Autoimmune Fatigue:

Unveiling the Hidden Causes & Solutions

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Conflict of Interest

THE confident clinician

I am an Expert Clinician with The Confident Clinician and am paid as an educational contractor.

I also have pay-per-use courses that I receive royalties on through The Confident Clinician on the topic I'm presenting on today.

Fatigue
OVERVIEW

- **THE REALITY OF AUTOIMMUNE FATIGUE**
- **DEEP DIVE: AUTOIMMUNE FATIGUE**
- **THE MITOCHONDRIA CONNECTION**
- **CNS, VAGAL NERVE & INFLAMMATION**
- **GUT HEALTH**
- **INFLAMMATION**
- **TREATMENT STRATEGIES**

“FATIGUE IS DESCRIBED AS

"profound," "debilitating," and "preventing them from doing the simplest everyday tasks," is a major issue for autoimmune disease (AD) patients, impacting nearly every aspect of their lives. It affects their mental and emotional well-being and their ability to work..”

the American Autoimmune Disease Related Diseases Association (AARDA)

Fatigue

WHAT OUR CLIENTS ARE SAYING...

- 98% of autoimmune patients surveyed report they suffer from fatigue.
- 89 % say it is a "major issue" for them and 59 % say it is "probably the most debilitating symptom of having an Autoimmune Disease.
- 70 % believe others judge them negatively because of their fatigue
- fatigue has a significant impact on AD patients' mental and emotional well-being.
  - 88% said they experienced an increased emotional distress
  - 76% said they had a sense of isolation
  - 72% said increase in anxiety
  - 69% experienced depression

7,838
Autoimmune Patients Interviewed

[1] Fatigue Survey Results Released • AARDA. Available online at: https://www.aarda.org/fatigue-survey-results-released/

Fatigue

THE REALITY ...

- Limiting their social life
- Limiting their physical activities
- Inability to perform daily routines
- Limiting their ability to work and provide
- Effecting their ability to parent
- Impacting their sense of independence and purpose
- Creating a financial hardship on the individual, family, society and healthcare

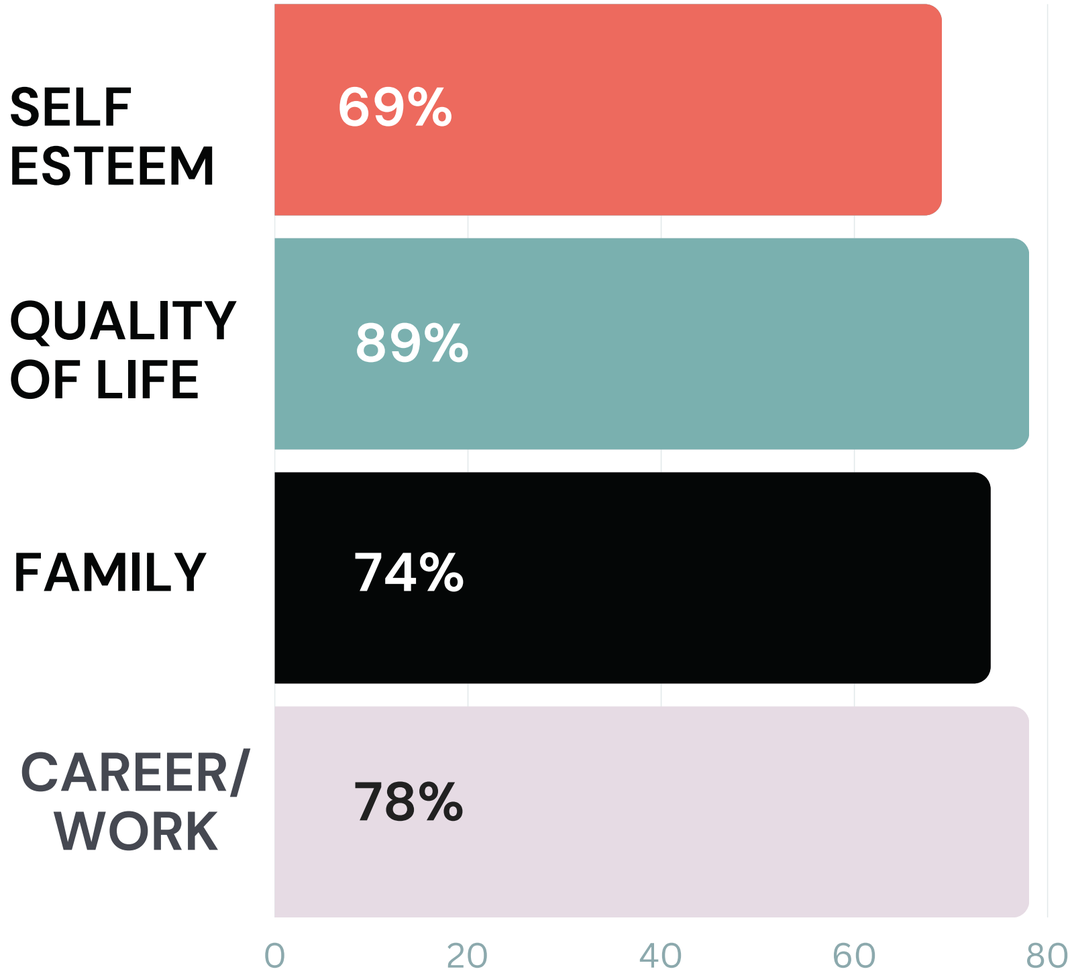
(Zielinski MR, 2019)

Over 2/3rd's of respondents reported that their fatigue was profound, and debilitating, preventing them from completing simple everyday tasks.

Fatigue Survey Results Released • AARDA.

Fatigue

THE IMPACT OF FATIGUE



Plus...

78% Romantic

21% Job Loss & Disability

[1] Fatigue Survey Results Released • AARDA. Available online at: https://www.aarda.org/fatigue-survey-results-released/

MEDICAL CARE ...

A study looked at 626 RA patients over 8 years and found that...

- "association between inflammation and fatigue is **statistically significant** but effect sizes are small, suggesting that non-inflammatory pathways mediate fatigue as well. **Improved treatment strategies did not result in less severe fatigue**. Therefore, fatigue in RA remains an ‘unmet need.” (Steenbergen, 2015)

The problem is...

with treatment, there is an improvement in disease activity and bloodwork but there was limited change in fatigue.

(Steenbergen, 2015)

87% Report they have discussed their fatigue with their doctor

59% Say they have not been prescribed or suggested treatment by their doctors.

MEDICAL GASLIGHTING

Conventional Medicine has acknowledge that autoimmune fatigue is a problem that they currently don't have a solution.

It has been identified as the #1 known Gaslighting symptom in conventional medicine for autoimmune

Global Autoimmune Institute
https://www.autoimmuneinstitute.org/articles/living-well/managing-mental-health/

This is where we shine...

There is so much we can do as Naturopathic Doctors.

WHERE WE SHINE...

Earlier Diagnosis

Help with the Overwhelmed of the DX

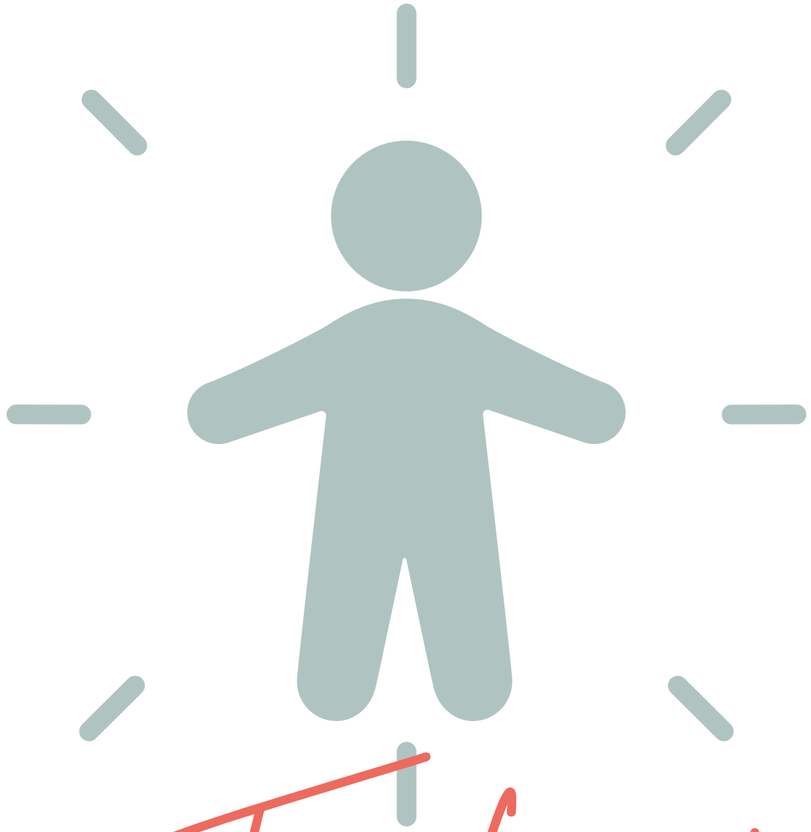
Educated and Inform

Provide Lifestyle Modifcation

Personalized medicine to help manage symptoms & **treat the whole**

Support and Accountability

Help them understand they don't need to do this alone



To Listen

They just want to be heard...

THE JOURNEY,

from their eyes.

Fatigue

THE FATIGUE EXPEREINCE

The Lead UP - 4-7 years

- It typically takes 4-7 years to get a diagnosis of autoimmune
- For many it’s years of making excuses of why they feel so exhausted

The Roller Coster of Autoimmune

- They finally get their Dx (HOPE), and they start medication - the pain, stiffness, and other symptoms resolved but NOT the fatigue.
- They JUMP ALL in to lifestyle changes - doing all of it

Knowledge Seeking (Dr. Google)

- Empowerment... “I want answers”. They are not getting the answers they need or want from conventional medicine so they turn to social media, dr. google etc...

I WANT TO TREAT THE...

The Root Cause

What our clients think...

IMMUNE STIMULATION

Viral, Bacterial, Parasite, Vax, toxins etc...

TRIGGERS INFLAMMATION & IMMUNE RESPONSE

REMOVE THE IMMUNE STIMULATION PROBLEM SOLVED.

CURED

UNFORTUNATELY, THIS IS VERY OVERSIMPLIFIED...

Fatigue

POSSIBLE CAUSES OF AUTOIMMUNE FATIGUE

- **Oxygen & Nutrient Supply**
- **Metabolism**
- **Mood & Mental Health**
- **Quality of Sleep**
- **Disease Activity - Inflammation & Oxidative Stress**

NOTE: inflammation is altered by many of the factors above that modulate fatigue and vice versa
Growing evidence indicates that neuroinflammation is a primary factor contributing to fatigue.

BUT BEFORE WE START

we need to rule out the obvious.

First, RULE OUT & FIX THE OBVIOUS....

- ☑ Anemia - Iron/B12 ** Ferritin is not enough
- ☑ Poor diet/malnutrition/malabsorption
- ☑ Allergies
- ☑ Dehydrated
- ☑ Stroke/Traumatic Brain injury
- ☑ Previous Chemo/Rad
- ☑ Blood sugar/Insulin Resistance
- ☑ Thyroid **full picture
- ☑ Pharmaceutical interactions/side effects
- ☑ Lack of exercise/too much exercise
- ☑ Anxiety/Depression
- ☑ Hormones
- ☑ Infection
- ☑ Vitamin D levels
- ☑ Inflammation
- ☑ HPA
- ☑ Sleep Disorders

MITOCHONDRIA

Cell Danger Response & so much more...

