

Alpha Times

Newsletter of Alpha-1 Organisation Australia inc

Issue 14 Spring 2023

From the President's Pen

Hi everyone,
Welcome to our Spring Edition,

In this issue we explore the important topic of inflammation, especially inflammation associated with Alpha-1 antitrypsin deficiency (AATD). As the Alpha-1 community waits for new therapeutic possibilities, including a possible cure for AATD, people with AATD (Alphas) are encouraged to actively manage chronic inflammation to minimise its destructive impact and improve quality of life. AATD is associated with various forms of inflammation including chronic bronchitis, bronchiectasis, liver hepatitis, fibromyalgia and worsening autoimmune disease. All causes of inflammation can reduce Alphas' quality of life. Scientists and Alpha-1 patients are aware that augmentation therapy reduces inflammation, as weekly infusions supply the missing Alpha-1 Antitrypsin, which is a known natural anti-inflammatory. The anti-inflammatory effect of Alpha-1 Antitrypsin has been known for decades but only more recently embraced in the Alpha-1 literature. However, this treatment is not available to all due to prohibitive cost and ineligibility for clinical trials. Concern about lung, liver and systemic inflammation could become less significant if emerging AATD therapies, currently under clinical trial and planned, prove to be safe and have clinical efficacy. A search of www.clinicaltrials.gov shows at least 18 active AATD therapeutic studies underway or soon to recruit, with further studies anticipated in 2024 (e.g., the Beam Therapeutics gene therapy - a potential cure for AATD - and BioMarin's BMN 349 orally administered therapy targeting the liver). With the promise of a range of new Alpha-1 specific therapeutic interventions being investigated, within the decade there is likely to be many therapeutic options available meaning that managing lung, liver and systemic inflammation should be a lot easier, particularly severely deficient Alphas (e.g., Pi*ZZ, Pi*Null Z). I am keen to see a smorgasbord of treatment options - inhaled, infused, injected, oral - providing choice for all Alphas.

Wishing you all the best,
Gaynor Heading
President A1OA

Vale Jean Gray



Jean was a founding Board member of the Alpha-1 Organisation and made an invaluable contribution in the early days of our organisation. Sadly, due to declining health she had to resign from the board. She remained an active member for as long as she could and was instrumental in establishing the Alpha-1 Peer Support group through the Lung Foundation, which she ably chaired with humour, and challenging ice-breaker questions. In recent months, Jean's health continued to decline, and sadly she succumbed to her ailments. Vale Jean. You'll be missed.



Inflammation

Inflammation. We all experience it at one time or another. It can be in response to a short-term injury or infection, aiding in killing harmful bacteria to allow for healing. The inflammation is due to the release of a variety of immune cells, including neutrophils, and cytokines (small proteins) that regulate the inflammation. This can last for several hours or days, which is why it's called acute or short-term inflammation.

Inflammation that persists turns into chronic inflammation where the body continues to produce cytokines and inflammatory cells over a long period. When this continues it leads to organ damage resulting in a variety of conditions, depending on the organs involved. Chronic inflammation has been linked to increased risk of diseases like cancer, cardiovascular disease, diabetes, Alzheimer's, depression, bipolar disorder, and more.

Lifestyle and environmental factors can cause or contribute to systemic inflammation (i.e., chronic inflammation) as can untreated or chronic infections, physical inactivity, inflammatory diet, exposure to pollutants, poor gut health, chronic sleep deprivation or disruption, prolonged social isolation and psychological stress, and underlying inflammatory health conditions such as Alpha-1 Antitrypsin Deficiency and its associated conditions like chronic bronchitis and hepatitis.

5 Signs of Chronic Inflammation

- You're constantly in pain.
- You're not sleeping well.
- You're much more irritable or anxious than usual.
- You're frequently sick.
- Your digestive system is acting up, e.g., irritable bowel syndrome.
- You have reduced lung function from tissue damage (Moldoveanu et al 2009).
- You have fatigue associated with liver scarring and portal inflammation (Clark et al 2018; Teckman 2013).

How to Manage Chronic Inflammation

- Healthy diet. Pre- and probiotics. (See below)
- Maintain a healthy weight.
- Stay physically active.
- Get good quality sleep.
- Avoid environmental irritants, such as dust, smoke, and chemicals.



Artist's impression of lungs and liver affected by Alpha-1 Antitrypsin Deficiency.

What are Prebiotics?

Prebiotics are foods (typically high-fibre foods) that act as food for human microflora. They are used with the intention of improving the balance of these microorganisms in the gut.

Fructo-oligosaccharides (FOS), galacto-oligosaccharides (GOS), and trans-galacto-oligosaccharides (TOS) are the most common prebiotics, along with other carbohydrates of varying monosaccharide chain lengths.

