ILSI 2021 Annual Symposium Session 8: COVID-19: Nutritional Vulnerabilities and Food Supply Challenges

Transcript of the presentation, Control of Viral Infection: what is the Role of Nutrition? Philip Calder, PhD, University of Southampton, United Kingdom

I'm going to kick off by talking about the immune system and how it works and then some different aspects of the interaction of nutrition and nutritional state with immunity, and how that might influence risk and severity of infectious disease, particularly viral infections. Just to start, this is my disclosures. As I say, I'm going to start by saying something about the immune system just to get everybody up to speed, talk briefly about why different people have different immune competence, sources of variation in immunity. Then, I'll mention the impact of obesity on immunity and susceptibility to infectious disease. Make some points about nutrition in general, and then say something about three different micronutrients that I think are very interesting in the context of immunity. And then, I'll summarize at the end.

The immune system is the way we protect ourselves from invading pathogens, things like bacteria, viruses, and so on. The immune system is composed of cells, but these often aggregate together in tissues like the spleen, lymph nodes, discrete pockets in the gut wall, and so on. But essentially, the immune system is our defense system. And we know that a well-functioning immune system provides good defense against pathogenic organisms. And we know that with certainty, because people who have immunosuppression or who are immunocompromised are at much greater risk of infections out of infections becoming severe, even fatal.

The four general functional features of the immune system are listed here. First, it presents an exclusion barrier to keep pathogens out. You could think of the skin, the mucosal linings of the gastrointestinal and respiratory tracks, and the acid pH of the stomach, as being components of the exclusion barrier. Secondly and really importantly, the immune system recognizes and identifies organisms if they break through the exclusion barrier. And this recognition is key to how the immune system protects us. Thirdly, it acts to eliminate those organisms that it recognizes as being harmful. It actually destroys those organisms, it kills bacteria, it kills virally infected cells, so viruses have no way to replicate. Finally, the immune system has a memory component, so this is immunological memory. Your immune system can remember many of the encounters it's had before. And what that means if a person has reinfected, the response is faster and more vigorous than it was the first time. And this memory component of the immune system is the basis of vaccination, which is very topical right now.

The immune system is pretty sophisticated with these recognition, elimination, and memory functions. And this high level of sophistication is brought about because of the many different components of the immune response. These are typically divided into innate or natural immunity and acquired or adaptive immunity. Innate immunity includes the barrier functions, but also some cellular functions like natural killer cells and other innate cells. And it includes the inflammatory response and the function of phagocytic cells, which engulf and destroy microorganisms. Acquired immunity includes the function of different T lymphocytes, and there are many different types of T-cells, and B lymphocytes. Each of the different cells involved in the immune response has its own specific function. For example, B lymphocytes are the cells that produce antibodies, T lymphocytes are the controllers, and phagocytes carry out this process of engulfing microorganisms. Some T cells like cytotoxic T cells and also natural killer cells, they can kill virally infected cells and also tumor cells.

So, what we see is different cellular components that each have their own individual roles in the immune response, but all of these different cell types have to communicate with one another and interact to make an effective response to a particular organism. And I capture that in this figure from a review I published last year with regard to antiviral immunity. The detail of this doesn't matter, but what you see as the many different cell types interacting with one another, ultimately aiming to defend us against invading viruses. We see the communication between phagocytes, T cells, B cells, the production of antibodies, direct attack on virally infected cells by some immune cell types. There's lots of interaction, there's lots of communication, and there has to be coordination.

Again, just to summarize, the immune system presents a barrier to keep pathogens out, but it contains these really sophisticated cellular components of both innate and acquired immunity that come into play if the barrier is weakened or if these organisms break through the barrier. Of course, in the last 14 months, weak immune systems have been exposed as a major public health challenge, at least in parts of the world where there was less concern at the current time about infectious disease, as Jeff alluded to. We've seen significant illness, significant mortality, as a result of the presence in our environment of a new virus, which of course is highly virulent.

Now, we know some people show severe COVID-19, some people die as a result of that, but in fact, probably most people who are infected so very mild symptoms. In fact, many will be asymptomatic. Some people are coping quite well with the presence of coronavirus. Others are not. Why is that? Well, maybe it's because they have different levels of immunity, if you like, different immune competency. Here I'll show some of the many factors that can influence the immune response, and of course, these factors will vary between people. There are some clear obvious things like genetics will determine the immune response, infection and infection history, vaccination, some illnesses, some medications. Things like cigarette smoking and alcohol consumption, they can impair the immune response. Stress. Physical, physiological, and psychological stress also impair immunity.

