Nutritional support and COVID-19

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Lecture objectives

• Discuss typical targets for intervention in infectious disease
• Discuss the role of nutrition in immune system function
• Describe dietary components including supplements that have been studied in relation to COVID infection
• Identify concerns with dietary supplements used in COVID treatment
Overview

• The SARS-CoV-2 virus is a pathogen that causes a wide range of symptoms, primarily respiratory.
• In addition to potentially-life-threatening acute symptoms, COVID-19 sufferers can experience ongoing health challenges.
• Increased age and/or preexisting health conditions such as obesity, diabetes, and lung disease can exacerbate risk.
Typical targets for intervention in Infectious disease

• Immune support*
• Antimicrobial or anti-infective treatment
• Symptomatic support
  – Acute symptoms
  – Effects on inflammation*
  – Post-recovery symptoms

*Key foci
Typical targets for intervention in infectious disease: Immune support

• Adequate nutrition supports the optimal functioning of the immune system
• Enhancement of immune system function and natural defenses most effectively allows the body to fight off infection
• Note that increased immune activity is not the same as increased immune function
Typical targets for intervention in infectious disease: Inflammation

- Inflammation is part of innate immunity
- Immune dysregulation could result in the hyperinflammatory state known as “cytokine storm” which is associated with severe acute lethal symptoms
- Chronic inflammation also underlies the health conditions that predispose to and/or result from COVID infection
- Note that free radicals and oxidative stress correlate with inflammation and can be important mediators of damage
Role of nutrition in immune system function

• Good nutrition is a foundation of health and optimal functioning of all systems, including the immune system

• Additionally, nutrition and lifestyle are key factors in preexisting conditions such as metabolic syndrome

• However, quarantine conditions can adversely affect food access and food choice, as well as other lifestyle factors such as exercise
Role of nutrition of immune system function: Lifestyle

- Moderate levels of exercise enhance immune function, but intensive training can impair function.
- Psychological stress increases susceptibility to infections.
- Increased social support is protective against upper respiratory infections.
- Components of the typical Western diet can have an adverse effect on immunity, as well as affecting obesity, diabetes, and other conditions increasing vulnerability.
  - Sugar
  - Saturated fat
  - Red meat
  - Salt
Role of nutrition in immune system function

Red = human studies show inhibition
Grey = animal/in vitro studies
Dashed = scientific disagreement

Role of nutrition in immune system function: Inflammation

- As previously described, acute inflammatory response can play a role in COVID-19 mortality via cytokine storm.
- Furthermore, chronic inflammation plays a role in both preexisting conditions promoting risk as well as chronic sequela of infection.

- Lifestyle factors affecting inflammation
  - Obesity promotes low-grade inflammation
  - Gut microflora can affect inflammation
  - Regular exercise decreases inflammation
  - Diet can play a role in chronic inflammation
Dietary approaches to addressing immune and inflammatory

**Diet: Decreased inflammation**

- Healthy diet: whole grains, fruits and vegetables, fish
- Vitamin C
- Vitamin E
- Carotenoids
- Zinc
- Omega three fatty acids
- Magnesium
- Mediterranean diet and other similarly healthy diets have anti-inflammatory effects

**Diet: Increased inflammation**

- Saturated and trans fat
- High glucose/high fat meals
Dietary components studied in relation to COVID infection

- Due to the complexity of the immune system, it is not surprising that a number of nutrients play a role in optimal immune function
- In general, while deficiency of a particular nutrient can clearly impair function, the benefits of supplementation are less clear
- Consumption of nutrients in foods, especially as fruits and vegetables, is likely to provide the most benefit
- However, as nutritional adequacy could be affected by quarantine conditions, supplementation could be helpful
Dietary components studied in relation to COVID infection

**Micronutrients**
- Vitamin A
- Vitamin C
- Vitamin D
- Zinc

**Macronutrients**
- Protein
- Omega-three fatty acids

**Other**
- Probiotics
- Echinacea
- Elderberry
- N-acetyl cysteine
Vitamin A: Background

• Enhances innate immunity
  – Needed for mucosal membrane integrity and function in producing mucus and clearing pathogens

• Binds nuclear receptor that alters transcription of immune-related genes
  – Increases regulatory T-cells
  – Increases IgA production

• Also alters immunoglobulin secretion in breast milk

• Present in foods as vitamin A and as the precursor beta-carotene
Global distribution of vitamin A deficiency

Calif Agr 65(3):130-135.
Vitamin A and COVID

- Prevention of vitamin A deficiency is likely helpful.
- Benefit suggested for COVID via effects on type 1 interferons.
- Note that vitamin A toxicity is a concern, especially in pregnancy, but beta carotenes do not have this risk.
Vitamin C: Effects

- Needed for immune function
  - May increase phagocyte and lymphocyte function
  - Has antioxidant effect

- Widely used for common cold
  - May shorten duration of common cold
  - May be more effective in individuals with physical stress, children
  - Does not appear to be protective for cold prevention