Prebiotics are found in foods such as whole grains, bananas, greens, onions, garlic, soybeans, and artichokes.

Probiotics on the other hand are foods or supplements that contain live microorganisms intended to maintain or improve the "good" bacteria (normal microflora) in the body.

Alpha-1 antitrypsin is recognized as having multiple direct immune-modulatory and anti-inflammatory effects, acting primarily on neutrophils “via a range of effects on key cytokines and chemo attractants”, which could happen in one of two ways: down-regulation of pro-inflammatory cytokines and chemokine protein (induce molecule migration) production. (McElvaney et al 2020).

Due to the role of cytokines in inflammation in AATD, anti-cytokines (cytostatic drugs) have been suggested as a possible intervention strategy (McElvaney et al 2020). Systemic inflammation is also associated with non-AATD COPD and once the inflammatory process in COPD is established it persists after smoking cessation. Both AATD-COPD and non-AATD COPD can involve emphysema, chronic bronchitis and acute exacerbations and associated respiratory inflammation, both involving innate and adaptive immunity and is pronounced in the bronchial walls of the small airways (King 2015).

Kokturk et al. (2023) identified that mild lung inflammation is even found in Alphas with normal lung function. The authors found three-fold higher neutrophil counts, two-fold increase in the protease levels, and two-to-four-fold higher levels of IL-8, IL-6, IL-1 β , and leukotriene B4 in the epithelial lining fluid compared to controls. Unfortunately, chemoattractants such as IL-8 and leukotriene B4 (LTB4) can allow cells to communicate with surrounding cells which activates neutrophils, spreading their release into the inflamed airway.

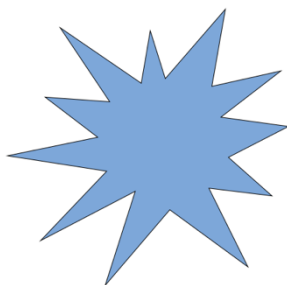
McElvaney et al (2020) suggest that early anti-inflammatory therapies may be a potential strategy to prevent progression of lung disease in AATD individuals. Hence our heightened interest in all things anti-inflammatory e.g., inhaled antitrypsin and AATD liver therapies under clinical trial and other trials planned (e.g., Beam in 2024- see below), as Alpha-1 Antitrypsin limits tissue injury linked to inflammation.

The currently prescribed inhaled COPD medicines including corticosteroids may assist with inflammation, but they are ineffective in stopping the progression of COPD (King 2015), therefore, new therapeutics are urgently required. The Alpha-1 community will be extremely grateful for new treatments that effectively control inflammation but also for those that target the causes of inflammation.

Anti-inflammatory Supplements

- Ginger
- Fish oil, omega-3 fatty acids
- Vitamin C
- Vitamin D
- Green tea
- Spirulina
- Sulforaphane (made when chewing cruciferous vegetables- broccoli, cauliflower etc).
- Bromelain (found in pineapple).
- Garlic
- Onion (contains quercetin).
- Cinnamon- causes liver damage in high doses. Limit to ½ teaspoon daily.
- Turmeric/ curcumin- causes liver damage in high doses. Limit to around ½ teaspoon daily.
- Resveratrol (found in red grapes).
- N-acetyl cysteine (NAC) and glutathione.

Some of these need to be taken carefully in recommended doses as they can be harmful at high doses. Check with your health professional if unsure and stop usage if any causes a reaction. It can be beneficial to cycle on and off supplements.



A1OA YouTube channel

<https://www.youtube.com/@alpha-1organisationaustral421>

Alpha-1 Organisation Australia, A1OA, now has a number of video resources available for viewing on our YouTube channel.



Alpha-1 Alphabet Challenge

Can you find more words associated with Alpha-1 lung issues?
This is what we have so far.