The immune response also changes with the life course. You're going to hear later on about the immune decline that happens as people age, so-called immunosenescence. Physically fit people have stronger immune systems than unfit people. As I'm going to show you, body fatness impacts on immunity. Frailty impacts on immunity. So, overweight people and also people with frailty have paired immunity. I'm going to talk about the influence of diet in general, and some specific nutrients that support the immune response, and the gut microbiota, which again you're going to hear a little bit about later on, is also important in regulating the immune response. So, there are many different factors involved that affect the immune response. Therefore, it's unsurprising that some people in the population have stronger immunity than others.

I'm going to start by talking about the effect of body fatness, and I'm going to start right on with COVID-19, because relativity early on in the pandemic, it was noticed that there seemed to be a disproportionate number of people with obesity who were hospitalized with COVID-19 and who were displaying severe COVID-19 symptoms. This is data from one of the first studies. These are French authors, where they simply related body mass index, from normal weight to BMI more than 35, to the need for mechanical ventilation in patients who are already in the ICU with COVID-19. These were all sick patients, but some of them required extra respiratory support. And what the authors identified was it's sort of a dose response relationship, if you like, between body mass index and the need for ventilation. In other words, the disease was more severe, the higher the body mass index.

Now, this may not be a surprise if you know about the literature on obesity and immunity, because it's very well described. Obesity impairs the activity of many cells of the immune system, including cytotoxic T cells and natural killer cells that are involved in antiviral immunity. Obesity reduces antibody responses and reduces the production of an important antiviral cytokine, interferon gamma. It was already known that people with obesity are more susceptible to infections, and they don't respond so well to some vaccinations, including the seasonal flu vaccination, compared with normal weight people. In the influenza pandemic of about 10 years ago, people with obesity showed poor antiviral responses and recovered poorly from disease compared to normal weight people. Also, even when obese people are vaccinated with the seasonal flu vaccine, they have a higher risk of developing influenza compared to normal weight people. The immune system is weak in people with obesity, this predisposes to poor vaccination responses and predisposes to infection. Paradoxically, obesity is associated with low grade inflammation. This is a real imbalance in the immune system. Not enough immunity, too much inflammation.

Now, this is a really interesting study where American researchers, this is Melinda Beck's group, took cells from healthy weight people or normal weight people, overweight people, and people with obesity. And they incubated those cells in a test tube with the influenza vaccine. They were looking at the ability of cells from people of different body mass index to respond to vaccination in a test tube. And the outcomes were activation of cytotoxic T cells, important in antiviral immunity, the production of this protein, which is one of the proteins that helps the immune system kill virally infected cells, and the production of interferon gamma. And you see that the response was always weaker if the cells came from people with obesity, compared to if the cells came from people of normal weight. And the cells from overweight people were somewhere in between. So, the immune cells of people with obesity have poor responses.

Let's move on to talk about specific nutrients. People often struggle with the idea that nutrition can be important in supporting the immune system. Here I list seven reasons for nutrition being vital for the immune system to function. Firstly, the immune system has a high demand for energy, and of course, the fuels required for energy generation come from the macronutrients that we eat. Secondly, the immune system is highly biosynthetic. I mentioned the production of antibodies, cytokines. Also, there's huge cellular proliferation. There's lots of biosynthesis going on. And, of course, the building blocks for this biosynthesis come from things that we eat. Some nutrients are very important regulators of the molecular and cellular aspects of the immune response. Zinc, vitamin A, vitamin D would be good examples of that. Some nutrients are substrate for chemicals involved in immunity. For example, the amino acid arginine is the substrate for nitric oxide production, and nitric oxide kills bacteria. As I'll show you shortly, some nutrients have specific anti-infection roles. Again, the zinc and vitamin D would be good examples of that, and vitamin A, and maybe selenium as well.

