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Nutrition, Immunity and Health: How Proper Nutrition can help Combat Infections and Promote a Healthy, Extended Lifestyle

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Abstract

Nutritional intake plays a critical role in health and wellbeing. During the most recent COVID-19 pandemic, a balanced meal plan has had a significant impact on patient outcomes, namely through promoting healthy immune system function and in turn greater rates of post-discharge recovery and survival. With consuming a well-balanced diet becoming ever so more important, it is vital to explore the biochemical mechanisms and public health impacts that certain foods can have. This paper aims to thoroughly describe key molecules and pathways that promote a healthy-functioning immune system, as well as connect this information to varying global public health outcomes.

Keywords: Natural immunity • Immunodeficiency • New pathogens • Biochemical mechanisms

Introduction

Amid the spread of COVID-19, many have questioned whether natural immunity can play a role in preventing the virus from causing severe illness and death. While the CDC recommends vaccination for all healthy populations, regardless of prior immunity, these people do have a valid point. Natural immunity refers to the antibody protection the body creates against a bacterial particle once an individual has been affected with it. For instance, those infected with measles for the first time may face severe symptoms, but it is unlikely they will face the same symptoms of measles following the initial infection, even without vaccination. One limitation to this aspect of natural immunity, however, is that protection against subsequent infection depends on numerous factors, such as the extent of natural immunity *vs.* immunodeficiency, case severity of the specific bacteria, and time passed from the original infection. For the average person, that translates to the original COVID-19 infection that they overcame not being enough to offer them protection against variants that may arise months down the road. But, if a person has received all vaccine doses, they may be left wondering what else they can do to improve their immunity if they were to catch the coronavirus again. The immediate answer that all physicians, nutritionists, and other healthcare professionals would resort to is eating right to promote natural immunity. The idea around utilizing nutrition to improve natural immunity revolves around how healthy food stimulates immune cell activity, and protects cells against oxidative damage, among other factors. In other words, proper nutrition essentially offers an indirect mechanism to ensure that natural immunity is operating at its optimal capacity to counteract even new pathogens.

Literature Review

Global health

In fact, these trends can be traced across cultures and regions and are strongly correlated to differences in life expectancies among different populations. For instance, Japan's population has the longest life expectancy out of all G7 countries, with Japanese men living an average of 81.1 years and Japanese women living an average of 87.1 years, and an overall average life expectancy of 84.4 years [1]. The extended life expectancy compared to other developed countries like the U.S. and U.K has been highly correlated to staples in the Japanese diet. Specifically, seasonings like Miso, commonly used in Japanese households, contain several B vitamins, niacin, zinc, and other probiotic bacteria that promote both proper immune system functioning as well as growth of essential gut bacteria. As a result, the Japanese population experiences reduced cases of viral infections like pneumonia and had an overall decreased risk of death or severe illness from COVID-19, as well decreased risks for chronic inflammation brought on by lifestyle diseases like Type II Diabetes and Heart failure. In fact, one study that examined 13,695 patients comprised of both Japanese and non-Japanese individuals in intensive care units found Japanese patients experienced less anaphylaxis and infectious disease, and while both populations stayed in the ICU for the same duration, Japanese patients tended to have pre-existing factors that allowed for better outcomes [2].

Proper nutrition

Introduction to proper nutrition: Before discussing the mechanisms and results that nutrition plays in immunity, it's important to define what constitutes proper nutrition. One main criticism of western diets is that it fails to fulfil daily vitamin requirements and leads to build-ups of unhealthy cholesterol, specifically Low-Density Lipoprotein (LDL), high levels of which can promote heart disease. In fact, one study found that at least half of the US population fails to meet the daily recommended intake of vitamin B-6, vitamin A, magnesium, calcium, and zinc. Further, nearly 33% of the population failed to meet daily intakes of folate [3]. Proper nutrition therefore constitutes consuming foods high in essential vitamins and those that include High Density Lipoprotein (HDL), a lipoprotein that removes cholesterol from the blood and counteracts heart disease. These foods simultaneously prevent the build-up of both unhealthy fat and inflammatory markers throughout the body. Examples of such foods include citrus fruits like oranges, kiwis, and grapes, which contain Vitamin C, as well as fish products like Salmon, which help reduce LDL levels in the blood [4].

The crucial role of vitamins

Vitamin B: Adequate vitamin intake is important because it allows for optimal performance of the cellular processes related to immunity. For instance, an important immune process that is reliant on vitamin intake is Oxidative Phosphorylation, which is needed to create ATP and power different

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energetic processes in the body [5]. Resting lymphocytes generate energy from Oxidative Phosphorylation, on top of fatty acid oxidation, whereas active lymphocytes rely on glycolysis [6]. In terms of Oxidative Phosphorylation, five important coenzyme substrates are used in this case: TPP (Vitamin B1), Lipoamide, Acetyl CoA (Vitamin B5), FAD (Vitamin B2), NAD^+ (Vitamin B3). Any deficiencies in these enzymes would inhibit this process and could potentiate structurally deformed or otherwise ineffective lymphocyte molecules. Foods that could be consumed to ensure that Vitamin B levels are at adequate amounts include brown rice, eggs, legumes, and fortified breakfast cereals. In tandem to this, alcohol should be avoided to prevent degradation of the Vitamin B molecule.

