almost unprecedented mortality from an emergent acute viral disease with pandemic proportions.

According to the most recent data [7], COVID-19 has infected 34.2M people worldwide with a mortality of 1.02M with the United States taking the lead for the highest number of cases (7.31M), followed closely by India (6.39M) and Brazil (4.85M).

It is well known that in the new age of modern medicine that we are living in, cardiovascular and metabolic diseases are the main cause of mortality and morbidity that we face. Conditions like hypertension, diabetes, obesity, and dyslipidemia are directly related to the risk of heart disease, stroke, and chronic kidney disease that are among the main causes of death [8].

From all those risk factors, obesity is taking dangerous proportions. The prevalence of childhood obesity increased between 1999 - 2000 and 2017 - 2018 from 15.8% to 19.3% and in adolescents from 16.0% to 20.9% [8]. Among adults, during the same period, the prevalence of obesity increased from 27.5% to 43%.

With the most recent data available, we know that the presence of obesity, type 2 diabetes, chronic kidney disease, or cardiovascular disease are known risk factors for severe illness for COVID-19 at any age.

Obesity is not just a result of the normal evolution of the modern world, it is a consequence of inequity. According to the 2020 Global Nutrition Report in the context of COVID-19, there are significant inequalities within countries and populations, with the most vulnerable groups being most affected by malnutrition in its different forms: undernutrition, overweight, and obesity.

It's intriguing to realize that COVID-19 does not treat us equally, the question is not just limited to the pre-existing health conditions, but includes aspects such as socio-economic inequities. Living in social or economic disadvantage will increase the risk of malnutrition, the risk of developing potentially fatal conditions such as stroke and cardiac disease, and ultimately will increase the mortality by COVID-19.

It is clear enough that COVID-19 will be present in our lives for the near future and it is important to understand that the world won't be the same again, we will be returning to a "new normal" where our social routines, working environment and personal behaviour will be different. And this should be seen as an opportunity to learn, correct, and establish new habits and a new lifestyle.

This is the time to address known cardiovascular risk factors that were never so prevalent and so related to our health and never represented such a relevant threat to our survival.

Since this virus is with us, we have learned that is possible to change old routines, its possible to have a different lifestyle, it's possible to eat differently, it's possible to do so much from home. The very use of time has changed, we have now the possibility to learn, research, and even to work from home.

This was the ultimate opportunity to build a "new normal" and to stop the progression of social inequity, unhealthy lifestyle, obesity, hypertension, and cardiovascular mortality.

COVID-19 should be seen as the ultimate opportunity to change things for the better.

Mediterranean Diet and Human Health

The orography of the Mediterranean basin is characterized by a rugged surface, with great climatic variations in nearby lands, which makes extensive cultivation difficult. For this reason, all the available land was used for culture, regardless of its extension, providing an enormous variety of culture, that is so characteristic of the Mediterranean basin.

In each village, the best land (flat and with water) was used for the cultivation of vegetables and cereals and the slopes for olive and vineyards. Although there are considerable differences between the North and the South, the East and the West, the Mediterranean region has always been characterized by the cultivation of vegetables, cereals, olive trees and vineyards, and the creation of birds, sheep, and goats. The association of cereals and the products of the olive tree and the vine is known for the "golden triad of the Mediterranean Diet".

Although there was a great diversity of food, due to the orography and the unpredictable climate, food resources were not abundant. This scarcity drove the creation of mercantile networks, converting the Mediterranean into a cultural and commercial network, due to the exchange between the diverse peoples of Antiquity. Greeks, Phoenicians and Egyptians, created a true network for the commercial exchange of a wide variety of food products. It was this phenomenon that contributed to the adoption of a food style with common characteristics throughout the Mediterranean basin. It would have been the first example of globalization, which characterizes current food trends.

The concept of the Mediterranean is a historical and cultural matrix. It is the result of the contribution of diverse people and cultures, who made a wide network of human and cultural relations, around the sea, exchanging goods, products, techniques, and ideas. The Mediterranean food tradition is a product of history that was continually regenerated and redefined itself. Many foods that are now part of the Mediterranean Diet are of extra-Mediterranean origin (Ex: tomatoes, peppers, potatoes, etc.).