CELL DANGER RESPONSE (CDR)

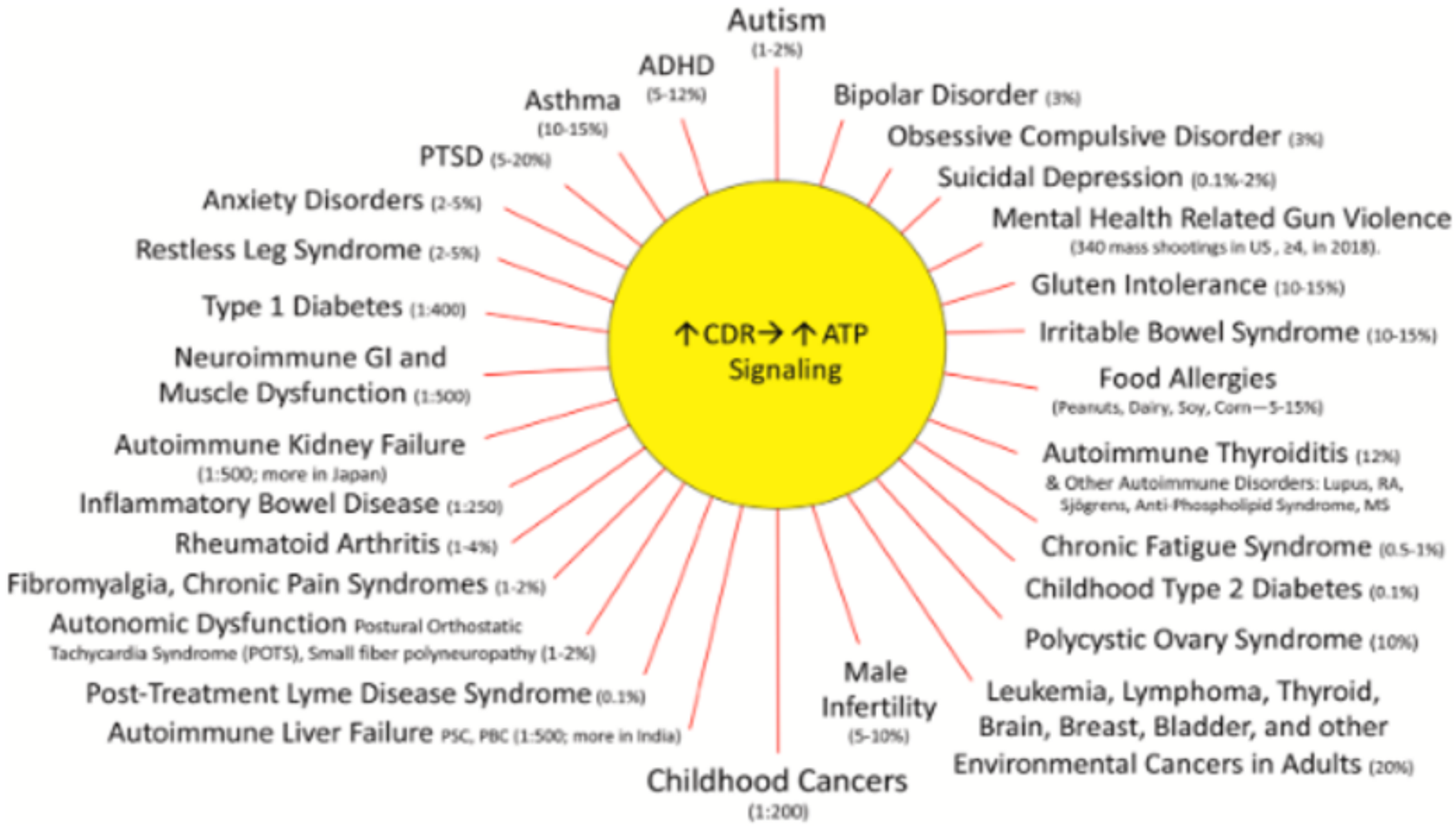
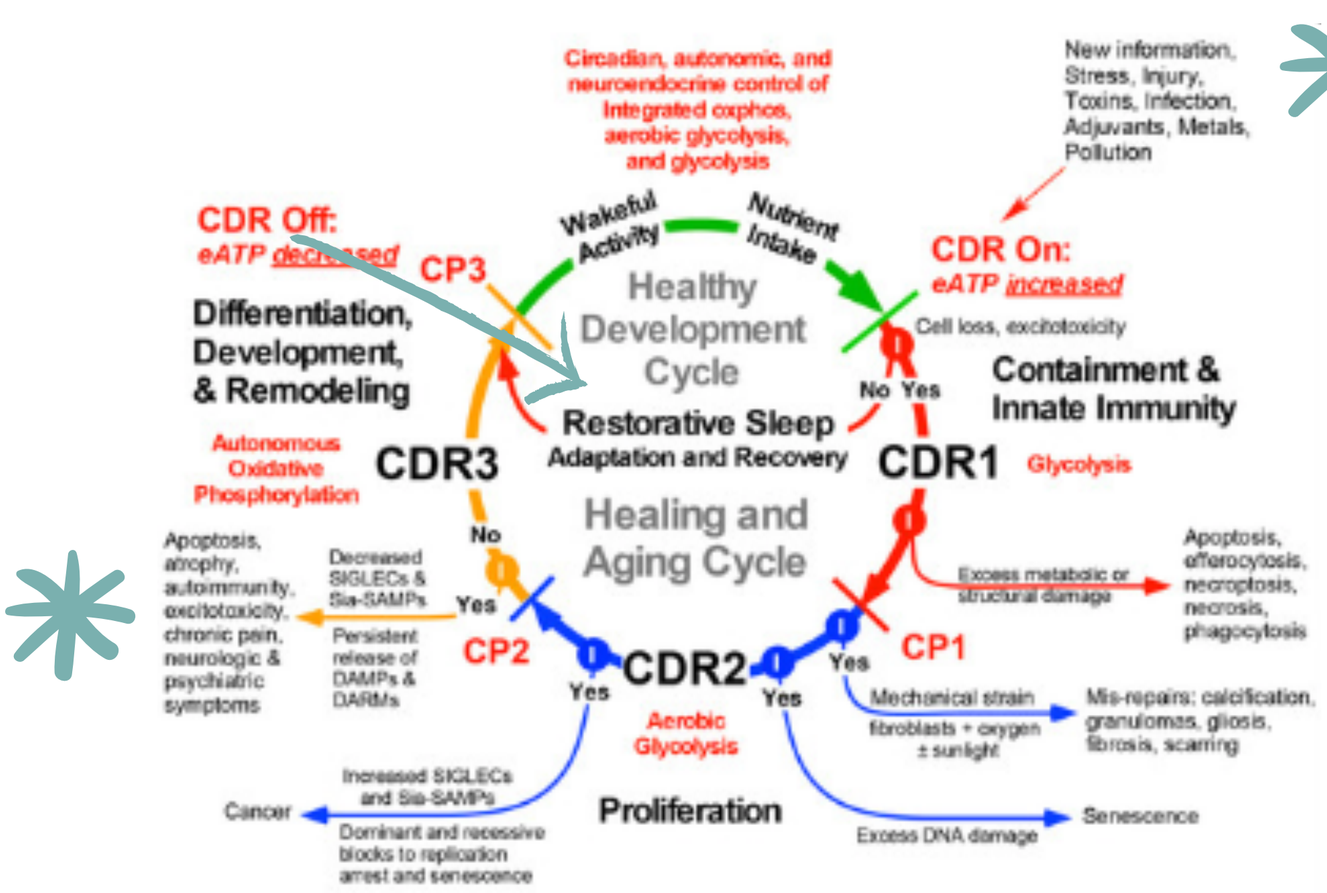


Fig. 1. Chronic Health Disorders that have Increased 2-100 times since the 1980s. Forty percent of children born in the US today and 60 percent of adults under 65 live with at least one chronic illness. ATP signaling is also known as purinergic signaling (Burnstock, 2018; Naviaux, 2018). **Abbreviations**: CDR, cell danger response; ATP, adenosine triphosphate; ASD, autism spectrum disorder; ADHD, attention deficit hyperactivity disorder; PTSD, post-traumatic stress disorder. Numbers reflect the population prevalence of each illness in the United States in 2018.

CELL DANGER REPSONSE



https://www.mdpi.com/2079-7737/8/2/27

CDR -1 - FIGHT

- is the initial protective cellular reaction to external threats, where cells go into a defensive state, potentially impacting metabolic and neurological functions

CDR -2 GROWTH

- Disease results from an extended biological RESPONSE to damage, rather than from the initial causative agent itself.

CDR -3- ADAPT

- pertains to chronic inflammation and altered cellular function, playing a potential role in the development of autoimmune disorders and impacting mental health

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WHAT IS THE CELL DANGER RESPONSE?

- **The CDR (Cell Danger Response) is activated in response to environmental threats or injuries.**
- **The healing process is halted until CDR stages are reset and prepared for new threats.**
- **They respond to various conditions within and surrounding the cell, linking cellular and environmental health**

"Mitochondria regulate the CDR by monitoring and responding to the physical, chemical, and microbial conditions within and around the cell. In this way, mitochondria connect cellular health to environmental health"

Robert K Naviaux, 2020

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WHAT IS THE CELL DANGER RESPONSE?

The Cell Danger Response (CDR) is a cellular mechanism that activates when a cell perceives a threat, like an infection or environmental stressor. This response aims to protect the cell and the organism by altering cellular functions, including energy production, and initiating repair processes.

- Energy Production:
  - Mitochondria are the primary energy producers in cells.
  - During CDR, cells might alter energy production to support defence mechanisms. The balance between mitochondrial fusion and fission is crucial here, as it influences the efficiency of energy production.
- Reactive Oxygen Species (ROS):
  - ROS are by-products of mitochondrial activity, acting as signaling molecules but also potentially damaging cellular components.
  - During CDR, ROS production might increase to combat pathogens, but excessive ROS can also signal cellular damage.

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WHAT IS THE CELL DANGER RESPONSE?

- Inflammatory Response:
  - The CDR often involves an inflammatory response. Mitochondrial dynamics, especially the state of fission, are linked to the function of inflammatory cells.
  - For example, fragmented mitochondria in macrophages and T cells are associated with inflammatory functions.
- Cell Survival and Apoptosis:
  - Mitochondrial dynamics influence cell survival and programmed cell death (apoptosis).
  - During CDR, cells might undergo apoptosis if the damage is irreparable, and the balance of mitochondrial fusion and fission plays a role in this decision-making process.
- Immune Cell Activation:
  - The activation and function of immune cells are influenced by mitochondrial dynamics.
  - In the context of CDR, the activation of immune cells is crucial for defending against perceived threats.

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CONSEQUENCES OF CDR

- Decrease Energy for survival
- Thick blood - Hypercoagulation
- Mast cells activated (histamine/allergy)
- Change in cholesterol patterns
- Change in Bowels - increased food sensitivities, Hyper-permeability, dysbiosis
- Increase Autoimmune - change in Th1 & Th2 stimulation
- Change in Vitamin D expression
- B6 reduction
- Change in Methylation

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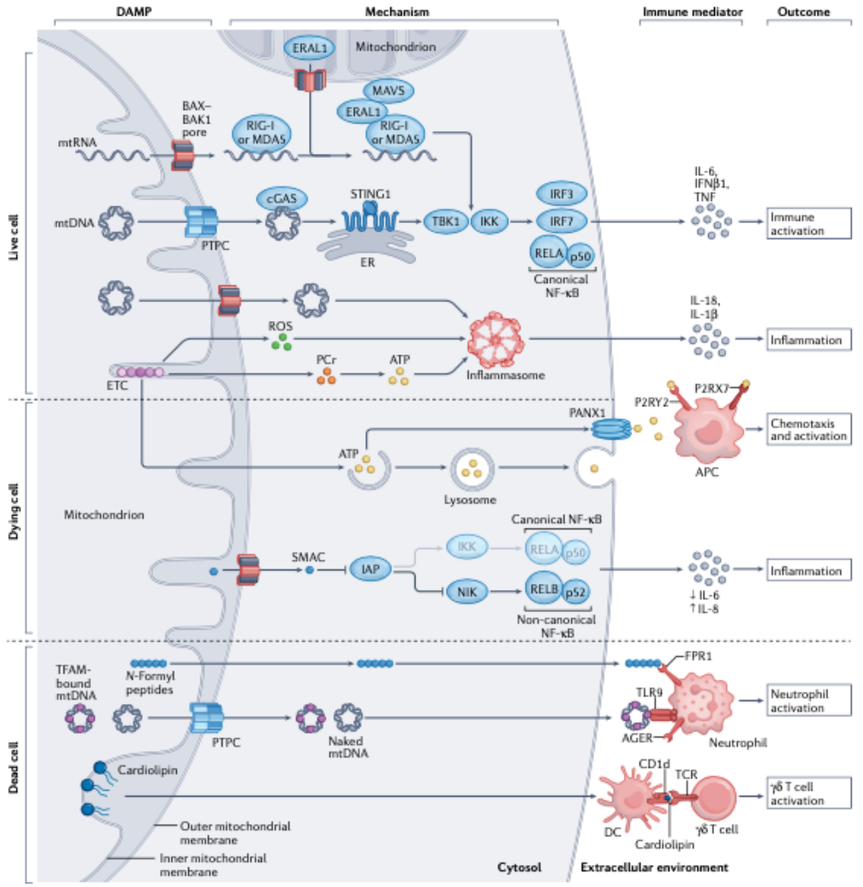
INFLAMMATION & MITOCHONDRIA