Lung words

- A alpha-1, anti-inflammatory, alveoli, air quality, asthma, ascites
- B breath, breathe, breathless, bronchioles, bronchi, bronchiectasis
- C CO₂, chronic, COPD, cirrhosis
- D DLCO (diffusing capacity for Carbon monoxide), density
- E Eupnea (Normal relaxed breathing), emphysema, energy, exercise
- F food- healthy diet, FEV, feeling, (lung) function, fibroscan
- G gas exchange, gasp
- H hypoxia (lack of oxygen), Hypopnea (Slow or shallow breathing)
- I iron (maintenance of low iron levels in the lung is crucial not only to prevent oxidative stress but also to sustain the pulmonary defence against inhaled pathogens)
- J (Juxtacapillary) pulmonary receptors- respond readily to chemicals in the pulmonary circulation
- K ketosis (keto diet has the potential to be anti-inflammatory, meaning it could reduce inflammation in the lungs. Although more studies are needed, some evidence suggests that low-carb diets may decrease the likelihood of COPD or become therapeutic in people with COPD)
- L lungs, lobe, liver
- M mucous, metabolic dysfunction-associated steatotic liver disease (MASLD), Metabolic-associated fatty liver disease, Mediastinum (a membranous partition between two body cavities or two parts of an organ, especially that between the lungs), money- needed for research, M (normal) allele
- N normal, non-alcoholic fatty liver, NTM, null phenotype
- O oxygen
- P pulmonology, pleura, pleurisy (inflammation of the sheet-like layers that cover the lungs (the pleura)), perfusion (designated Q) refers to the flow of blood to alveolar capillaries, pulmonary hypertension, pneumonia, pulmonary oedema
- Q perfusion (designated Q) refers to the flow of blood to alveolar capillaries
- R respiratory system, respiration, RSV, rehabilitation (exercise)
- S symptoms, smoke, sleep apnoea, S allele, sickly
- T trachea, transplant
- U unhealthy, urine test (cirrhosis), ultrasound
- V ventilation, vaping, (lung) volume
- W water on the lungs- pulmonary oedema (congestive heart failure)
- X x-ray
- Y yoga (breathing based exercise)
- Z ZZ allele

Challenge 2

Send us your liver related words for a list next issue.

Interesting New Research

Ginger consumption May Mitigate Neutrophil Dysfunction

<https://www.medscape.com/viewarticle/996737>

September 25, 2023, Based on Ramadan A. Ali, MD, et al.

Blood samples from healthy adults show an inhibition of neutrophil extracellular trap formation (NET) after 1 week of daily ginger supplements.

METHODOLOGY:

- Researchers recruited nine healthy adults aged 18-38 years to receive a 100-mg oral ginger supplement daily for 7 consecutive days.
- Blood samples were collected at baseline and on days 7 and 14, with isolation of neutrophils, peripheral blood mononuclear cells, and plasma.
- The researchers measured NET formation (NETosis) as a way to show the effect of ginger on inflammation.

TAKEAWAY:

- Measures of neutrophil cyclic AMP (cAMP) were significantly higher after 7 days of ginger supplements compared with baseline levels, although these levels returned to near baseline by 1 week after discontinuing ginger consumption.
 - Oral ginger supplements reduced neutrophil phosphodiesterase (PDE) activity by 40% from baseline, similar to results seen with synthetic PDE4 inhibitors.
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Promising Clinical Trial to be undertaken by Beam Therapeutics

Beam Therapeutics Inc. is an American biotechnology company conducting research in the field of gene therapies and genome editing.

In 2024 Beam will be commencing a trial, BEAM-302, to correct a specific gene that causes alpha-1 antitrypsin deficiency, i.e., mutation of the E342K gene.

The technique will specifically edit the C base to change it to T. [Bases are the part of DNA that stores information and gives DNA the ability to encode phenotype- a person's visible traits. These are: adenine (A) and guanine (G), cytosine (C) and thymine (T).]

BEAM's technique differs from conventional CRISPR gene editing, which introduces double-strand breaks that can lead to off-target effects, in that it avoids double-strand breaks, thereby minimizing errors.

Phase I and II will be conducted as a combined phase as it would be unethical to gene edit healthy individuals.

This stage will be conducted in countries where Alphas don't have access to augmentation therapy, such as Australia and New Zealand.

Aunty Alpha

*Dear Aunty Alpha,
I was diagnosed with Alpha-1 Antitrypsin Deficiency a few years ago. Is there any dietary advice for people with Alpha-1?
Regards Geoff*

Dear Geoff

Eating a healthy balanced diet is beneficial for Alphas and indeed everyone. Health professionals recommend eating a mainly plant based diet with plenty of fresh fruit and vegetables, including nuts, seeds, and whole grains. Eat oily fish, lean meats, and dairy products in moderation. Limit your alcohol intake, especially if you have liver symptoms. It might be necessary to cut out alcohol all together. Avoid processed food and fast food. There is information on eating to reduce inflammation in some sections of this issue of *Alpha Times*.

Regards
Aunty

If you have a question about anything raised in this issue

write to Aunty Alpha, who is always happy to answer your questions, or contact the A1OA through contactus.a1oa@gmail.com

Mental Health First Aid

Alpha-1 Organisation Australia has an accredited Mental Health First Aider who is ready to help if you are not coping after a diagnosis of A1AD for yourself or a family member. A new diagnosis can cause mental distress, anxiety, or depression. Please reach out to mentalhealth.a1oa@gmail.com



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