In this context, the concept of the Mediterranean Diet is a complex reality. It is not limited to a set of dietary rules. It also implies historical, cultural, and everyday lifestyle concepts. It is the result of the culture of the Mediterranean peoples and of the relations that the migratory movements allowed to establish with other peoples.

In Arab culture, wine and pork were banned and bread did not have the same symbolism that it had in Christianity. In the desert, the diet was based on cereals, few vegetables, and little fish. However, it was the expansion of the Arab world that introduced other foods to the West, such as rice, sugar cane, and citrus fruits. From the influence of the Germanic peoples came the relationship with the forest and hunting and livestock.

The discovery of the new world (American continent) introduced new foods and flavors to the Mediterranean diet, starting in the 16th century. Tomatoes, peppers, potatoes, and corn are some examples. Feeding is an anthropological and cultural issue, based on the premise that the human being is an omnivorous animal, that in some parts of the world suffers and dies from nutritional deficiencies and that in others, it gets sick and dies from excess food.

The dietary model underlying the concept of Mediterranean Diet seems to be one of the healthiest and most preventive, characterized by an abundance of plant foods; olive oil, as the main source of fat; moderate consumption of fish, shellfish, poultry, dairy products, and eggs; consumption in small quantities of red meat and wine during meals;

It is a diet that provides small amounts of saturated fatty acids and large amounts of monounsaturated and polyunsaturated fatty acids, long-chain carbohydrates, and fiber.

The culinary culture of the Mediterranean is not based on recipes, but on how to create dishes, most of them beneficial to health. Products are just as important as how to combine and make them. This combination arose from the interaction between man and the environment, the wise use of nature, and the accumulation of knowledge, which were transmitted throughout the Mediterranean basin.

Do not confuse Mediterranean cuisine with a Mediterranean diet. Mediterranean cuisine is the set of all recipes used in the Mediterranean. The Mediterranean diet includes only those that, due to their composition, are beneficial to health.

The food of the Mediterranean diet provides a diet with a high content of antioxidants and monounsaturated and polyunsaturated fatty acids and low content of saturated fats. In the case of a varied diet, many of the compounds have synergistic effects, with each other. Olive oil, the fat par excellence of the Mediterranean Diet, is rich in monounsaturated fatty acids. Fish is rich in omega 3 fatty acids and fruit and vegetables are rich in folic acid, antioxidants (carotenes, Vitamin C, polyphenols, etc.), and fiber.

In 2008, Francesco Sofi *et al* [10] published a meta-analysis on health and adherence to the Mediterranean Diet at BMJ. They reviewed 12 prospective scientific studies, that analyzed the relationship between adherence to the Mediterranean Diet and mortality and incidence of chronic disease. These twelve scientific studies included a total of 1574299 individuals, observed at a follow-up for 3 to 18 years. The authors concluded that adherence to the Mediterranean Diet was associated with a significant increase in health status. Global and cardiovascular mortality were reduced by 9% and cancer mortality by 6%. The incidence of Parkinson's and Alzheimer's disease has decreased by 13%.

The same authors presented at the European Congress of Cardiology, in 2016, a small prospective study with 50 individuals, divided into two groups, submitted to isocaloric diets. One of the groups was on a traditional Mediterranean diet and one group was on a vegetarian diet. After 3 months, the conclusion was that the benefit in body composition and anthropometric measurements were similar in both groups, but in the group undergoing the Mediterranean diet, there was a significant improvement in the cardiovascular risk profile, with a reduction serum biomarker, in particular of triglycerides, glucose, and insulin.

In 2008, M Á Martínez-González *et al* [11] published the results of a scientific study that aimed to assess whether adherence to a diet, based on the Mediterranean diet, would be associated with a lower risk of diabetes. The study included 13380 Spanish university students, without diabetes, with a follow up for 4.4 years and divided into three groups (those with low, moderate, and high adherence to a diet based on the Mediterranean diet). At the end of the study, when compared with the low adherence group, it was found that the risk of diabetes was lower in the moderate adherence group and much lower in the high adherence group. In this group, the reduction in the relative risk of diabetes was 35% (incidence ratio 0.65; 0.44 to 0.95), with a significant inverse linear trend (P = 0.04) in the multivariate analysis.