- Mitochondrial constituents and metabolic products, acting as damage-associated molecular patterns (DAMPs), can initiate inflammation when released, contributing to human disorders related to autoimmunity and inflammation.
- While there are safeguards like autophagic disposal to prevent harmful inflammatory reactions caused by mitochondria, these systems can be overwhelmed or defective, leading to pathogenic inflammation.
- Dysregulated inflammatory responses due to mitochondrial DAMPs can also facilitate the development or progression of infectious and neoplastic disorders, highlighting the importance of understanding and regulating these pathways. (Marchi, 2023)

RA (Rheumatoid Arthritis)

- The activity of mitochondria impacts the differentiation, activation, and longevity of both immune and non-immune cells



Marchi, S., Guilbaud, E., Tait, S.W.G. et al. Mitochondrial control of inflammation. Nat Rev Immunol 23, 159–173 (2023). https://doi.org/10.1038/s41577-022-00760-x

So if the mitochondria are acting to signal danger ...this will definitely be a factor in autoimmune fatigue

HPA & CNS

But well all have Stress...

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STRESS AS A TRIGGER...

- Studies have shown that more than 80% of patients with autoimmune report a stressful event before onset, leading up to the diagnosis
- Individuals with autoimmune diseases are reported to have increased stress levels compared to the general population.
- There is emerging evidence that shows that stress can modulate brain inflammation in autoimmune diseases such as multiple sclerosis.
- Stress hormones lead to an alternation of the immune response by increasing cytokine production and release

[Karagkouni, 2013]

THE EYE ROLL FROM EVERY PATIENT
WHEN YOU MENTION STRESS...

NEUROENDOCRINE-IMMUNOLOGICAL AXIS

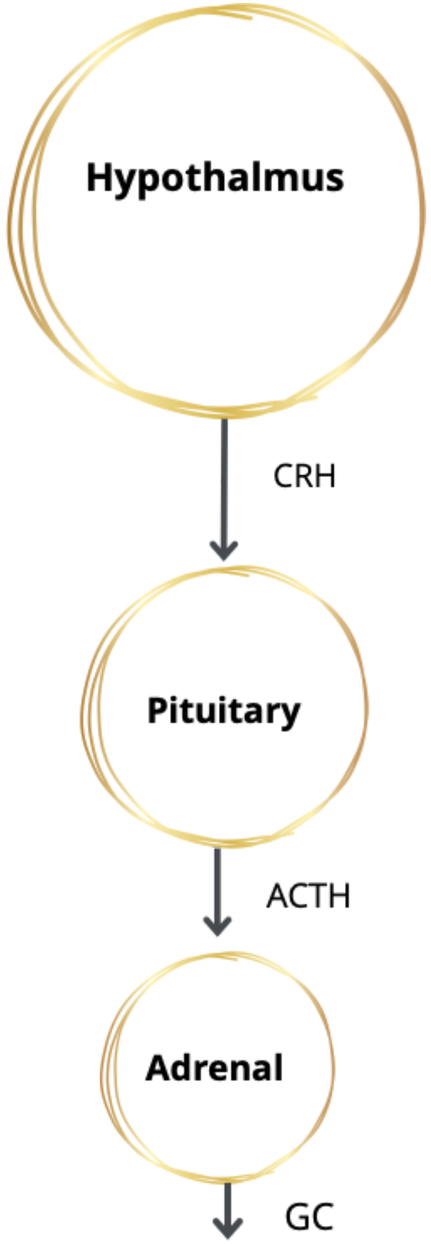
are the key players in autoimmune diseases.

HPA AXIS & AUTOIMMUNE

- **Abnormal HPA response has been shown in RA, SLE, Sjorgens and Fibro**

  - Hyporesponsive stress axis (blunted HPA) found in RA, SLE, Fibro, SS
  - Animal studies have demonstrated that a hyporesponsive (blunted) HPA increases susceptibility to developing autoimmune

  - One of the primary roles of cortisol is to act as an anti-inflammatory agent to help regulate the immune response and suppress the inflammatory processes by inhibiting IL-1β, IL-6, and IFN-γ, COX, PG's
  - The more inflammatory cytokines that are released (IL-1β, IL-6 and TNF-α) can stimulate the HPA to increase ACTH and cortisol which will inhibit pro-inflammatory molecules



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LOW CORTISOL & HYPORESPONSIVE STRESS RESPONSE:

- **With low cortisol levels, the body's natural anti-inflammatory mechanism is impaired. Leading to heightened inflammation, as cortisol can't effectively keep the immune response in check.**
- **Chronic stress, such as those undergoing chronic health/autoimmune, can reduce glucocorticoid sensitivity to promote inflammatory signalling.**
- ALSO...**This can partially result from the reduced sensitivity to cortisol signaling, the varied functions of monocytes, or the decreased capability of monocytes to process cortisol signals. Any of these factors can lead to an increase in inflammatory cytokines (Miller, 2014).**

BUT THERE IS MORE TO THIS STORY...

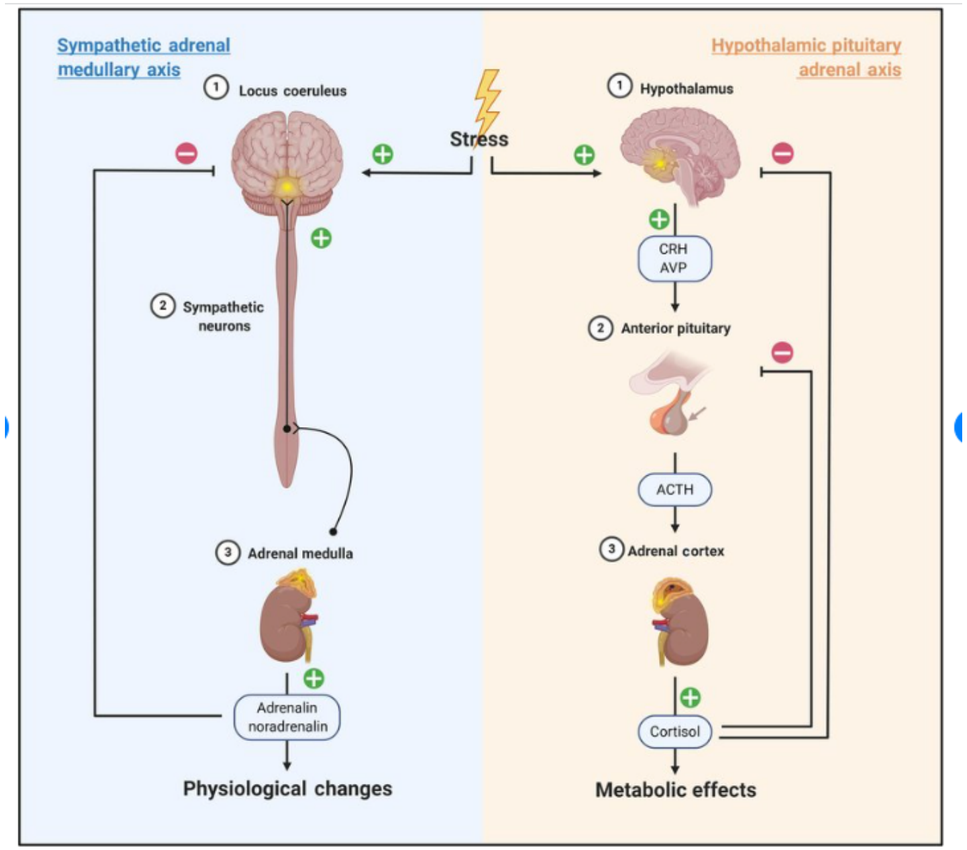
Neuroendocrine-Immunological Axis

are the key players in autoimmune diseases.

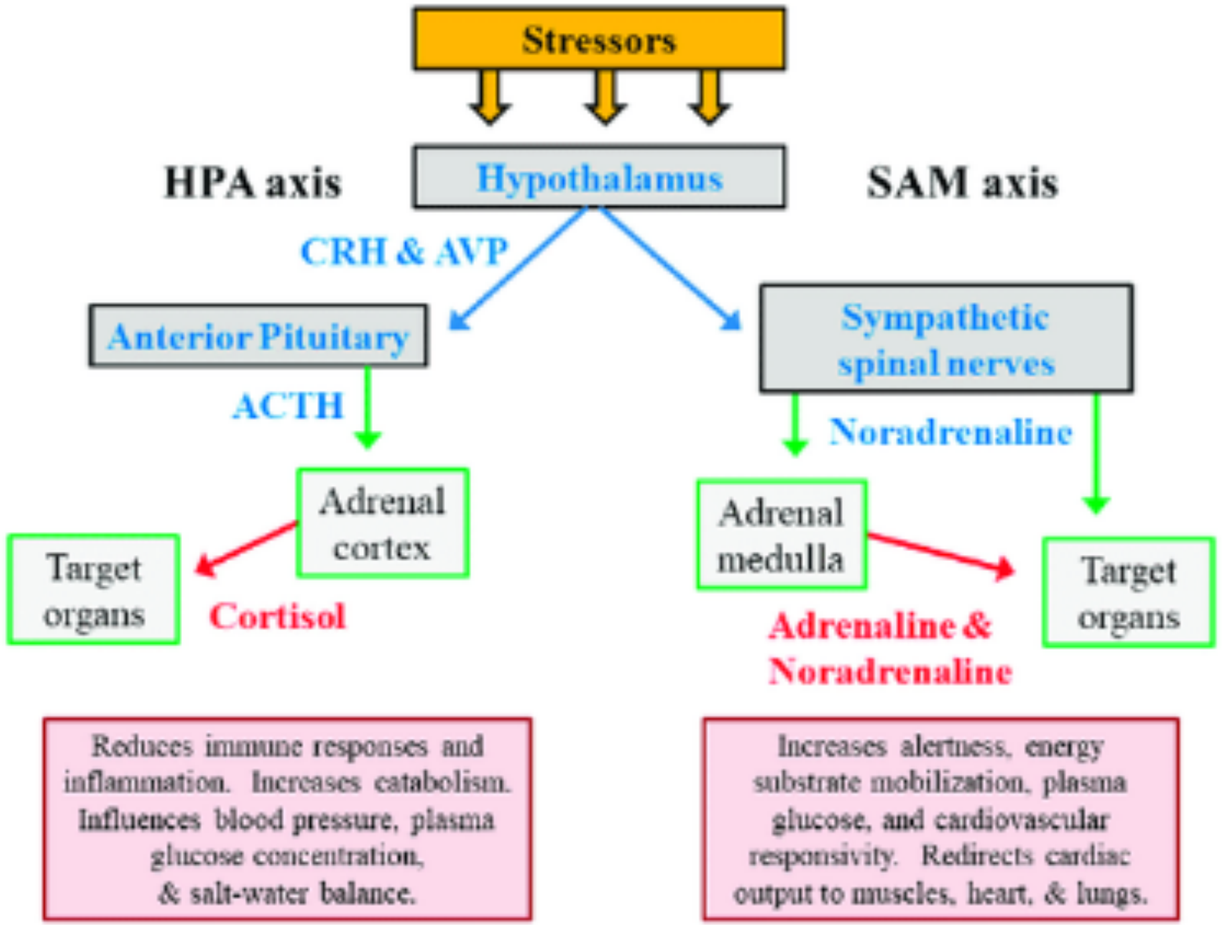
Fatigue

SYMPATHETIC-ADRENO-MEDULLARY AXIS (SAM)

- With SAM, a stressor is perceived via the sympathetic nervous system, triggering the production and release of hormones such as epinephrine and norepinephrine by the medulla in the adrenal gland.
- SAM activation occurs within seconds when encountering a stressor and allows for adaptive responses to stress.
- The HPA axis responds more slowly, releasing corticosteroids like CRH, ACTH, and cortisol, which leads to the suppression of the immune system. (Joëls and Baram, 2009; Tank and Lee Wong, 2015)



Carlton, Morgan & Voisey, Joanne & Parker, Tony & Punyadeera, Chamindie & Cuttle, Leila. (2021). A review of potential biomarkers for assessing physical and psychological trauma in paediatric burns. Burns & Trauma. 9. 10.1093/burnst/tkaa049.