- Also has antioxidant effects
Vitamin C and COVID

- Vitamin C deficiency impairs immune function, so vitamin C adequacy is important.
- There is interest in supplemental Vitamin C for COVID due to its use for the common cold.
- Searching the National Institutes of Health ClinicalTrials.gov website for “COVID” and “vitamin C” yielded twenty-one randomized controlled trials for COVID and vitamin C alone or in combination as treatment.
  - The majority of these trials are in early stages.
- High doses of vitamin C are widely used with relative safety, although increased risk of kidney stones is a possible consequence.
Examples of registered clinical trials involving vitamin C and COVID

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<td>Administration of Intravenous Vitamin C in Novel Coronavirus Infection (COVID-19) and Decreased Oxygenation</td>
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Vitamin D: Effects

• Most known for its effects on calcium regulation and maintenance of bone strength
• However, receptors are found on many other cells in the body, including the immune system
• Low vitamin D could predispose to respiratory infections
  – Supplementation could help in cases of severe vitamin D deficiency
Vitamin D and COVID

• Vitamin D deficiency has been correlated with increased COVID severity

• In regard to mechanism, Vitamin D could increase protection against infection in the respiratory tract as well as decreasing inflammation contributing to cytokine storm

• ClinicalTrials.gov cites four trials including vitamin D in COVID treatment
Zinc: Effect

- Essential mineral used as a cofactor for multiple enzymes, considered antioxidant
- Deficiency produces a number of adverse effects on growth, immune function, and cognition
- Used topically and orally for multiple purposes
- Commonly used for decreasing severity and duration of common cold but evidence is conflicting
- Might decrease incidence of pneumonia in undernourished children
- Elderly might be more likely to be zinc-deficient
Zinc and COVID

• ClinicalTrials.gov cites fifteen randomized controlled trials for COVID and zinc alone or in combination as treatment
• Note that nasal zinc gel can damage the sense of smell, which can be a sign of COVID
• Oral zinc can affect the sense of taste and cause GI upset, also COVID symptoms

• Note that deficiencies in selenium and iron have similarly been shown to correlate with increased COVID mortality
Protein: Effects

- Protein deficiency is known to impair immune function, particularly immunoglobulins and gut-associated lymphoid tissue.
- Specific amino acids such as arginine and glutamine play a particularly important role in immune cell function.
- Protein deficiency has been associated with increased viral susceptibility and decreased response to influenza vaccination.
- High quality protein is of course important for general health.
Omega-3 fatty acid: Effects

• Omega-3 fatty acids are essential dietary components that are widely used for decreasing serum triglycerides
  – Prescription fish oil is presumed to be more effective due to higher concentrations and greater purity
• Needed for neurological development and function, especially in children
• Can also modulate the inflammatory cascade by serving as precursors to anti-inflammatory mediators
Omega-3 fatty acid: Effects on inflammation

Omega-6

Linoleic acid
18:2ω-6

Desaturation
Elongation
Desaturation

Arachidonic acid
20:4ω-6

Eicosapentaenoic acid
20:5ω-3

Desaturation
Elongation
Desaturation

Docosahexaenoic acid
22:6ω-3

Elongation
Desaturation
Beta-oxidation

Inflammation-resolving lipid mediators
Resolvins
Protectins
Maresins

Proinflammatory lipid mediators
Leukotrienes
Lipoxins*
Prostaglandins

COX-2 and LOXs

Cancer Prev Res May 1 2015 (8) (5) 359-364
Omega-3 fatty acid: Effects

• Fish oil contains the omega 3 fatty acids DHA and EPA (docosahexanoic acid and eicosapentanoic acid)
• Krill oil is also a source of DHA and EPA

• Plant-derived *alpha-linolenic acid* can be converted in part to EPA and DHA
  – Flaxseed
  – Walnuts
  – Chia
Omega-3 fatty acid supplementation, in particular the fish oils DHA and EPA, has been suggested as having a benefit in cytokine storm
- Oral, enteral, and intravenous lipid emulsions are possible dosage forms

The cardiovascular benefits of omega-3 fatty acids could also play a role in decreasing risk factors and mitigating chronic sequelae of COVID
- E.g., Deep vein thrombosis

ClinicalTrials.gov lists seven trials containing omega-3 fatty acids, three with the prescription EPA product icosopent ethyl

Omega-3 fatty acids are generally considered beneficial and are fairly safe
Probiotics: Effects

• Probiotics have traditionally been used in treating various forms of infectious diarrhea
• Less directly, the immune system can be affected by altering gut microflora
  – Alters immune regulation
  – Alters intestinal permeability (leaky gut)
• Effects depend greatly on the type, amount, and viability of the probiotic being used
Probiotics: Effect