Olive oil is one of the most important components of the Mediterranean Diet. It is 99.8% in liquid and has characteristics of aroma, flavor, smell, and color that depend on the type of olives used. The visual aspect of the olive oil should be clean, without impurities and straw yellow, golden or greenish in color and may even be intense green. It should have a fruity aroma of ripe or green olives, apple or green leaf, and a fruity, fresh, and vegetable flavor. The olive oil, which supplies 9Kcal per gram, consists of a saponifiable fraction, another that is not saponifiable, and water.

The saponifiable fraction is glycerides. It corresponds to 99.5% of the olive oil composition, being: 61 to 83% oleic acid (monounsaturated 18: 1); 2 to 18% linoleic acid (polyunsaturated 18: 2); less than 1.5% linolenic acid (polyunsaturated 18: 3); 7 to 18% palmitic acid (C16);

The non-saponifiable fraction corresponds to 0.3% of the chemical composition of olive oil and consists of: sterols; tocopherols (α, β, γ e ϕ, being α the most important, due to its function as vitamin E, acting as an antioxidant); the pro-vitamin A (which is a carotene); pigments (chlorophyll; xanthophylls, etc.); volatile compounds (which give the olive oil its aroma); Water represents only 0.2% of the chemical composition of olive oil.

Talking about olive oil, in summary, it can be said that it is an excellent energy source and that it has active participation in the constitution of the cell membrane and as a vehicle for fat-soluble vitamins. Oleic acid, which is its predominant polyunsaturated fatty acid, decreases the serum cholesterol concentration. The high amount of Vitamin E and other phenolic components gives it a powerful antioxidant action.

We know that the intake of monounsaturated and polyunsaturated fats is more beneficial for human health, but the value of the maximum recommended intake is unknown. It is thought that it should be less than 10% of the total caloric intake, but there is no scientific confirmation for this hypothesis. Olive oil is rich in monounsaturated fatty acids, which make LDL more resistant to oxidation and also seems to act on the metabolism of prostaglandins and the synthesis of peroxide radicals. The consumption of olive oil and the intake of other vegetable fat is inversely related to the incidence of Type 2 Diabetes Mellitus and associated with a lower serum level of triglycerides, total cholesterol, and LDL and an increase in HDL.

The benefit of eating olive oil and consuming other vegetable fats was confirmed by a scientific study done in Spain and published in 2013 in BMJ [12]. The participants, who had at least three risk factors for cardiovascular disease, but with no history of the disease, were divided into three groups, with the diet of two of them based on the Mediterranean diet. However, in one of the groups, the diet was enriched with 1 liter of extra virgin olive oil per week and in the other, it was enriched with 30g of dry fruits per week (nuts,

almonds, and hazelnuts). Control group participants received weekly non-food gifts. Participants were followed for 5 years and at the end of that period, in groups with a diet based on the Mediterranean diet, there was a significant reduction in stroke, myocardial infarction, and death from cardiovascular disease. The reduction of risk was three events per 1000 people/year and similar in both groups.

Dietary recommendations advise to reduce the intake of saturated fats, to improve the lipid profile and health status. It seems, however, that the effect of the different fats will also be related to their origin and not just because they are saturated, monounsaturated, or polyunsaturated. In 2018, Kay-Tee Khaw *et al* [13] published a study of 160 individuals, which they divided into three groups. In one group the diet was supplemented with extra virgin coconut oil, in the other with extra virgin olive oil, and in the other with unsalted butter for 4 weeks. The biometric parameters (weight, waist perimeter, and blood pressure) were similar in the 3 groups. However, the biochemical parameters were significantly different. In the groups supplemented with coconut oil or olive oil, when compared to the group supplemented with butter, the serum LDL cholesterol value and the relationship between total cholesterol (TC) and HDL cholesterol (HDLc) and non-HDLc, were lower, with statistical significance ($P < 0.0001$), but with no significant difference between these two groups ($P = 0.74$). Thus, two different saturated fats, butter, and coconut oil, but one being of animal origin and the other of vegetable origin, showed to have different effects on lipid metabolism, being more beneficial than of vegetable origin.