Hyporepsonsive (blunted)

- GC Sensitivity
- Lacking the ability to suppress inflammation immune response

Increase in Catecholamines

- Increase NK cells
- Increase Monocytes
- Change in CD4 & CD8
- Increase ESO
- Change in Leukocytes

(Image: Armstrong, 2022)

HPA & SAM RESPONSE

- The HPA axis and the SAM system are potent regulators of the TH1/TH2-balance probably by suppressing IL-12, a potent TH1 cell inducer.
- When stress occurs and activates these systems, having an altered response of the HPA axis and the SAM system will further increase the risk of a dysregulation of the TH1/TH2 cytokine pattern. (Romagnani, 2000).
- Also: Increased Catecholamines released from the sympathetic Nerve endings suppress CD8+T cells and allow the progression of the infection

**Elevated cortisol is required to turn off the SAM response

TRENDS IN HPA & CNS WITH AUTOIMMUNE

Hypo-reactive with HPA
Hyper-reactive SAM
→ **Atopic Dermatitis, RA, SLE**

Hypo-reactive with HPA
Hypo-reactive SAM
→ **IBD, MS**

Hyper-reactive SAM
→ **Psoriasis**

(Bucsek, 2018)

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CONSEQENCESOF CNS IMPAIRMENT IN AUTOIMMUNE

RA:

- **60% of RA patients have hyperactive SNS based on a systematic review of 40 studies as of 2022**
- **reduced heart rate variability (HRV) and high resting heart rate (RHR).**
  - **Impact on Disease Activity**
    - **Uncontrolled release of inflammatory cytokines like TNF, IL-1, and IL-6, causes damage to joints, and bones, and increases atherosclerosis risk.**
    - **Poor acetylcholine binding in joints**

SLE

- **Reduced Heart Rate Variability (HRV) and increased sympathetic modulation are seen in SLE.**
- **Study on 35 SLE patients: Impaired HRV linked to increased inflammatory cytokines (like TNF) and disease activity.**
- **In mice with SLE, restoring the vagal cholinergic anti-inflammatory pathway reduced blood pressure and inflammation.**
- **Another study on 91 SLE patients links cardiac autonomic dysfunction to QTc prolongation.**

(Bellocchi., 2022)

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CONSEQENCESOF CNS IMPAIRMENT IN AUTOIMMUNE

Systemic Sclerosis (SSc)

Raynaud Phenomenon in SSc:

- **Sympathetic overactivity leads to vasoconstriction.**
- **Raynaud phenomenon arises due to microvascular damage, often triggered by cold and stress.**

- **HRV impairment correlates with microvascular damage in SSc.**
- **Study on 27 SSc patients: Positive relationship between digital microvascular damage and parasympathetic modulation, which encourages VEGF release to stimulate vasodilatation.**
- **GI Issues in SSc (~90% of SSc patients experience GI problems)**
  - **There is a link to ANS dysfunction, especially in the vagal branch which usually controls GI motility and stress response.**
  - **Esophageal dysmotility in SSc is tied to ANS dysfunction.**
  - **Severe GI issues in SSc lead to more dysautonomia symptoms and related emotional distress**
- **Cardiovascular dysautonomia in SSc relates to poor sleep, increased pain, and depressive symptoms.**

(Bellocchi., 2022)

STILL MORE...

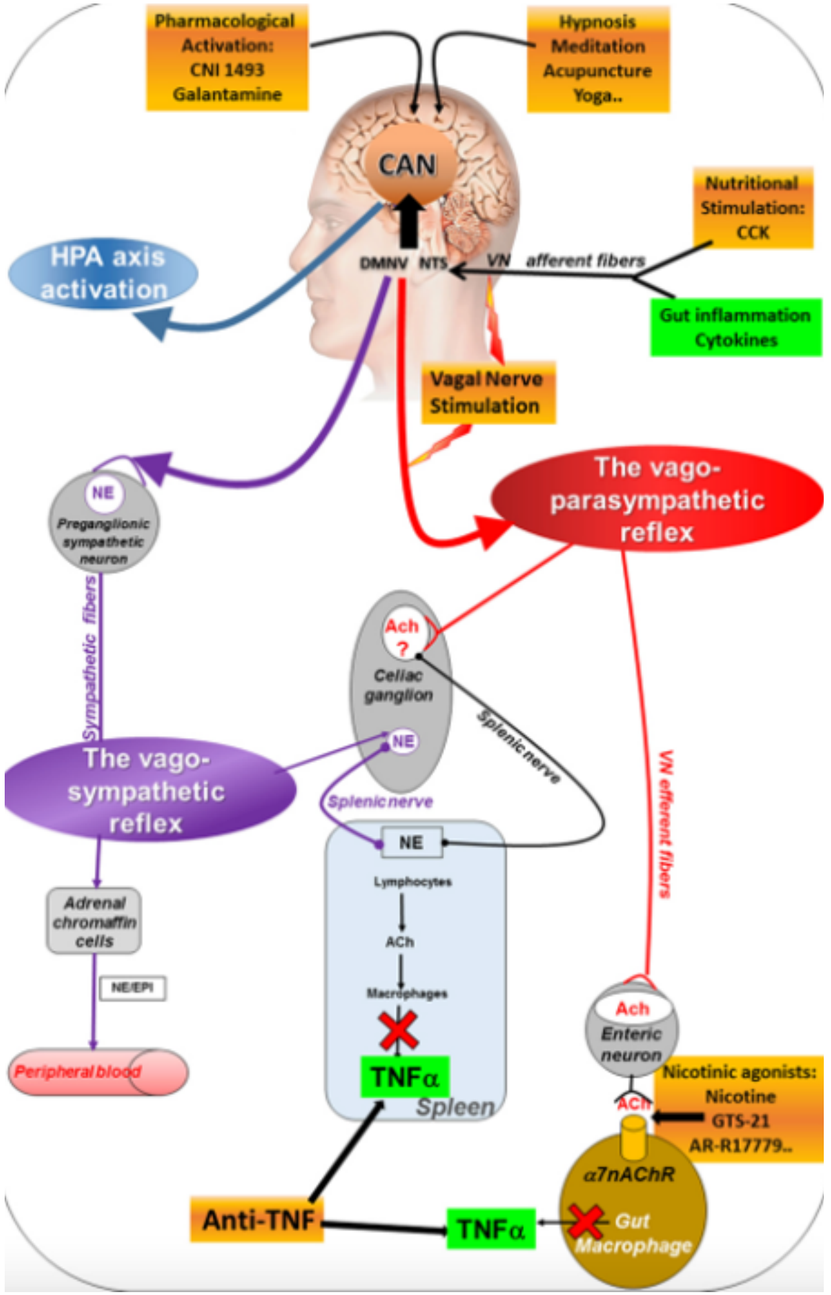
Neuroendocrine-Immunological Axis

are the key players in autoimmune diseases.

VAGAL NERVE CONNECTION

- Regulates the HPA
- Vagal Nerve Afferent fibres
- Vagal Nerve Efeerent fibers
- Splenic Nerve/vago-sympathetic-pathway (through the spleen

- The vagus nerve facilitates two-way communication between the brain and the peripheral organs. It carries sensory information (afferent signals) from the body's organs to the brain and motor information (efferent signals) from the brain to the organs.
- Parasympathetic Nervous System: The vagus nerve is a major component of the parasympathetic nervous system (a subdivision of the autonomic nervous system within the CNS). It plays a vital role in regulating bodily functions like heart rate, digestion, and respiratory rate during rest and relaxation.



vhttps://www.frontiersin.org/articles/10.3389/fimmu.2017.01452/full

Does Autoimmune...
START IN THE GUT?

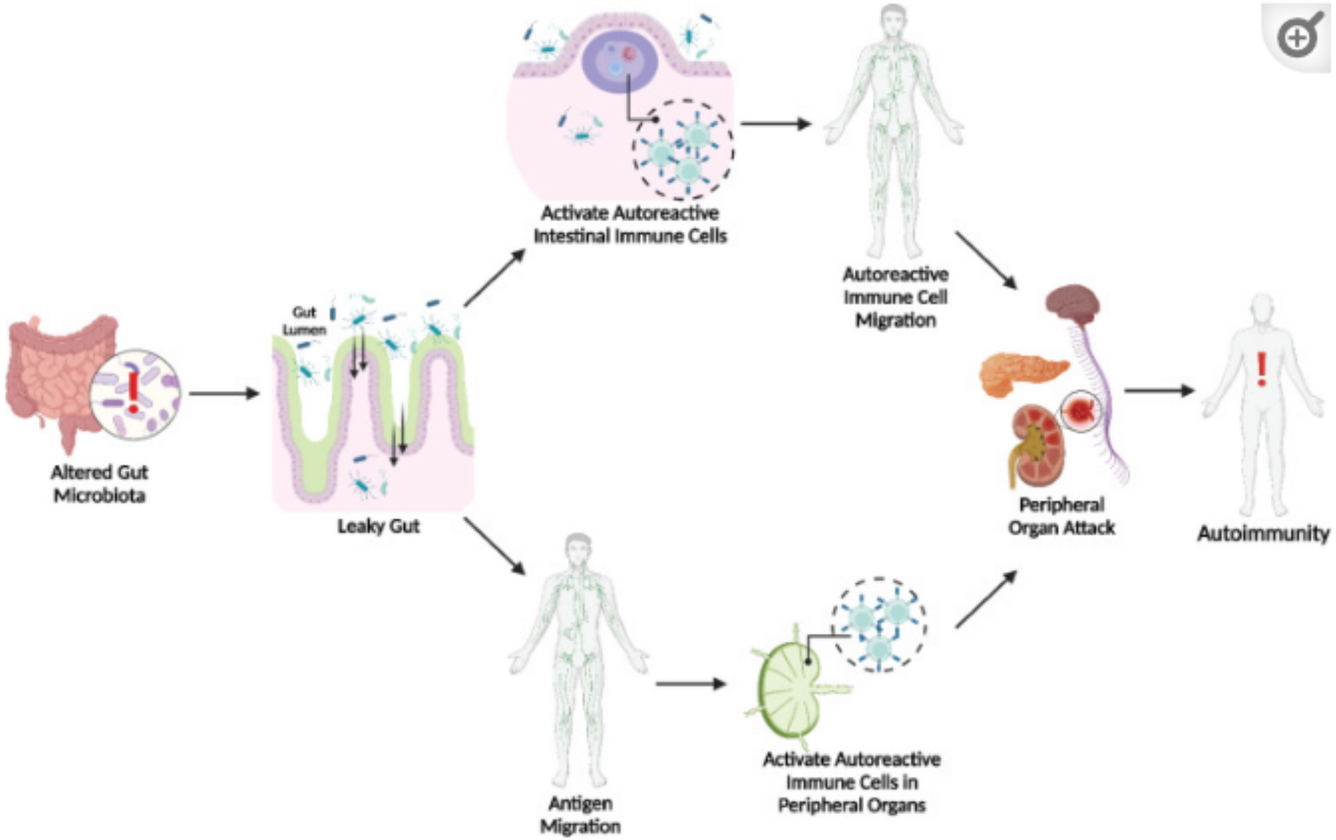
GUT HEALTH

Do we know the whole picture?