Part of the immune response involves inflammation, and the aim of inflammation is to create a hostile environment for pathogens. That environment is also dangerous to our own cells, so we have to be protected from the oxidative stress and the inflammatory stress that the immune response imposes, and many antioxidants, vitamins, minerals, other nutrients might be important there. And then, finally, as I mentioned already and as you'll hear later on, the microbiota is really important supporting the immune response. And, of course, our diet controls our microbiota.

One way to think about this is nutrient supply influences nutrient status and nutrient stores, and that influences the immune function. And in turn, immune function determines our ability to defend against pathogens. If we have an inadequate nutrient supply, too little protein and energy, micronutrient deficiencies, we have inadequate status and stores, we have impaired immunity and we have impaired ability to defend against pathogens, that means we have more infections, more severe infections, infectious illness, and death.

People are being interested in which nutrients are really important in supporting the immune response. Researchers have been looking at this for decades now. Now, it's been identified in fact that there are multiple nutrients that are really vital for the immune system to function optimally. This includes fat-soluble vitamins, particularly A, D, and E, water-soluble vitamins, all of the B vitamins, vitamin C, many minerals including zinc, copper, selenium, and iron, essential and other amino acids, essential and other fatty acids. And also, some of the polyphenolic compounds from plants all seem to have important roles.

If you're interested in micronutrients, about a year ago, this review on micronutrients, immunity, infection, a very comprehensive review was published in nutrients. And this is a figure from that review, which hopefully you can see. What the authors have got is the barrier function here. They've got the cellular components of the innate immune response here, the inflammatory response, antigen presentation, T cell-mediated immunity, and B cell-mediated immunity. And then, these darker circles are the nutrients, the micronutrients, that are really important for supporting that component of immunity. So, within any of these circles, you see multiple micronutrients listed. For T cell-mediated immunity, you see vitamins A, D, C, E, B6, B12, folate. We see zinc, iron, copper, and selenium. So, multiple micronutrients are important for all these aspects of immunity. And in fact, the same micronutrients are listed in multiple boxes. So, multiple micronutrients have multiple roles in supporting the immune response.

I'm going to talk about three of these in the context of COVID-19. Vitamin D, zinc, and selenium. First of all, vitamin D has many roles in the immune system. Immune cells have the vitamin D receptor, so that means they can respond to vitamin D. And interestingly, some cells of the immune system, including macrophages and dendritic cells, produce the active form of vitamin D, 1,25-dihydroxy-vitamin D. Normally, we think of that being produced by the kidney. That's the sort of the classic pathway of synthesis of the active form of vitamin D. But, in fact, as I say, dendritic cells and macrophages also produce the active form. And I think the fact that the immune system produces the active form of vitamin D tells me that vitamin D must be very important to immunity. Vitamin D plays roles in controlling the function of antigen presenting cells, T cells, and B cells. It also promotes the release of antibacterial proteins like cathelicidin, beta defensins. And overall, it has important role in both antibacterial and antiviral defenses.

This is a meta-analysis of the effect of vitamin D deficiency on the response to seasonal flu vaccination. The seasonal flu vaccine includes three different strains of the flu virus. The H1N1, the H3N3, and the B strain. You can measure in a person's blood antibodies to each of these three viral strains after a person has been vaccinated. And what the meta-analysis shows is that vitamin D deficiency impairs the response to the B strain and the H3N2 strain of the flu virus. So, vitamin D deficiency impairs the vaccination response, so it impairs the immune response. That would translate into increased susceptibility to infection with low vitamin D status.

These are data from over 7000 middle-aged British adults who gave blood in different parts of the year. Vitamin D was measured, that's the gray histogram on the left here. And so, you see vitamin D levels are highest in summer, lowest in winter. Respiratory tract infections were monitored in those same individuals across the year. Respiratory tract infections are high in winter, low in summer. This is an inverse association between vitamin D status and respiratory infections. Now, on the right, if you look within any season, winter, spring, summer, autumn, and you look at the effect of vitamin D status within a season on respiratory infection, and whether it's winter, spring, summer, autumn, those individuals with highest vitamin D status always have the lowest risk of respiratory infection. Of course, this is just an association. It doesn't show cause and effect. Cause and effect would come from randomized control trials giving people vitamin D.