No scientific approach to olive oil will be complete without including the PREDIMED study (PREvención con DIeta MEDiterránea) [14]. In this study, they have included 7216 individuals with high cardiovascular risk, to assess the association between olive oil intake and the variation in cardiovascular risk. PREDIMED was a multicenter, randomized, prospective, and controlled clinical trial. The participants, whose diet was based on the Mediterranean diet, were divided into three groups. One group was supplemented with nuts, another with olive oil and another (the control group) made only a low-fat diet. The follow-up, to evaluate cardiovascular events (stroke, myocardial infarction, and cardiovascular death), was carried out for 4.8 years. In the end, the conclusion was that in individuals with high cardiovascular risk, the consumption of olive oil is associated with a significant risk reduction. In total, there were 277 cardiovascular events and 323 deaths. The higher consumption of olive oil was associated with a 48% reduction in the risk of cardiovascular death (HR: 0.52; 95% CI: 0.29 to 0.93) and for each 10gr increase in olive oil consumption, the cardiovascular risk (risk of disease and death) decreased by 10%.

Together with olive oil, wine and wheat are the other constituents of the triad of gold of the Mediterranean diet.

Moderate wine consumption has been associated with one of the benefits of the Mediterranean diet (the so-called French paradox) and perhaps it will be because it is rich in antioxidants, in particular, some polyphenols, such as tannins, flavones, phenolic acids, and resveratrol. It was in 1992 that the designation of the French paradox was introduced in the scientific literature, to describe the low incidence of cardiovascular diseases in the French population, despite the high level of intake of saturated fats. It was then hypothesized that cardiovascular protection could be attributed to moderate wine consumption. Since then, the association between wine intake and cardiovascular risk has been intensively investigated and it is now well established that light to moderate intake of wine has a beneficial effect on human health and delays the evolution of

the atherosclerotic process. We know that many of the components of wine, such as resveratrol and other polyphenolic components, are associated with the reduction of oxidative stress, the inhibition of lipoprotein oxidation, and the greater bioavailability of nitric oxide. The cardiovascular benefits related to wine intake may be due to the combined, additive, or synergistic effects of its various components, with the consequence of improving endothelial dysfunction and insulin sensitivity, inhibiting platelet adhesion, and decreasing plasma levels of fibrinogen and the factor VII of coagulation. Ingestion of red wine is associated with a significant decrease in the expression of several cardiovascular risk markers, at the level of the cell membrane and plasma. However, despite the benefits of alcohol consumption, it should be noted that excessive consumption (more than 2 to 3 Units per day - 16 to 24g of alcohol) is not advised as it is harmful to human health.

Among the various components of alcohol, one of the most studied has been one of the polyphenols, the resveratrol. It has been the subject of an in-depth study due to its potent antioxidant effect (which translates into the neutralization of free radicals) and its anti-inflammatory, anti-cancer, and anti-aging action, by inhibiting the degradation of telomeres. It is found in the seeds and skin of black grapes and fruits as diverse as blueberries and peanut skin. The root of a vegetable, the sorrel, contains resveratrol in concentrations 100 times higher than the skin of black grapes.

In a scientific study, published in the BMJ in 2014, by Marta Crous-Bou *et al* [9], telomere length was analyzed in a population that used the Mediterranean Diet as a food base. An analysis was made of a subgroup of 4676 Nurses, to whom telomeres length was measured and a food questionnaire was applied. The authors concluded that adherence to the Mediterranean Diet was associated with longer telomeres, health promotion, and greater longevity.

The beneficial effects of resveratrol have been demonstrated in several laboratory and clinical studies. Some of these effects are related to the increased expression of NO Synthase (Nitric Oxide Synthase), which increases the production of Nitric Oxide (NO) at the level of endothelial cells, that results in a moderately lowering blood pressure in hypertensive patients. Resveratrol also inhibits the synthesis of Endothelin 1 and the oxidative stress in endothelial and smooth muscle cells. The result is the inhibition of the proliferation of smooth muscle fiber and the infiltration of the vascular wall by immune cells, inhibiting the angiogenesis. Resveratrol's role in modulating the immune system is also known. According to Lucia Malaguarnera [15], resveratrol is also associated with the regulation of immunity through sirtuins (SIRTs), adenosine monophosphate, and other kinases and NF-κB. At the cellular level, it also modulates glycogenesis, lipid metabolism, and mitochondrial biogenesis. Thus, we realize why resveratrol lowers blood glucose in diabetic patients and improves the lipid profile in patients with dyslipidemia.