Vitamin C: Vitamin C is another critical enzyme that, while not many in the west lack to the extent of Vitamin B and D, is still critical to consume to ensure optimal immune system activity. Specifically, Vitamin C (Ascorbic Acid), serves as a cofactor in immunoglobulin cells, which are antibody cells that recognize and bind to the antigens of foreign bacteria and viruses. This means that during sickness, when immunoglobulin cells are being activated, it supplies coenzymes that are needed to bind to the immune response enzymes. Specifically, ascorbic acid works as an electron donor and acts as a cofactor for fifteen enzymes, including for sodium dependent transporters and renal excretion, among other uses [7]. Simultaneously, Vitamin C also serves as an antioxidant, eliminating free radicals that, as aforementioned, can lead to the cellular damage of immune cells and in turn cause an inefficient immune response. Fortunately, Vitamin C can be found in low-calorie foods that already makeup a healthy diet. These foods include citrus fruits like oranges, lemons, and grapes, as well as tomatoes, bell peppers, and leafy green vegetables. Since humans are unable to naturally produce the vitamin, it's essential to obtain it from the diet.

Vitamin K: While not as commonly seen in public health reports, Vitamin K is another critical enzyme that is important to consume, namely because it is involved in the coagulation/clotting cascade that is intended to detect breaches in the immune system from external particles. Specifically, this cascade works in the following manner: cell distress at a certain location in the body, potentially due to physical breaking of the cell from a foreign object, triggers inflammation that then alerts interleukins to travel to the affected area and initiate some response, likely clotting of the blood and to degrade the foreign object that may have entered the bloodstream [8]. Vitamin K is the first step in activating this cascade pathway that ultimately leads to a fibre network of enzyme clumps which are then deposited in the injured area: diving deeper into this process, normally Vitamin K Reductase reduces Vitamin K, which allows it to send enzyme clumps into a certain area, which then creates proteins to clot blood and take care of the injury, and Vitamin K is finally re-oxidized to complete the process. Similar to many other vitamins, Vitamin K is found in foods commonly available in western countries yet in those not consumed as frequently as is recommended: in green leafy vegetables such as kale, spinach, turnip greens, as well as in products like liver, eggs, and cauliflower.

Vitamin D and calcium: During the pandemic, reports primarily from Nordic countries such as Norway and Sweden have also highlighted the role of Vitamin D in mounting an effective immune response. Vitamin D is one of the fat-soluble vitamins that helps retention of calcium and phosphorus, and has also been proven to reduce the growth of cancerous cells and control infections while simultaneously preventing inflammation. Mechanistically, Vitamin D essentially serves as a prohormone that requires type b ultraviolet sunlight rays to photolyze 7-Dehydrocholesterol to (provitamin D3) to previtamin D3. The conversion of D3 into an active compound is done by a two-step enzymatic hydroxylation process, which converts a carbon-hydrogen to a carbon-hydroxyl bond.

This takes place at the liver, where both are converted to 25-hydroxyvitamin D [25(OH)D] by 25-hydroxylase which belongs to cytochrome P450. The kidney is the second place that this reaction occurs where 1a-hydroxylase turns 25(OH) D to 1, 25 - dihydroxyvitamin D_2 or D_3, calcitriol [9]. This is regulated by the parathormone and regulators such as calcium, phosphate, and calcitonin. Vitamin D in its active form 1, 25 $(OH)_2 D_3$ binds to its receptor Vitamin D Receptor (VDR) and works as a transcription factor. It then transcribes several genes, one of which is then translated into the Calcium Binding Protein CaBP-9K that activates two calcium channels TRPV6 and TRPV5 [10]. The importance of this mechanism is to allow maximum retention of calcium. Immunologically speaking, calcium plays a critical role. For instance, a calcium signal control dictates whether immune cells can uptake nutrients to then promote growth and multiplication of immune cells. Additionally, in the T lymphocyte cells of the immune system, calcium is necessary to control gene expression and prevent an over activation of the immune system. Immune system activation is associated with inflammation, so constant activation can lead to chronic inflammation that has the potential to degrade healthy cells. In fact, this is what is commonly seen with prolonged stress, whereby high cortisol levels that signal immune system activation reduce immune system efficacy in the long run. Further, for lymphocytes, calcium acts as a secondary messenger.