Fatigue

GUT HEALTH & AUTOIMMUNE

- Hyper-permeability
- Dysbiosis
- Pathogenic Infection
- Increased inflammation
- Altered IgA



Front Immunol. 2022; 13: 946248.
Published online 2022 Jun 27. doi: 10.3389/fimmu.2022.946248

How do we fix this?

- **Restrictive diet changes**
- **Antimicrobials, Antibiotics**
- **Supplements to heal the gut**

is that really the fix?

LET'S DIG DEEPER... 

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GUT HEALTH & AUTOIMMUNE

Acute Stress:

- **A rat study showed that <u>acute stress</u> stimulated**
  - **neuroinflammation**
  - **Increase hyper-permeability**
  - **translocation of endotoxins**

INTERESTING...

Acute Stress continued...

- **However, when pre-treated with antibiotics “pre-stress” the neuroinflammation was prevented**
  - **Also found a reduction in hyper-permeability**
  - **reduction in endotoxins**

- **When pre-treated with probiotics (Lacto. farciminis) they had a similar outcome**

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GUT HEALTH & AUTOIMMUNE

Chronic Stress (hypercortisomia)

- **long term permeability of the barrier**
- **endotoxemia**
- **low-grade inflammation**
- **delayed wound healing**
- **more susceptible to infections**

Stress influences:

- **gut motility**
- **digestive secretions (HCL, enzymes etc..)**
- **mucus production *****

Which alters the environment, the habitat for our microbiome

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GUT HEALTH & AUTOIMMUNE

Increase SAM

- **intestinal wall is innervated by androgenic synapse fibres**
  - **when stimulated increases water and sodium retention**
  - **increase in hyper-permeability**
  - **alter gastric motility**
  - **increase in glucose absorption**

Increase GC

- **similar to the above response but triggered by GC's**
  - **when stimulated increases water and sodium retention**
  - **increase in hyper-permeability induced by CRH --> but is suppressed by the mast cells**
  - **intestinal mast cells when stimulated look for pro-inflammatory molecules like IFN-y and TNF-α which impact tight junctions**

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GUT HEALTH & AUTOIMMUNE

Microbiota:

- **influences inflammation**
- **alters metabolic pathways**
- **maintains the homeostasis of the intestinal barrier and function**
- **influences the development of the HPA and immune system**
  - **exposure to LPS (lipo-polysaccharides) at developmental exaggerate the HPA and Immune response to stress**
  - **ALSO exposure to social stress has been shown to alter the gut microbiome**

Fatigue

GUT HEALTH & AUTOIMMUNE

Inflammation in the GI tract

↓

Change in Microbiota

↓

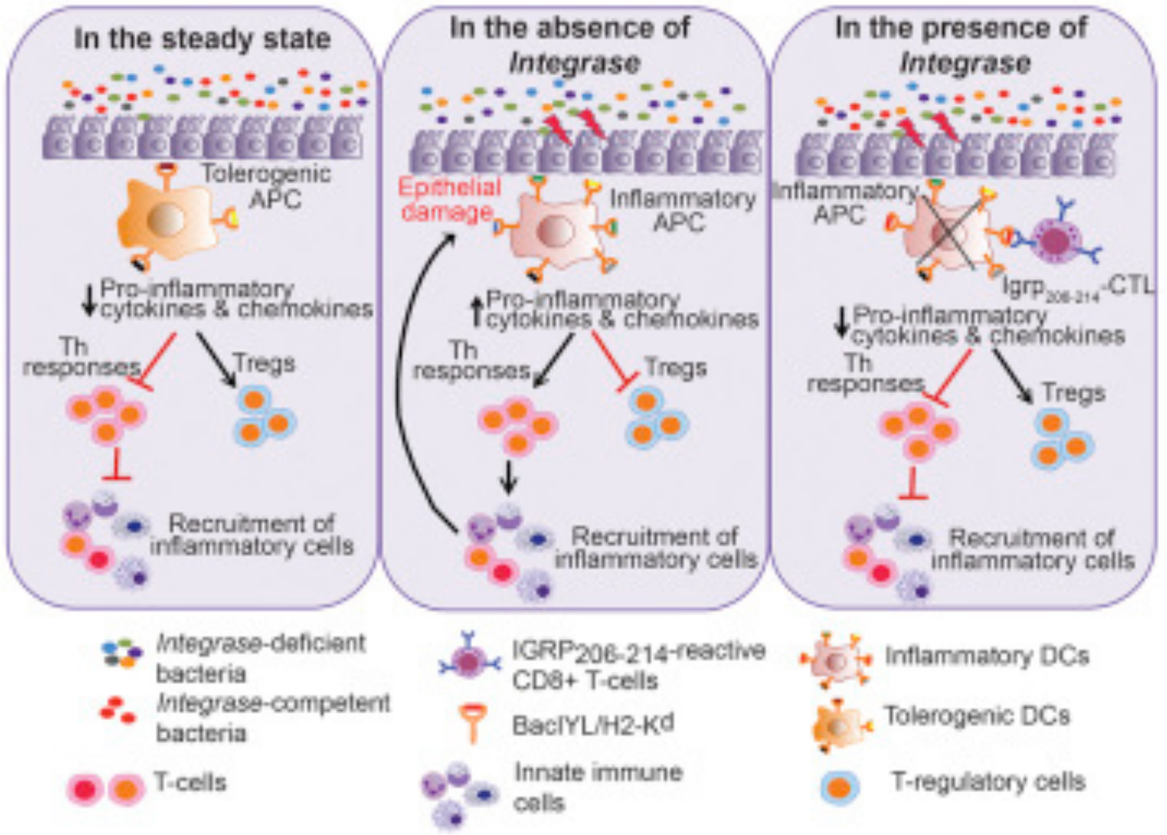
Intestinal Barrier imparied

↓

Translocation of Microbes & their byproducts

↓

Increase In Th17 & The Enteric Nervous system



INFLAMMATION

Putting it all togther

Fatigue

INFLAMMATORY TRIGGERS - SUMMARY

Immune Cells

- **Immune cells trigger inflammation by recognizing and responding to foreign pathogens or damaged cells in the body. Upon detection, they release inflammatory cytokines and chemokines that attract additional immune cells to the site, amplifying the inflammatory response to contain and eliminate the threat**

Oxidative Stress

- **In a pathological state, the immune cells produce excessive ROS which increases inflammation and then alters the balance in the immune cells -- [Negative feedback system]**

HPA & SAM

- **Acute stress [SAM] triggers NK cells, monocytes, and eosinophils, and shows a change in CD4, CD8, and leukocytes expression**
- **HPA - GC is anti-inflammatory via inhibiting IL-1Beta, IL-6, IFN-gamma, COX's, PG's BUT IL-1Beta, TNF Alpha, IL-6 all stimulate the HPA**

Microbiome/GUT

- **The microbiome influences gut inflammation by maintaining a balance of beneficial and harmful bacteria. Disruption in this balance, known as dysbiosis, can lead to an overactive immune response, triggering inflammation in the gut. This inflammation can further alter the microbiome composition, creating a cycle of chronic inflammation**

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OXIDATIVE STRESS

- **Autoimmune is linked to chronic inflammation and impaired antioxidant defence**
- **Autoimmune disorders are marked by a rise in the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS).**
- **The inflammation-driven presence of neutrophils results in a significant increase in ROS and RNS free radicals. This surge in ROS and RNS compromises the body's antioxidative defence mechanisms.**

This causes damage to :

- **molecules, cell structures,**
- **signaling pathways**
- **tissue structures**

Which then in turn triggers more inflammation and creates more oxidative stress

INFLAMMASOMES

Inflammasomes have been shown to be **hyperactivated** in autoimmune diseases, in particular, **NLRP3**

They are important for modulating

- Sleep (Opipari, 2018)
- Cognition (Zielinski, 2017)
- Anxiety & Depression (Dempsey, 2017)

Turned on by:

- HPA/SAM
- Cytokines & Oxidative stress (ROS)
- Mitochondrial DNA (mtDNA) is released into the cytosol (Kopitar-Jerala, 2017)

TESTING & APPROACH

Testing vs Guessing

Fatigue

TREATMENT GOALS - MULTI-LEVEL APPROACH

✓ IDENTIFY IF THERE IS A TREAT OR DANGER

- Active virus, dysbiosis, infection, pathogen, etc...

✓ SUPPORT SAM & HPA

- Rule Out ACE's
- Support the stress response
- GET THEM SLEEPING!

✓ REDUCE INFLAMMATION & OXIDATIVE STRESS

- Remove inflammatory triggers (above)
- Support oxidation needs which also supports the mitochondria

Hard CONVERSATIONS

WE MUST HAVE

Management vs Remission

Managing Expectations

Medicine Remission

A Natural Alternative

BLOOD WORK

Anemia

- Ferritin is not enough *falsely elevated
- CBC Full iron panel - plasma iron, transferrin, and iron (transferrin) % saturation B12 **This panel will give you an idea of absorption**

Inflammation

- CRP, ESR, **Urate**, Calprotectin, Ferritin, Fibrinogen

Infection

- WBC (trends) - N:L (2:1)
- Total: IgG, IgA

Sleep study

CBC

- Changes in platelet parameters, especially Mean Platelet Volume (MPV) and Platelet Distribution Width (PDW) may be indicative of systemic inflammation.

BLOOD WORK AS A TRACKER FOR FATIGUE

MS

- CRP levels in blood work did not correlate with fatigue (Giovannoni, 2001)

SLE:

- up to 92% of patients with SLE are fatigued, without correlation with disease severity.
- Significantly higher TNFα and lower IL-10 levels have been shown in depressed SLE patients and have been associated with worse depression scores

RA

- There is a positive correlation between CRP levels and depression severity in RA patients. (Kojima, 2009)
- Serum CRP levels along with erythrocyte sedimentation rate (ESR), a marker for the severity of inflammation, also have a significant correlation with fatigue (Madsen, 2009).

Fatigue

FUNCTIONAL TESTING

IDENTIFY THE THREAT:

- Pathogen testing - Cyrex Array 12
- Stool Analysis PCR & Culture
- Organic Acid Testing

METHYLATION

- Genetic profile - SNP
- Homocysteine Markers

INFLAMMATION & OXIDATIVE STRESS

- Cytokine testing
- *-OH

TECHNOLOGY - HEART RATE VARIABILITY

SAM Information

HRV is simply a measure of the variation in time between each heartbeat. This variation is controlled by a primitive part of the nervous system called the autonomic nervous system (ANS). It works behind the scenes, automatically regulating our heart rate, blood pressure, breathing, and digestion among other key tasks.

The ANS is subdivided into two large components: the sympathetic and the parasympathetic nervous system, also known as the fight-or-flight mechanism and the relaxation response.

December 1, 2021, Harvard Health

STRATEGIES

Putting it all togther

LIFESTYLE: EXERCISE

Impact of Physical Exercise on Fatigue in Primary Sjogren's Syndrome (pSS)

- The review found that there's a link between fatigue and decreased physical activity/cardiorespiratory fitness in pSS patients.
- Key Findings:
  - Walking Program Study:
  - Improved FACIT-fatigue scores in pSS women compared to controls.
  - Benefits in cardiorespiratory fitness, exercise tolerance, and overall patient perception were observed without worsening disease activity.
  - Improved fatigue scores correlated with reduced depression and better quality of life (QoL) metrics.
- **Nordic Walking Exercise Study: (NON-RCT)**
  - **Result:** Notable improvement in fatigue levels.
- **Resistance Exercise Program Study (RCT)**
  - **Result:** While fatigue was not directly assessed, there were enhancements in functional capacity and QoL in pSS women.

(Mæland, 2021)

LIFESTYLE: EXERCISE & DIET

2019, 24-week RCT - 144 women with low RA disease activity

- 1 - Mediterranean Diet (MD) + Dynamic Exercise Program (DEP)
- 2- DEP
- 3 MD
- Control

DEP =

- warm-up (10 min),
- aerobic - bike (20 min) @ 65% HR,
- anaerobic (20 min) interval with 90 sec on and 30-60 sec rest,
- recreational games (20 min),
- cool down
- (2 times per week)

MD=

50% carbohydrates, 30% fats, and 20% proteins.