The discovery of sirtuin enzymes and their relationship with resveratrol and the genes that regulate metabolism has led to the development of a new area of research in human nutrition and the development of new dietary proposals, to reduce obesity and to prolong longevity. One of the best-known publications is "The Sirtfood Diet" by Aidan Goggins and Glen Matten, which presents the foods and recipes considered most beneficial for human health. However, we continue to wait for new scientific evidence to prove the long-term benefit of resveratrol and sirtuins.

Vegetables, cereals, and fruits provide fiber, which controls the glycemic index and improves the lipid profile. They also provide long-chain carbohydrates, folic acid, and vitamins, which have an important antioxidant action and act as cofactors for the conversion of homocysteine to methionine.

Diets low in Vitamin B6 and B12 and folic acid are always accompanied by increased serum levels of homocysteine and today we have consistent evidence of the relationship between homocysteine and Coronary Disease (hyperhomocysteinemia is an independent risk factor). It was Kilmer McCully, a pathologist at Massachusetts General Hospital, who first suggested that high plasma levels of homocysteine could be associated with the development of the atherosclerotic vascular disease. Today we have scientific confirmation that elevated plasma homocysteine levels are an independent risk factor for coronary artery disease, peripheral vascular disease, cerebrovascular disease, and venous thrombosis. hyperhomocysteinemia is present in about 30% of patients with premature occlusive arterial disease.

Dietary fiber has a protective function against colon cancer because it reduces the time of intestinal transit, decreases the time of exposition to various carcinogens, decreases the pH of the colon, and increases the production of short-chain Fatty Acids. As demonstrated by Shanshan Li *et al* [16], a higher fiber intake diet is associated with a significant reduction in all other causes of mortality, including cardiovascular. The conclusion was drawn by reviewing two prospective studies (the Nurses' Health Study and the Health Professionals Follow-Up Study), which included a total of 4098 patients.

Foods rich in antioxidants are also protective against some malignant epithelial tumors. Vitamin A protects against the formation of oxygen free radicals and the peroxidation of lipids. Beta-carotenes are efficient neutralizers of oxygen free radicals. Folic acid appears to have an important role in preventing colon cancer. Vitamin C appears to protect against cancer of the esophagus and stomach. Vitamin E protects against breast, lung, and intestine cancer, probably due to its antioxidant action.

Blue scale fish, such as sardines and mackerel, so characteristic of the Mediterranean Diet, are rich in Omega 3 Fatty Acids, which have a potent action in reducing the production of VLDL (Very Low-Density Lipoproteins) and in thromboxane and in increasing production prostacyclins and fibrinolytic activity.

The Psychological Aspects of COVID-19 in Nutrition

From a general perspective, the consequences of the COVID-19 pandemic for the population go far beyond physical health. We believe that it is essential to investigate the negative impact of COVID-19 on mental health among the general population, exploring the psychological and social effects of those who live with and near the pandemic. Symptoms related to COVID-19 tend to increase psychological distress, e.g., stress, anxiety, worry, and severe fear, which probably can be more contagious than the virus itself. For example, when we are on permanently alert, anxiety ceases to have the positive effect of security, through personal and social protection strategies and behaviors, to incapacitate us and exaggerate the potential outcomes.

The most common indicators of distress-related to outbreaks can be divided into three factors: behavioral, emotional, and cognitive. So, primarily, behavioral signs can be an increase or decrease in energy and activity; more worrying, irritability, crying, anger, and frequent arguing; difficulty in sleeping or relaxing; an extra

necessity to be alone most of the time; having difficulty communicating and listening. Emotional signs can be feeling anxious, depressed, fearful, guilty, angry, heroic, euphoric; not caring about anything; feeling overwhelmed by grief. Finally, cognitive signs can be having trouble remembering things; feeling confused; having trouble thinking clearly and concentrating, and also making decisions.

Consequently, the COVID-19 pandemic related-changes in daily routine boost the coping strategies to deal with psychological distress. For example, lockdown and social isolation, lack of work routines, easy access to unhealthy foods (e.g., high-calorie snacks, fast food) can contribute to a vicious cycle of emotional eating as a strategy for coping with psychological distress (e.g., stress, anxiety, dysphoria). The decrease in social support, access to health professionals, and social awareness content, including advice on food and physical exercise at home, can contribute to increasing variations in eating habits [17].