In fact, quite a number of those trials have been done, vitamin D versus placebo, looking at respiratory tract infection. This is a meta-analysis published in British Medical Journal in 2017, of 25 trials and 11,000 adults and children, giving vitamin D with different dosing regimens and different doses and, obviously, different durations, and then reporting on respiratory tract infections. And what the researchers found was that those individuals given vitamin D had a lower risk of respiratory tract infections than those individuals given a placebo. In other words, vitamin D prevents some, most, the risk of respiratory tract infections. In subgroup analysis, they noted that patients who were vitamin D deficient gained most from vitamin D supplementation, which, of course, makes sense.

People have been quite interested in vitamin D in the context of COVID-19, and there are dozens of papers associating low vitamin D status with incidents of COVID-19 and severity of COVID-19. Of course, again, these are just associations. They have been subject to systematic reviews and to meta-analyses. This is one of the systematic reviews that identified that studies show that blood vitamin D status determines the risk of infection with COVID-19, seriousness of COVID-19, and mortality from COVID-19.

This is a meta-analysis looking at vitamin D deficiency, showing that Vitamin D deficiency increases the risk of severe COVID-19, compared to vitamin D sufficiency. Vitamin D deficiency increases the risk of hospitalization with COVID-19, and vitamin D deficiency increases the risk of death from COVID-19. Again, all from association studies, but quite convincing data.

There are some randomized control trials of different robustness looking at giving people vitamin D or not, and outcomes from COVID-19. Often, these have been done in people once they reach hospital with COVID-19, giving them normal care with them without usually a high doses of vitamin D over the first few days of hospitalization. In fact, these trials have already been subject to meta-analysis. This is the effect of vitamin D supplementation on length of ICU stay. And you see vitamin D supplementation reduced length of ICU stay by about 90% in the meta-analysis of these three studies. So, vitamin D supplementation in people hospitalized with COVID-19 seems to improve outcome.

Let's look at zinc now. Zinc also supports the function of many different cell types, contributes to antioxidant protection, reduces inflammation, and as I'll show you in the next slide, it has very specific antiviral actions. Supplementation studies with zinc, some older studies, some newer studies, show that giving people with low zinc status or low zinc intakes, these are usually older people in these trials, giving them supplemental zinc has been demonstrated to increase, to improve some immune biomarkers like T cell function, for example. There are also some studies showing zinc improves response to vaccination, and there are quite a few trials looking at the ability of zinc to treat infectious illness, both diarrheal and respiratory infections. And indeed, there are meta-analyses showing that zinc can be used to treat severe pneumonia. So, zinc seems to be important in supporting the immune system, preventing viral infection, and maybe even treating viral infection.

One of the intriguing things about zinc is it has specific antiviral actions. This is coronavirus, the genome of coronavirus is single-stranded RNA. For the virus to replicate, it has to produce another copy, a new copy of its genome, it has to produce viral protein, and then the virus subunits assembled. Now, the first step in both the RNA synthetic pathway and the protein synthetic pathway is catalyzed by this enzyme, RNA-dependent RNA polymerase. And it turns out the zinc is an inhibitor of RNA-dependent RNA polymerase. So, zinc may have a specific role in preventing replication of corona virus. This is nicely shown in this paper from 11 years ago by Dutch researchers, where they did cell culture studies, looking at the effect of zinc on coronavirus replication.

They infected epithelial cells, you remember, coronavirus infects respiratory epithelial cells amongst other cells. They infected epithelial cells in a laboratory with coronavirus. These are the different coronavirus, RNAs, that are produced. And then, they added to the culture medium, increasing concentrations of zinc. And you see, as the concentration increases, so the amount of viral RNA decreases. Of course, this wasn't the only experiment they did, but their experiments showed quite clearly that zinc can prevent coronavirus replication. The concentration of zinc in the bloodstream is around about here. We may be able to get additional antiviral effects by raising the concentration of zinc in the bloodstream or in interstitial fluids. Now, just coincidentally, about 18 months ago, there was this really nice review on zinc and antiviral immunity and advances of nutrition, that talks about the different parts of viral biology that zinc interferes with. So, that's pretty interesting.