• *Prebiotics* make the gut more welcoming for probiotic growth
  – Prebiotics such as fiber have shown beneficial effects
  – For example, both probiotics and prebiotics have demonstrated increases in the effectiveness of influenza vaccine
• Increased prebiotic effects could contribute to the health benefits of whole grains, legumes, and other plant products
• Use of the prebiotics fructan and galactan in particular have been cited
Typical targets for intervention in immune and inflammatory disorders:

![Diagram of gut microbiota and immune response](image)

American journal of physiology. Gastrointestinal and liver physiology. 298. G807-19
Probiotics and COVID

- A number of studies demonstrate benefits of specific probiotic products for respiratory tract infections though not for COVID specifically
  - ClinicalTrials.gov lists nine trials of probiotic products
- Note that COVID can also result in GI symptoms, which are a more typical application of probiotics
- Benefits are likely to depend on the use of specific strains and not common probiotics available commercially
- Relatively safe although possible risk of infection in immunocompromised patients
  - Prebiotics do not have this risk
Echinacea: Effect

• Commonly used for prevention/treatment of common cold
• Can have effects on both specific and non-specific immunity, affects cytokine production
• Also may have direct antimicrobial and anti-inflammatory activity
• Some studies suggest decreased severity and duration of cold symptoms if started immediately and used 7-10 days
• Evidence of benefit is not established, especially in children
Echinacea and COVID

• Not studied directly but based on effects in other respiratory diseases, has been suggested as promising
• Concern with increasing autoimmune effects and exacerbating cytokine storm, but decreases in proinflammatory cytokines have been reported
Elderberry: Effect

- Used alone or in combination for upper respiratory infections
- Immunomodulatory and possibly antiviral effects
- Increases cytokine production
- Has been reported to reduce flu symptoms and duration when given within 48 hrs of initial symptoms
Elderberry and COVID

• Not studied directly but based on effects in other respiratory diseases, has been suggested as promising
• Elderberry lectins have been postulated to interfere with coronavirus spike proteins
• Relatively safe
N-Acetyl Cysteine: Effect

- Sulfur-containing antioxidant used in-hospital as mucolytic agent and antidote for acetaminophen toxicity
- Also available as a dietary supplement
- Increases levels of the antioxidant glutathione, can increase T-cell proliferation, decrease inflammatory cytokines
- As a supplement, decreased incidence of incidence and severity of influenza symptoms
N-Acetyl Cysteine and COVID

- Can increases levels of the antioxidant glutathione that is depleted in COVID
- Could inhibit binding of coronavirus spike proteins to functional receptor used for entry into cells
- Relatively safe
- Potential use as a supplement in prevention, high dose use in treatment
- ClinicalTrials.gov lists 7 trials including NAC
Concerns with dietary supplements used in COVID treatment
Concerns with dietary supplements used in COVID treatment

FDA list of COVID-19 related fraudulent products

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<th>Date Issued</th>
<th>Firm Name</th>
<th>Product Name and Image</th>
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<td>Health Mastery Systems DBA Pure Plant Essentials</td>
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<td>Homeomart Indibuy</td>
<td>Homeopathic drug products</td>
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Concerns with dietary supplements used in COVID treatment

FDA list of COVID-19 related fraudulent products (continued)

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Concerns with dietary supplements used in COVID treatment: Essential oils

- Used topically, by inhalation, or orally (diluted) as antimicrobial agents
- Many oils do have antiseptic properties and molecules that could have antiviral activity, especially due to their high concentrations
- Despite interest in use for COVID, studies thus far are theory-based or in vitro
- However, the concentrated nature of the oils makes them potentially toxic when taken internally
- Many oils are also irritating to the skin
Colloidal Silver: Effect

• Sub-microscopic/nano particles of metallic silver
• Used topically and internally for antibiotic effect
  – Historically, silver nitrate, and silver sulfadiazine have been used as topical anti-infectives
  – Silver has multiple possible antibacterial effects including binding to cell membrane to initiate apoptosis, proteins, and DNA
• Increased surface area by decreasing particle size increases efficacy of binding

• Could result in argyria, bluish color in skin (not reversible) even when used as a nose drop or topically

• Could also result in neurological, renal damage, deposits in other organs
References


References

• Bhardwaj V, Jami MM. Fish oil and COVID-19 thromboses [published online ahead of print, 2020 Jul 15]. J Vasc Surg Venous Lymphat Disord. 2020;S2213-333X(20)30407-8. Torrinhas RS,
• Conte L, Toraldo DM. Targeting the gut-lung microbiota axis by means of a high-fibre diet and probiotics may have anti-inflammatory effects in COVID-19 infection. Ther Adv Respir Dis. 2020;14:1753466620937170.
References

• Kang Zhao, Jucun Huang, Dan Dai, Yuwei Feng, Liming Liu, Shuke Nie, Serum Iron Level as a Potential Predictor of Coronavirus Disease 2019 Severity and Mortality: A Retrospective Study, Open Forum Infectious Diseases, Volume 7, Issue 7, July 2020, ofaa250,
References


• www.clinicaltrials.gov