Specifically, while resting lymphocytes have low levels of Ca^{2+} once the antigen receptors on immune cells are engaged, there is a calcium flux through the calcium channels CRACM1 and STIM1 [11]. While many people consume calcium frequently through dairy and nut products, one main issue is calcium retention. Foods and products that deplete the body's calcium stores include food cooked with excessive salt (sodium). When sodium intake becomes too high, the body gets rid of sodium through the urine through a natural homeostasis response, which also causes the release of calcium, a process called calciuria. If too much calcium is being released from the urine, this can also lead to the formation of kidney stones and other urinary tract problems [12]. In tandem with avoiding salts, foods that promote Vitamin D production include salmon, egg yolks, tuna fish, and orange juice. While many of these items are easier to obtain in western countries, in many impoverished nations Vitamin D deficiencies will be seen more frequently as these food items are rarely consumed due to its cost.

Health ailments

Obesity: As seen in lower socioeconomic areas even within wealthy countries like the U.S, diets impacted by a lack of resources tend to be richer in sugar and fat which contribute to obesity. Obesity, defined by a Body Mass Index (BMI) greater than 30, in turn leads to many secondary health effects like chronic inflammation that can impact proper immune functions. The more obese someone is, for instance, the more Vitamin D they will need given that less of the fat-soluble vitamin will be available for use in calcium absorption. Evidence of this lies in studies showing a higher association between lower serum levels of 25(OH) D and obesity [13]. As previously references, BMI is the index to measure an individual's nutritional status and is calculated by weight in kg divided by the square of the individual's height in meters. Ratios of weight/age and weight/height like BMI can be useful tools in measuring nutritional health, especially in children to then introduce early interventions. Correlations between a person's weight and their age or height provide insight into if they are getting enough nutrients to maintain an appropriate weight and build a healthy body mass and conversely if they have too much mass than is manageable for the body.

Starvation: On the opposite side of not consuming vitamins through unhealthy, processed food is a lack of vitamins from starvation, which can be just as dangerous if not more. A primary issue faced by those living in impoverished countries is a lack of adequate and non-contaminated food, which leads to starvation and deficiencies in essential vitamins, which even over a short period of time can lead to cellular degradation, reduced immunity, and a plethora of other health issues. During periods of starvation, the body converts stored glycogen to glucose, and uses this as an alternate source of energy in a process called Glycogenolysis. This mechanism is intended to utilize pre-existing glycogen as a temporary food source until nourished again. However, during starvation epinephrine and glucagon, a hormone that stabilizes blood glucose levels in the body, is in high concentration in the blood. As a result, fats stored in adipose tissue are released from fat cells as free fatty acids, and when they're broken-down ketone bodies begin to accumulate in the blood and lower the pH in a mechanism in a process known as ketoacidosis. Overtime, ketoacidosis can lead to complications that many diabetic patients face, including pneumonia and other infections, unconsciousness and even death due to a homeostatic disruption.

Simultaneously, cholesterol levels can fall to dangerously low levels, thereby impairing brain activity due to insufficient hormone production [14]. Over a longer period, as blood glucose decreases further and glycogen reserves run out, catecholamines, which are hormones produced in response to stress, will be secreted to initiate "backup" mechanisms such as Gluconeogenesis, a process where new glucose is made from non-carbohydrate molecules such as amino acids in the muscle [15]. While not a harmful mechanism in the short run, Gluconeogenesis will prevent muscle mass gain and long-term continuation will deplete amino acid stores, which are also needed for tissue repair and formation of hormones and can't be continuously converted to glucose. These include signaling hormones that could be used to activate the immune response, or trigger adaptive immunity, and would now be lacking due to the body's need to supply glucose to the brain.

Healthy food habits and consumption: One main benefit of consuming foods that satisfy vitamin deficiencies is that they also tend to be rich in antioxidants, which protect against oxidative stress that leads to cellular damage and, down the road, conditions like cancer and other inflammatory disorders. Oxidative stress refers to when there is an imbalance between increased levels of reactive oxygen species (ROS), namely free radicals, and a low presence of antioxidants, which then allows local cellular structures to be damaged [16]. Typically, immune cells use oxygen species to induce free radicals that destroy viruses and bacteria in a mechanism that involves an oxidative burst. However, when macrophages, a type of white blood cell involved in immunity, produce free radicals to fight off germs, any leftover radical species can cause cellular damage to healthy cells in the area and trigger an unwanted inflammatory response as a result.

Accumulation of these radicals from a lack of antioxidants will also continue to damage healthy cells in the area, promoting chronic inflammation down the road that would both decrease immunity directly through immune cell damage and indirectly through bone marrow damage [17], which can prevent subsequent production of T and B lymphocyte cells for an effective immune response. Vitamins like C and E are excellent sources of antioxidants and are especially helpful in maintaining the reductive nature of the cytosol membrane, thereby preventing compounds like thiols from leaving and causing damage elsewhere in the cell [18]. Since the outside of the cell is an oxidative environment, antioxidants go into the cell and sequester any oxidative processes within the cell to maintain this internal to external difference. One study found that spices and herbs have the highest antioxidant quantity, followed by plant-based foods that include broccoli and legumes.