In a worldwide study, investigators found several changes in participants eating behaviors during the COVID-19 pandemic [18]. For example, consuming more unhealthy food, higher frequency of snacking among core meals, eating without self-control, contrasting with recommendations of the World Health Organization [19]. The presence of anxiety or tedium, less motivation to preserve healthy eating, and an increase in emotional eating, are described as the main causes of the negative changes in eating habits through the COVID-19 pandemic period.

A recent study, where 1,400 Portuguese adults participated during the social lockdown of the pandemic COVID-19, investigators also observed changes in eating habits [20]. Nearly half of the participants (45.2%) recognized eating more frequently, in greater quantity (31.6%) and did not bother food qualitative selection (58.1%). Therefore, corroborating other investigations, people with higher stress and anxiety tend to manage their emotions through food [21,22].

Another investigation explored the relationship between the psychological condition and emotional eating (impulse to eat as a reaction to negative feelings or stress) among the Italian population [23]. Like other studies, an increase in caloric food consumed, and in the amount of elaborated homemade foods with higher caloric value, boost the link between food ingestion and emotions in people who are less competent to manage their diet [23,24]. Gender also influences the emotional eating, with women having more hunger anxiety and need to increase food consumption compared to men [2]. The relation between anxiety, depressed mood, and food dependence that could lead to eating addiction was also found [25].

Addictive habits (e.g., smoking, alcohol abuse) and behaviors that negatively influence physical and psychological health (e.g., changes in sleep patterns, emotional eating) could serve as strategies to cope with pandemic-related psychological distress in a short term basis [26]. However, in a long term, there is a strong possibility and an increased risk of major psychological problems (e.g., anxiety disorders, mood disorders), physical health complaints (e.g., pain), and chronic health problems (e.g., obesity, diabetes).

As the social confinement period is crucial to the safety of public health (helping to reduce the risk of contamination), it is essential to comprehend people's lifestyle behaviors (e.g., nutrition, sleep, physical activity). It's also important to explore the psychological factors with a substantial impact on people's quality of life and well-being (e.g., anxiety, depression, anguish, emotional distress). However, regarding eating

behaviors, it is vital to develop strategies to increase healthy habits, principally by selecting healthier food. Therefore, recognize which groups might struggle in adopting healthy behaviors (e.g., healthy food preferences, sleep routines, physical activity), and develop an intervention directed to each group's characteristics and needs, became crucial. It´s also essential to include mental and emotional coping strategies [27], specifically to improve knowledge, awareness, and self-replication to reduce the risk of isolation, anxiety, and depression among the more vulnerable population.

Conclusion

The chronic inflammatory state, that is connected to several co-morbidities, conditions an immunodepression state and constitutes an aggravating factor for COVID-19. It is this inflammatory state, which associated with the "cytokine storm", found in severe infections by COVID-19, determines the high lethality rate associated with the severe forms of COVID-19.

The nutritional status, which is known to influence the prognosis of many infections, may also play an important role in SARS-CoV-2 infection, as there are several nutrients that are associated with the reduction of oxidative stress and inflammation. The benefit of these nutrients is particularly relevant in COVID-19's "cytokine storm" period, as it is the period of greatest disease inflammatory reaction.

Obesity is one of the most important risk factors for severe forms of COVID-19. Its prevalence is associated with conditions of social inequality between countries and populations, with the most vulnerable groups being the most affected.

The Mediterranean Diet is the known food model as to be the healthiest and the most balanced and preventive. It provides a diet rich in antioxidants and mono and polyunsaturated fatty acids and a low content of saturated fats. It uses olive oil as a fat of excellence and is rich in vegetables, fruits and fiber.

In addition to physical health, COVID-19 infection is also associated to psychological distress. The reaction to the pandemic, by the population, institutions and governments of the countries, showed that stress, anxiety and severe fear could be more contagious than the virus itself.

Confinement, social isolation and changes in work routines are associated with eating more frequently and in greater quantities and without qualitative selection of food, with the consequence of an increase in the prevalence of obesity and overweight.

COVID-19 will go to be present in our lives in the near future. It is important to learn how to establish new life habits so that we can lessen their impact. It is very important to integrate nutritional and psychological care into the strategy to approach and prevent SARS-CoV-2 infection. Our priority should be the consumption of healthy foods, eating a diet balanced in nutrients and adopting strategies of mental and emotional control, aimed at reducing the risk of isolation, anxiety and depression, among the population.

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