- olive oil or canola oil as the main fat,
- whole grains (1–2 portions per meal),
- fruits (2–4 portions per day),
- vegetables (2–3 portions per meal),
- fish (>2 portions per week),
- oilseeds (1–2 portions per day),
- legumes (>2 portions per week),
- red meat (<2 portions per week).

Which groups had the best outcomes for Mental Health? Fatigue? Disease activity?

(García-Morales, , 2019)

LIFESTYLE: EXERCISE & DIET

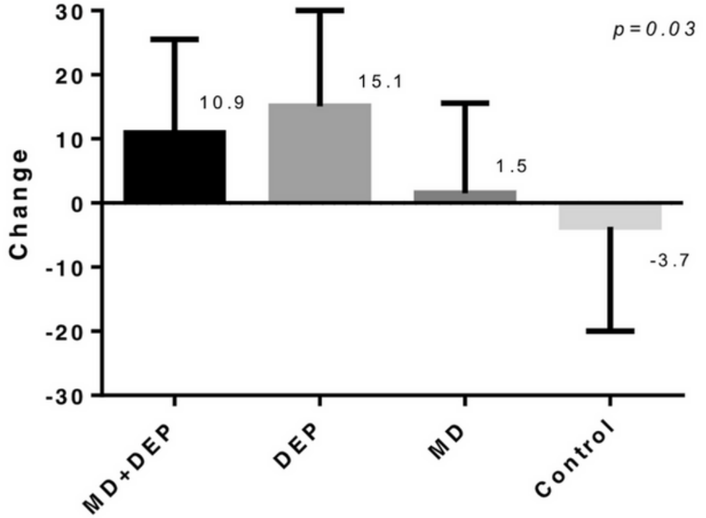


FIGURE 4. Delta of the mental component after 24 weeks.

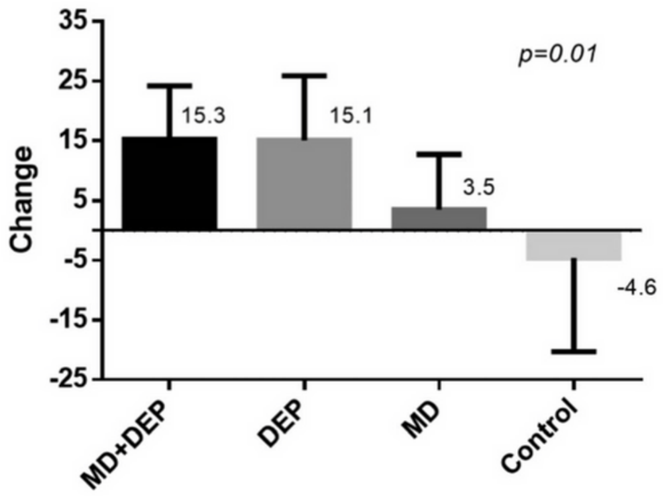


FIGURE 2. Delta of the global punctuation SF-36v2 after 24 weeks.

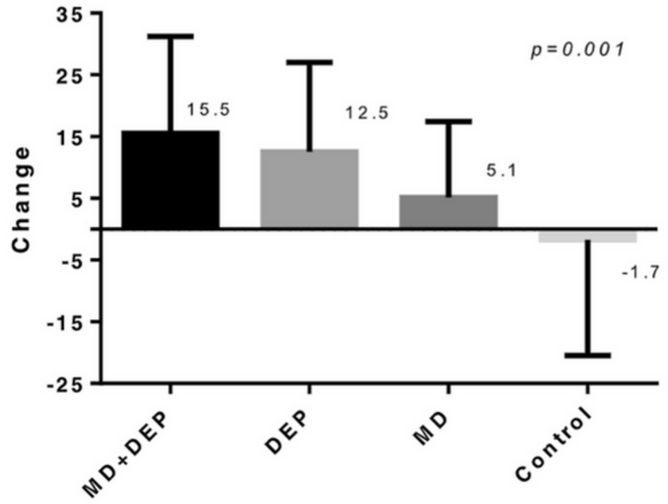


FIGURE 3. Delta of the physical component after 24 weeks.

- DEP - SIG improvements in the mental health
- MD+DEP - SIG improvements in physical components
- MD+ DEP & DEP - improved the SF-36v2 (36-item Short Form Health Survey 36 - health assessment for QoL)

LIFESTYLE: NUTRITION

- A low glycaemic index (GI) diet showed evidence of reduced weight and improved fatigue in patients with lupus. (Jiao, 2022)

- **Increase in Antioxidants**

- Increase in Polyphenols (2 cups per day - Kapolou, 2021)
  - Berries
  - Cocoa
  - Coffee and tea
  - Nuts and seeds
  - Red wine
  - Olives (and olive oil)
  - Beans

Focus on Addition vs Subtraction

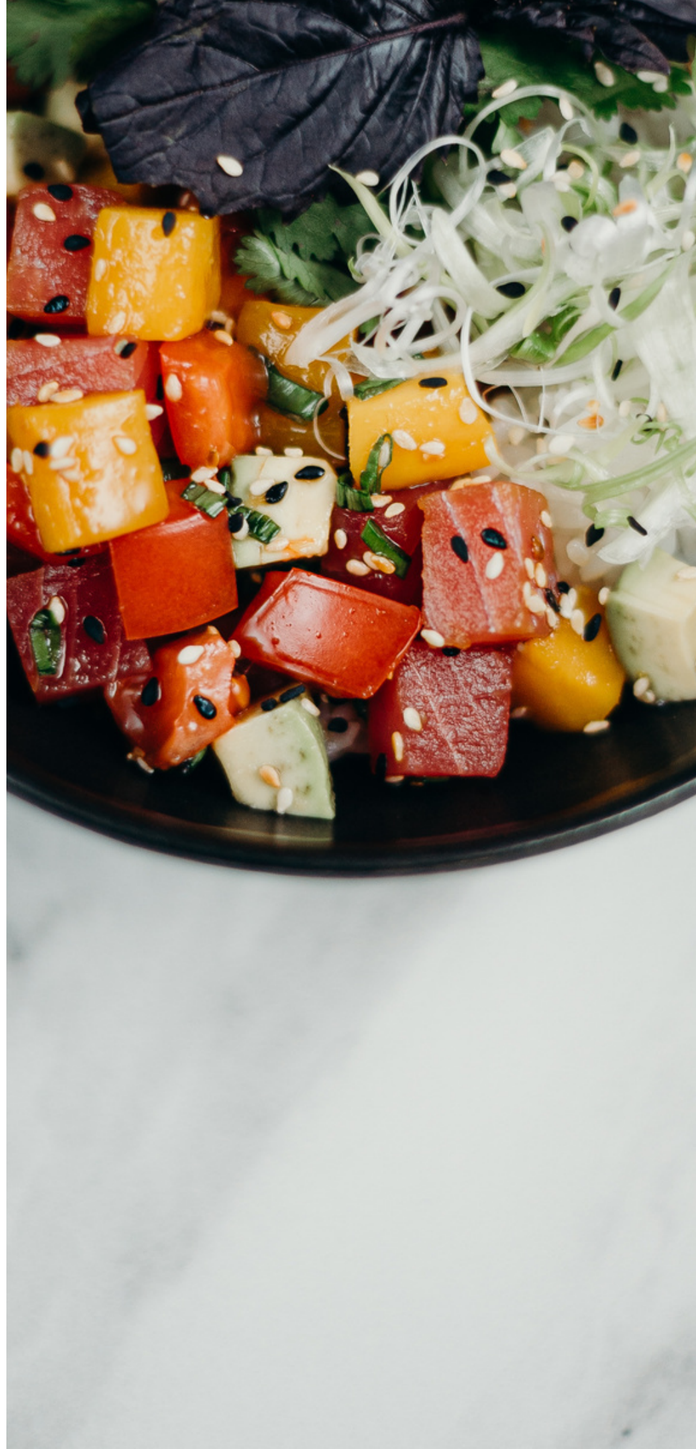
LIFESTYLE: NUTRITION

- Mediterranean Diet
- Blood sugar control
- Fiber – improves the microbiome
- High vegetable intake

Restrictive Diets

- Little to no evidence of fatigue, may notice improvement short term but long-term can create more issues
  - Elimination Diet
  - Autoimmune Paleo (AIP)
  - Keto-genetic
  - Food Sensitivities (IgG)
  - Salt Gluten-Free

Focus on Addition vs Subtraction



NAC & RA

4 small RCTs using NAC vs placebo

- All using medical treatment with the study
  - Dose 600 mg BID for 3 months (Esalatmanesh, 2022)- 74 people
  - compared to baseline NAC significantly reduced morning stiffness, ESR, hs-CRP, LDL-C, Nitric Oxide, MDA (malondialdehyde) increased GPX, HDL-C
  - No remarkable difference between the NAC and Placebo groups
- Dose 600 mg BID for 8 weeks (Jamali, 2021) - 41 people
  - statistically significant reduction of the DAS28-ESR in the NAC group compared to the control
  - no change in cytokine activity
  - improvements in the patient global assessment, number of tender joints, number of swollen joints, and the ESR rates were in favour of the NAC group but not (Statistically significant
- Dose 600 mg BID for 12 weeks (Hashemi, 2019) - 42 people
  - The NAC group had a significant decrease in MDA, NO, IL-6, TNF-α, ESR and CRP were significantly lower,
  - a significant increase in the antioxidant biomarkers: the serum level of TAC and TTG from baseline
  - Only NO, MDA and TTG showed a significant difference between groups
- Dose 600 mg BID for 12 weeks (Batooei, 2018)
  - no significant differences between the two groups in DAS28 score and ESR
  - Global Health (GH), VAS (Pain), and HAQ scores were improved significantly in the NAC group compared to the placebo group.

NAC & PROGRESSIVE MS

- Not effective at a dose of 1250 mg TID for 12 weeks (Krysko, 2021)

NAC & SLE

A randomized double-blind placebo-controlled study. (Lai, 2012)

- 36 SLE patients
- Dose: received a daily placebo of 1.2 g, 2.4 g or 4.8 g of NAC for 3 months
- NAC was tolerated by all patients up to 2.4 g/day - 33% of those receiving 4.8 g/day had reversible nausea.

Results:

- Placebo or 1.2 g/day NAC did not influence disease activity.
- 2.4 g and 4.8 g NAC reduced disease activity by blocking mTOR in T lymphocytes and reduced ds-DNA

(Lai, 2012)

RESVERATROL - AUTOIMMUNE

- RCT for 100 RA patients
- Dose 1000 mg plus conventional medication for 3 months
  - Clinical Biomarkers: were significantly lowered in the RSV-treated group
    - the 28-joint count for swelling and tenderness & disease activity for the joints
  - Biochemical markers - all significantly decreased in RSV-treated patients
    - CRP, ESR, MMP-3. TNF-alpha, IL-6, undercarboxylated osteocalcin,

COQ10 - AUTOIMMUNE

(Khojah, 2018)

- RCT for MS
  - Dose 500 mg per day for 12 weeks vs placebo
  - **Statical significant decrease in fatigue and depression in the CoQ10 group compared to the placebo group. (Sanoobar, 2016)**

- RCT for RA
  - Dose 100 mg per day for 8 weeks
    - CoQ10 group showed decreased serum MDA and suppressed overexpression of TNF-α
    - There was no significant difference in TAC (oxidative stress) and IL-6 levels between groups.

QUERCETIN & RA

Study Design:

- Randomized, double-blind trial with 50 medicated RA women, with a quercetin (500 mg/day) group and placebo for 8 weeks.

Results:

- Quercetin Group:
  - Reduced Early Morning Stiffness, and morning and after-activity pain.
  - Lower DAS-28 and HAQ scores.
  - Fewer patients with active disease.
  - Decreased plasma hs-TNFα levels ($p < 0.05$).
  - Tender Joint Count (TJC) decreased post-intervention.
- No Significant Differences:
  - Initial TJC and Swollen Joint Count (SJC) similar in both groups.
  - Non-significant effect on ESR ($p > 0.05$).