Berries and berry products, including other fruits, also contain high antioxidant quantities [19]. Fortunately, many of these products are easily available globally, especially in impoverished areas found in Asia and Africa where spices and naturally grown fruits are integrated in the day-to-day diet. Interestingly, these food items consumed less frequently in western countries, where more processed food lacking fruits and vegetables is present. In fact, one study even linked the reduction in antioxidants from spices found in the Indian diet to a decreased risk of Alzheimer's, as well as numerous bacterial infections [20]. For viral infections like COVID-19, antioxidant consumption can alter the quantity of effective T cells being released. Since T cells are responsible for storing the immune memory of past infections, decreased T cell count can translate to a reduced immune memory of the coronavirus antigens and hence greater risk for subsequent infections.

Folate: For many populations that lack access to foods containing the essential vitamins, or those that otherwise cannot eat these products due to dietary restrictions, supplements found in capsule form can still be used to fulfill these vitamin requirements. In fact, for specific populations such as pregnant women who receive less calcium and folate due to the fetus up taking these resources, supplementation is necessary to maintain optimal immunity and health overall. Folate, the natural form of Vitamin B9, is an important molecule for DNA replication. It is also important for enzymatic reactions as it acts as a substrate for amino acid synthesis. Folate needs increase during pregnancy as it is required for growth of the fetus. To become active, folic acid is converted to dihydrofolate (DHF) which in turn converts to tetrahydrofolate (THF) through reduction catalyzed by DHF reductase (DHFR) an enzyme. THF in turn is converted to the active form L-methyl folate by methylene tetra hydrofolate reductase (MTHFR). MTHFR is an important enzyme involved in a wide variety of processes involving the metabolism of folate and methionine, while L-methyl folate is required for carbon transfer reactions such as methyl donations [21].

These are important for purine/pyrimidine synthesis during RNA and DNA assembly required for DNA methylation. Ultimately, this contributes to the formation of immune cell structures like T cells and bone marrow for other white blood cell types in both the mother and fetus. Like nearly all medication and healthy foods, however, overconsumption of vitamins like folic acid (vitamin B9) can have negative impacts. The recommended intake of folic acid for adults is 400 mcg/day. Women who are planning to get pregnant should take 400 to 1,000 mcg/day, but one issue many people face is that folate is also found in commonly consumed foods like fruits, nuts, and fortified foods like cereals and pasta. One clinical study found that even supplementing 1 mg of folic acid in study participants increased the chances of prostate cancer significantly, compounding any folic acid received from diets and other supplements [22].

Extensive folic acid consumption, for instance by both consuming foods with lots of folic acid while also taking folic acid oral supplements, can promote the growth of cancer cells, particularly prostate cancer, likely tied in with folic acid's role in DNA synthesis. As afore mentioned, one function of folic acid metabolism is the support of DNA synthesis and repair through forming new nucleic acid building blocks. This metabolic process is the *de novo* synthesis of deoxythymidine Monophosphate (dTMP) from deoxy Uridine Monophosphate (dUMP) through addition of a methyl group by the enzyme thymidylate synthase. This conversion from dUMP → dTMP is fostered by Tetrahydrofolate (THF), also called Tetrahydrofolic acid, a derivative of Folic Acid. Overproduction of enzymes like thymidylate synthase from folic acid consumption can induce the body to overproduce degradation enzymes like proteases.

Conclusion

Conclusively, ensuring an adequate amount of nutrients are consumed in one's diet is important for health maintenance, especially in terms of ensuring optimal immune system activity. Values like Recommended Daily Allowances (RDAs) are safe and adequate nutrient levels that should encompass the variability amongst people and are based upon the average physiological need for an absorbed nutrient but then adjusted to account for bioavailability and variation. They are also based on different age groups, but are accurate enough that it covers up to 97% of the U.S. population, and is likely applicable to other populations as well. In many western countries, namely the U.S. and the U.K, while nutritious food is commonly available in grocery stores and supermarkets, these tend not to be the first choice for many consumers. In turn, long term health and immunity is impacted, and susceptibility too many illnesses greatly enhanced. While food like green leafy vegetables and fruits tend to cost more than fast-food, the ultimate individual and economic cost from an unhealthy lifestyle and its associated disease management tend to outweigh the minute cost of more expensive groceries. Many programs in the U.S. and other developed nations have started to teach young children about healthy nutrition, and as early interventions lead to the best outcomes, these programs need to be promoted globally in particularly lower socioeconomic and underserved populations where unhealthy food may be seen as a cheaper, quicker option.

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