Now, again, people have been interested in zinc and COVID of course, so these are the sorts of studies that have been produced so far. This is a study looking at the zinc status in healthy controls and people hospitalized with COVID-19. People hospitalized with COVID-19 have lower zinc status than healthy controls. Those who are discharged from hospital had better zinc status than those who died as a result of COVID-19. Another study showing low zinc status in patients with COVID-19 compared to healthy controls. And another one showing zinc is lower with severe COVID-19 compared to mild to moderate COVID-19. And then, this is a receiver operator characteristics plot, where the authors identified that low zinc was a very highly sensitive and specific marker or predictor of critical illness in COVID-19. There are a couple of randomized controlled trials of zinc in patients hospitalized with COVID-19 showing that the zinc can improve outcomes and reduce mortality.

The last nutrient to talk about is selenium, which I think is much overlooked. Selenium supports the function of many cell types, contributes to antioxidant protection, reduces inflammation. It improves immune biomarkers, at least in some studies. And it has been used in various viral infections with some benefits. Now, there's been quite a lot of research on selenium deficiency in mice, and these studies show that selenium deficiency impairs the immune response, increases susceptibility to viral infection. Selenium deficiency allows viruses to mutate, including the flu virus, and it allows normally weak viruses to become more virulent. And I think this is really interesting in the context of the emergence of coronavirus variance, whether these emerge because some people have a nutritional environment, physiological nutritional environment, that permits viral mutation. I think that's an interesting question.

Now, for me, the key study of selenium and immunity is this study carried out in Liverpool, published in 2004. This is a study in adults with low selenium status, who were put into a randomized control trial, and they received placebo, 50 or a hundred micrograms of selenium per day for a period of time. And then, they would give him the oral polio virus vaccine. The polio virus vaccine given orally, it's not injected, and it's a live polio virus. It's live but attenuated. It's still alive, but it's not dangerous. Then, they took blood from these people, and they stimulated the blood in a test tube with the polio virus. This is interferon gamma production. Before vaccination, these cells from these people don't respond to polio virus. Post vaccination, they do, they produce interferon gamma. This is interferon gamma at 7, 14, 21 days, and the placebo group in the dark bars. But you see, interferon gamma production is increased at 50 micrograms of selenium per day, and it's increased even more at a hundred micrograms of selenium per day.

So, giving selenium seems to improve T cell responses and interferon gamma production in response to polio virus exposure. Now, because the polio virus is alive and has given orally, if it's not eliminated from the body, if it's not destroyed, if it's not contained, the virus appears in the feces. This is the number of people, 20 per group, who had polio virus in their feces at one, two-, and three-weeks post vaccination. In the control group, even three weeks post vaccination, 14 out of 20 individuals had polio virus in their feces. This was lower, it was nine in the 50 micrograms per selenium per day. And even lower, seven out of 20, at a hundred micrograms of selenium per day. So, selenium results in better viral clearance.

The other thing these researchers looked at was mutant viral sequences in the feces. On the left of the bottom panel, these are fecal samples from the controls, 50 micrograms of selenium in the middle, and a hundred micrograms of selenium on the right-hand side. This is the normal polio virus sequences here. In the control group, you see the emergence of these mutant sequences. So, even over the course of a few days to weeks, the polio virus is mutating in the individuals in the control group. That seems to be less at 50 micrograms of selenium per day. And it seems to be almost absent at a hundred micrograms of selenium per day. So, giving supplemental selenium prevents viral mutations in humans. Or to put up the other way around, selenium deficiency permits viral mutations to occur in humans just as it does in mice. So, again, people have been interested in selenium status in COVID-19. Again, these are data showing selenium status is lower in people hospitalized with COVID-19 compared to healthy controls. It's higher in those who are discharged compared to those who died.

To summarize, what I've told you is the immune system is central to protection against infection. It's highly complicated, it's highly sophisticated. I mentioned that obesity is associated with impaired immunity, so is frailty. So, under nutrition and over nutrition both impair immunity. I've talked about the role of specific nutrients and particular vitamins and minerals that have important roles in supporting the immune system. I've told you that low intakes and status of these nutrients impairs the immune response and makes people more susceptible to infections, including viral infections. And this situation can be prevented or reversed by repletion. Zinc, and maybe vitamin D as well, has special roles in antiviral immunity. And I think this effect of selenium, which no one is really talking about very much, is really intriguing. So, I think, to really wrap it up, nutrition has a key role in dealing with pathogens, both bacteria and viruses, and in preventing infection becoming more severe. And micronutrients are really vital for this. Thanks very much for your attention.