Conclusion:

- 8-week quercetin supplementation (500 mg/day) improved symptoms, disease activity, hs-TNFα, and HAQ in RA women.

GARLIC & RA

Study Design: Moosavian (2020), Randomized Controlled Trial (RCT).

- 70 RA women, receiving either 500 mg garlic tablets (equivalent to 2500 mg fresh garlic, 2.5 mg allicin) or placebo daily for 8 weeks.
- All participants were under treatment with disease-modifying anti-rheumatic drugs.

Results:

- Garlic Group:
  - Increased serum levels of Total Antioxidant Capacity (TAC) compared to placebo (26.58 vs 16.11 nmol of Trolox equivalent/mL; P = .026).
  - Decreased Malondialdehyde (MDA) levels (-0.82 vs 0.36 nmol/mL; P = .032).
  - Reduction in pain after activity and HAQ scores compared to placebo (P < .001).

Conclusion:

- 8-week garlic supplementation improved antioxidant capacity reduced oxidative stress and pain and improved HAQ scores in RA women.

SAFFRON MS FATIGUE

- RCT - with 30 MS patients
- Dose: saffron syrup (0.5% saffron extract) every 8 hours and were evaluated at 30 and 60 days
- Statical significance
  - 30 days after intervention 32% in fatigue,
  - After 60 days 50% reduction in fatigue
    - (based on Fatigue Self assessment - FSS (9 items range of 1-7)

(Ashtiani, 2020)

ANDROGRAPHIS & RA

Study Design: Prospective, randomized, double-blind, placebo-controlled study on patients with active Rheumatoid Arthritis (RA).

- 60 patients received tablets (Paractin) made from A. paniculata extract (30% total andrographolides) three times daily for 14 weeks, following a 2-week washout period.

Results:

- A. paniculata Group:
  - Joint pain intensity decreased compared to placebo, though not significantly.
- Significant weekly reductions were observed in:
  - Tender joint count (-0.13; $p = 0.001$).
  - Number and total grade of swollen joints (-0.15 and -0.27 respectively; $p = 0.02$ and $p = 0.010$).
  - Number and total grade of tender joints (-0.25 and -0.47 respectively; $p = 0.033$ and $p = 0.002$).
  - HAQ scores (-0.52; $p < 0.001$).
  - SF36 health questionnaire scores (0.02; $p < 0.001$).
  - Associated with reductions in rheumatoid factor, IgA, and C4.

Conclusion:

- A. paniculata (Paractin) may be a beneficial natural supplement for RA treatment,

(Burgos, 2009)

ANDROGRAPHIS & MS

- Study Design:
  - Exploratory pilot clinical trial on patients with non-active Progressive Multiple Sclerosis (PMS).
  - Participants received either **140 mg oral** Andrographolide (AP) or a placebo twice daily for 24 months.
- Results:
  - 44 patients were randomized: 23 in the AP group and 21 in the placebo group, with a median baseline EDSS (Expanded Disability Status Scale) of 6.0 for both.
  - AP Group Findings:
    - Experienced less brain shrinkage than the placebo group (0.679% vs. 1.069% annually).
    - 30% had disability progression over 3 months, compared to 41% in the placebo group.
    - Disability scores slightly improved in the AP group, while they worsened in the placebo group.
    - Adverse events related to AP included mild rash and altered taste (dysgeusia).
- Conclusion:
  - AP was well-tolerated and showed the potential to reduce brain atrophy and disability progression in non-active PMS patients. Further evaluation in larger clinical trials is necessary.

(Ciampi, 2020)

MELATONIN

- Melatonin is secreted by the pineal gland, regulates circadian rhythms, and has anti-inflammatory and anti-oxidant properties.

- Melatonin receptors are expressed on **CD4 and CD8 T-cells and B-cells. Additional evidence suggests that melatonin attenuates the expression of IL-1β, TNF-α, IL-6, and IFN-γ.**

- The anti-inflammatory properties of melatonin occur, in part, through the inhibition of NF-κB. An association between multiple sclerosis and melatonin has been observed clinically.

- Melatonin therapy has been shown to **attenuate inflammatory cytokines and related pathways in both animal models and human studies of multiple sclerosis, type 1 diabetes, inflammatory bowel disease, and systemic lupus erythematosus, and thus could potentially be beneficial in combating fatigue.**

Lin G-J, et al, 2013

MELATONIN --CAUTION??

There is evidence showing there are receptors for melatonin on synovial macrophages which promote the release of some Th-1-type proinflammatory cytokines such as IL-12. it has also been pointed out that the higher blood concentrations of melatonin in arthritic patients, especially in the early morning, may help to explain the morning stiffness and joint swelling experienced by patients - but that doesn’t mean that melatonin should be avoided (this was based on animal studies)

MELATONIN --CAUTION... NOT REALLY

- **Forest (2007) Study:**
  - Design: Randomized Controlled Trial (RCT) with 75 RA patients over 6 months.
  - Dosage: 10 mg per day of the studied drug.
  - Results:
    - Elevated ESR and Neopterin (inflammatory markers) were observed at the 6-month mark.
    - No reported clinical changes in symptoms.

- **Esalatmanesh (2021) Study:**
  - Design: RCT with 64 RA patients, administering 6 mg of Melatonin daily for 12 weeks.
  - Results:
    - Significant decreases from baseline in DAS-28 (50.5%), ESR (59%), MDA (97%), and LDL-C (13%) with Melatonin (all $P<0.001$).
    - TAC increased by 89% ($P=0.013$) and HDL-C by 22% ($P<0.001$).
    - Post-treatment, significant differences between Melatonin and placebo groups were only observed in serum MDA ($P<0.001$) and LDL-C ($P=0.007$) concentrations, adjusted for baseline.
    - No significant changes were noted in DAS-28, ESR, TAC, triglycerides, total cholesterol, HDL-C, FBS, and insulin levels when compared to the placebo group (all $P>0.05$).

Vagal Stimulation & Neuroinflammatory Regulation

Vagal stimulation research has expanded to include its effects on neuroinflammatory regulation for RA and IBD

- This approach offers a potential relief route for chronic pain and depression symptoms.
- Transcutaneous Vagus Nerve Stimulation (tVNS):

Benefits in RA:

- VNS might be an effective alternative for RA patients who don't fully respond to standard drug therapies.
- Study findings:
  - 42-day stimulation led to reduced TNF levels.
  - Around 70% of treated patients saw significant clinical improvement.
  - Discontinuation of VNS for 2 weeks reversed the benefits.

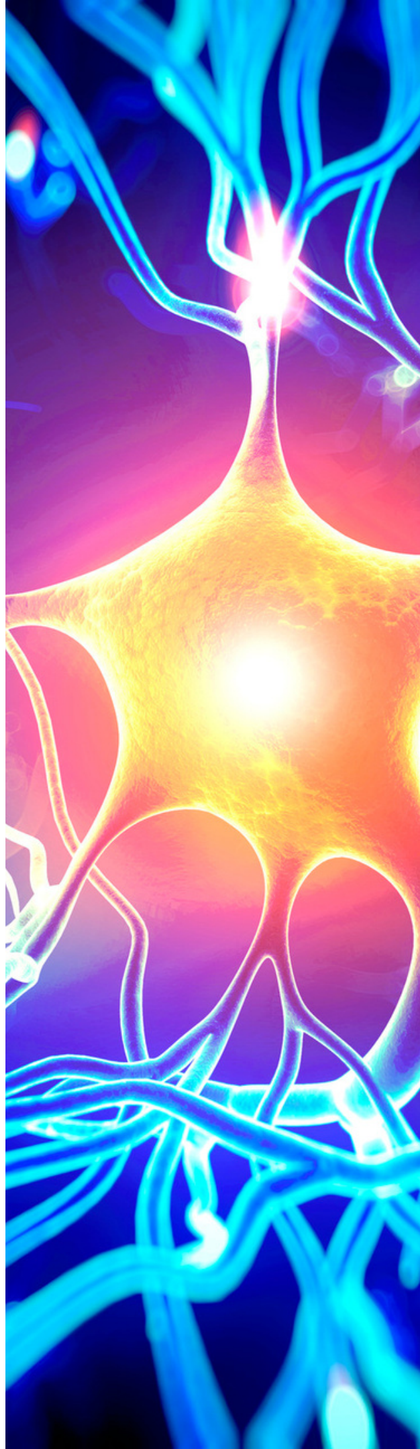
Potential in SLE:

- Preliminary research supports the use of VNS for SLE.
- A pilot study on 18 SLE patients:
  - tVNS notably reduced pain and fatigue compared to sham stimulation.

SSc & tVNS:

- Study on 17 SSc patients:
  - Patients displayed altered HRV.
  - Prolonged use of tVNS normalized sympathovagal balance and improved GI symptoms.

(Bellocchi., 2022)

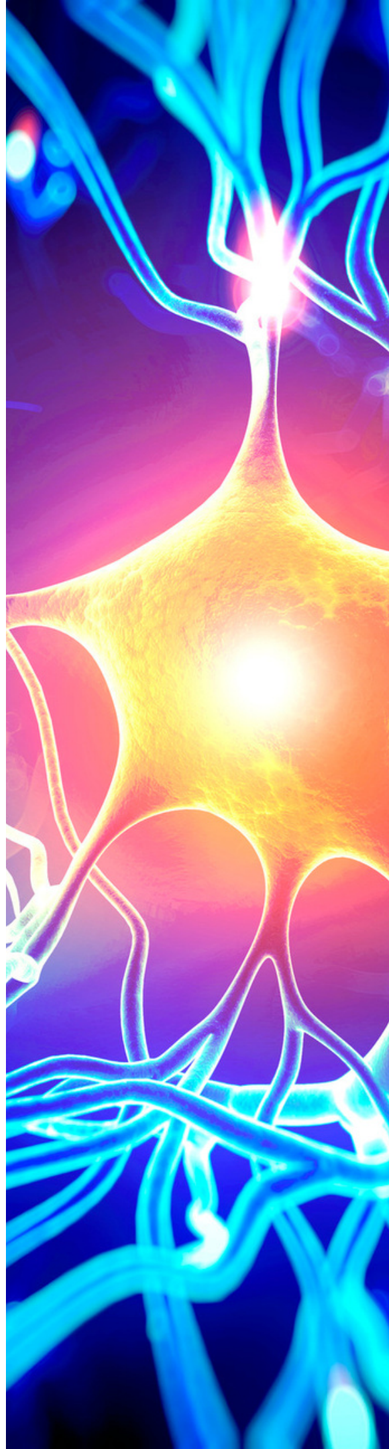


VAGAL STIM

Vagus Nerve Stimulation & Its Effects on Primary Sjögren's Syndrome (pSS) Fatigue.

- The gammaCore device stimulates the cervical vagus nerve noninvasively, potentially impacting immune responses and pSS symptoms.
- Study Design:
  - Participants: 15 female pSS patients, Duration: 26 days.
  - Intervention: Twice-daily use of the noninvasive vagus nerve stimulation (nVNS) device.
  - Measurements: Bloodwork, fatigue-related outcomes (EULAR patient-reported outcome index, profile of fatigue, visual analogue scale of abnormal fatigue, and Epworth sleepiness scale).
- Key Findings:
  - Fatigue (Pro-F) and sleepiness (ESS) scores showed notable improvements across all visits.
  - After LPS stimulation, significant reductions in levels of various immune factors (IL-6, IL-1β, IP-10, MIP-1α, and TNFα).
  - Changes in specific NK- and T-cell subsets were observed
  - Fatigue score reductions correlated with baseline lymphocyte counts.

(Tarn, 2019)

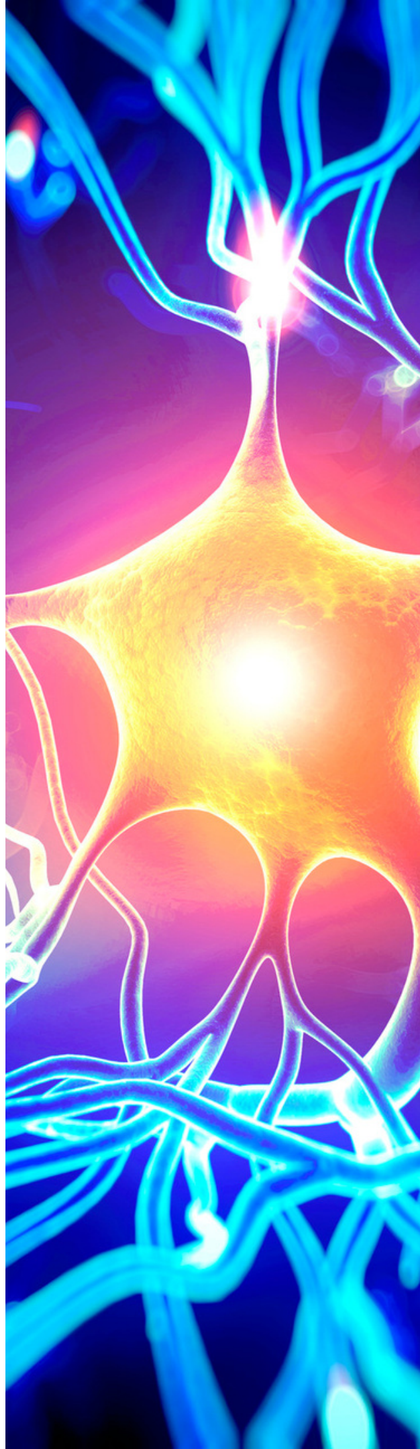


VAGAL NERVE STIMULATION

Stimulation of the inflammatory reflex — such as by sending electrical impulses to the vagus nerve — has the potential to treat RA by reducing the body's production of inflammatory cytokines.

Several studies in the last 2 years have been published showing an overall disease improvement with joint pain and reduction of cytokines, even for people that have not had relief from pharmaceutical intervention.

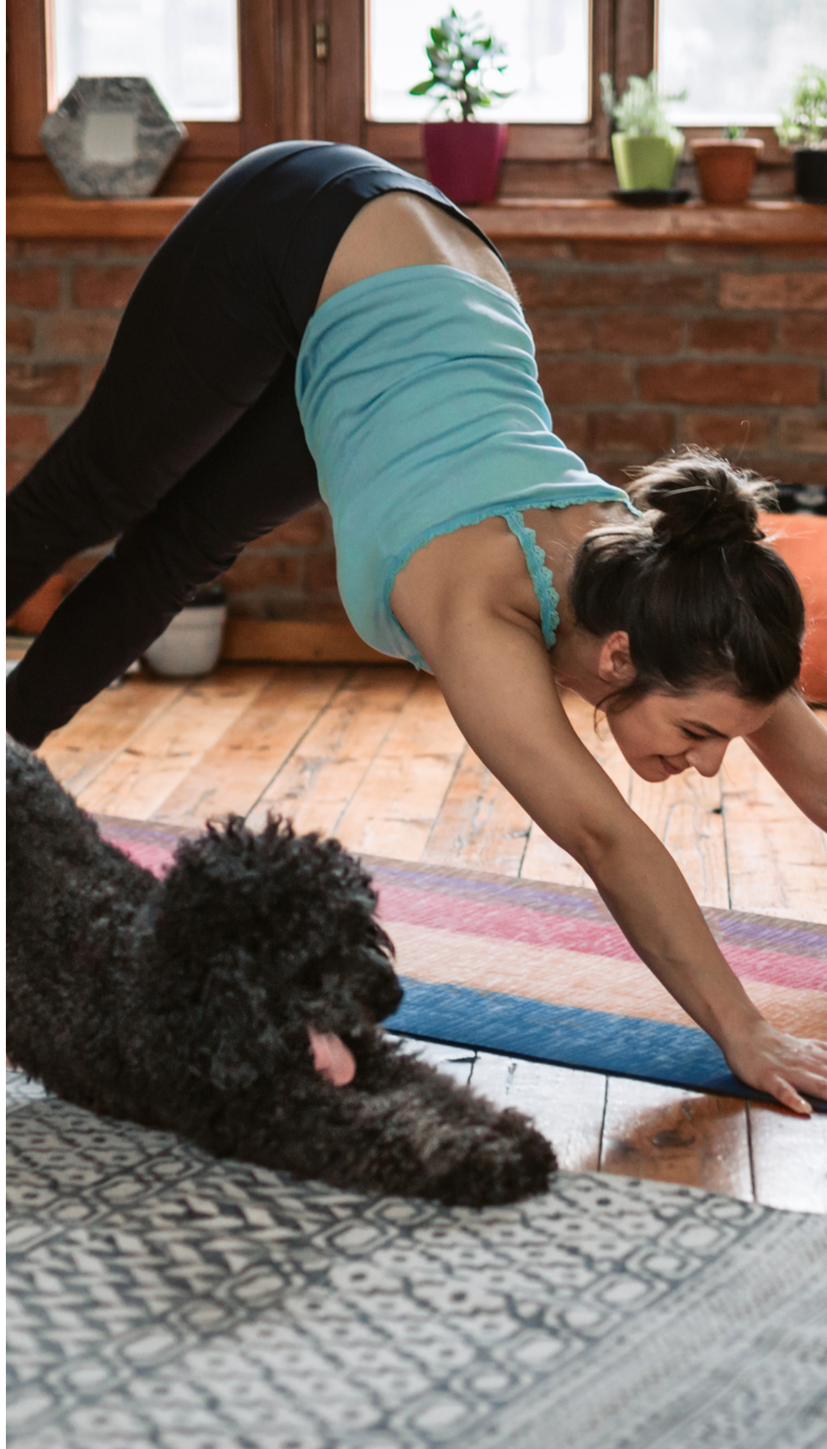
- DAS28-CRP at 12 weeks:
  - A decrease of -1.4 was observed from a starting average of 5.3.
  - 37% of patients achieved a DAS28-CRP score of 3.2 or lower.
  - 23% of patients reached a DAS28-CRP score below 2.6.
- HAQ-DI Changes:
  - The average change was a decrease of -0.5 from an initial average of 1.6.
  - 57% of patients achieved a minimal clinically significant difference of 0.22 or greater.
- ACR Responses:
  - ACR20: Achieved by 53% of patients.
  - ACR50: Achieved by 33% of patients.
  - ACR70: Achieved by 17% of patients.
- Safety: Four non-serious adverse events were reported, all resolved without intervention.



LIFESTYLE: YOGA & ACUPUNCTURE

- Acupuncture and meditation might help IBD patients by activating the cholinergic anti-inflammatory pathway (CAP).
- These therapies can reduce heart rate and inflammation, possibly by increasing activity in the **vagus nerve.**
    - Acupuncture has been shown to reduce the release of an inflammatory substance (TNFα) in mice.

- Yoga and mindfulness meditation also increase activity in the vagus nerve.
    - A study by Cramer et al. found that practicing yoga for 90 minutes weekly improved the quality of life for patients with a type of IBD called ulcerative colitis (UC).
    - Compared to a control group, patients who practiced yoga experienced a better quality of life and less disease activity after 12 and 24 weeks.



LIFESTYLE: EXERCISE & VAGAL TONE

Regular exercise can increase the resting activity of the vagus nerve and the production of serotonin (5-HT) in the brain. Increased brain serotonin levels, in turn, enhance the activity of the vagus nerve, as observed in studies with rats

DHEA ON FATIGUE

women with pSS.

- Design: Multicenter, investigator-based, powered, randomized controlled clinical trial (crossover, washout design)
  - Participants: 107 pSS patients with severe fatigue and low levels of serum DHEA/DHEAS.
  - Dose: 50 mg/day of DHEA.
  - Primary Outcome: Fatigue.
  - Findings: All fatigue metrics improved from the baseline, but the differences between DHEA and placebo were negligible. Even in DHEA-deficient and severely fatigued patients with pSS, DHEA treatment was no better than placebo.

(Mæland, 2021)

OTHER CONSIDERATIONS

Magnesium

- Foundational nutrients, needed for more than 300 enzyme
- A study was done on rugby players: The results suggest that magnesium supplementation might influence the change of parameters of HPA axis activity and reduce the immune response activation after strenuous physical exercise. (Dmitrašinović, 2016)
- 400 mg per day improves HRV (Wienecke, 2016)

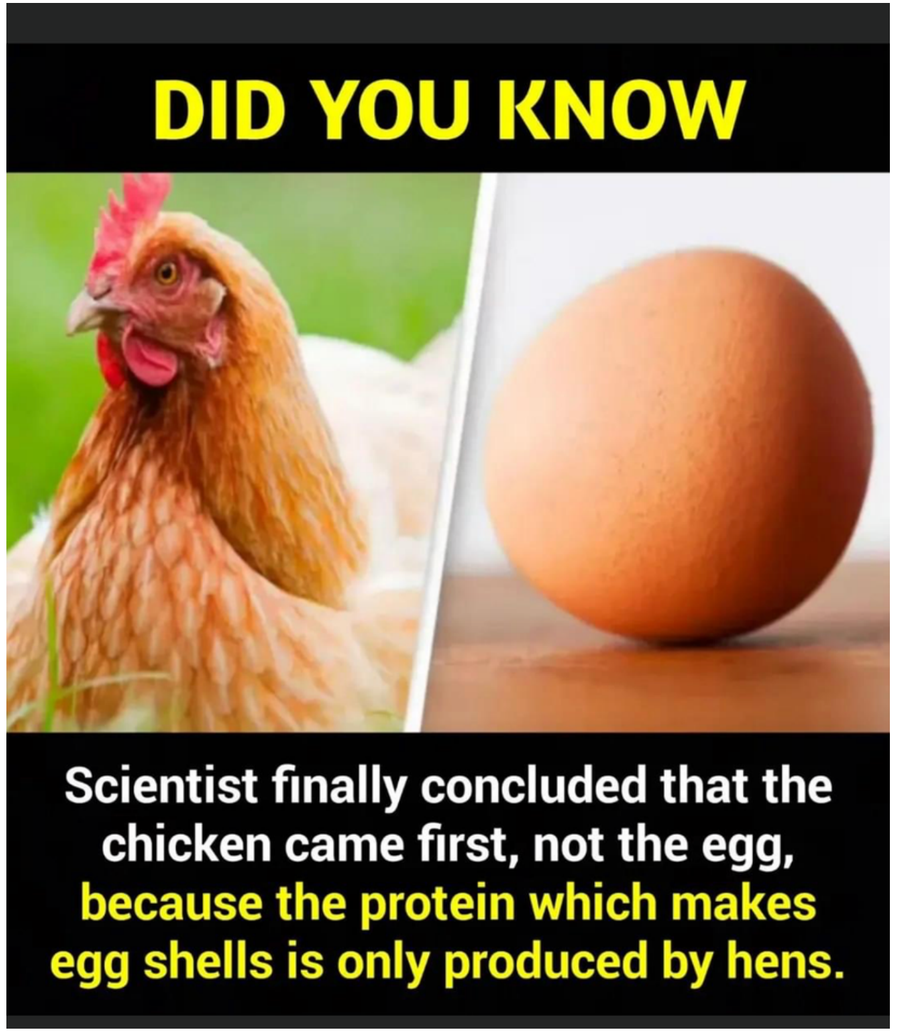
Omega 3 (Thesing, 2018)

- Omega-3 fatty acids are essential for the HPA axis's proper functioning.
- Deficiency in omega-3 fatty acids can lead to:
  - Boosted production of stress-related hormones.
    - Increased levels of corticotropin-releasing hormone (CRH).
    - Higher salivary cortisol levels in the evening.
  - A continuous cycle of inflammation and an overactive stress response causes the HPA axis to malfunction.
- omega-3 fatty acids have been shown to:
  - Promote a healthier stress reaction.
  - Reduce inflammation.
  - **Enhance heart rate variability, a key indicator of stress management.**

Does Autoimmune...
START IN THE GUT?

Chicken or EGG

I still have so many questions...



Reference: Facebook (believe at your own risk)

We have the ability to make an incredible impact.


Thank You!

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