7th ANNUAL Functional Pharmacy Symposium

FUNCTIONAL MEDICINE Continuing Education

Inflammation and Autoimmunity: Building Patient Programs for Patient Transformation

By Melody Hartzler, PharmD, BCACP, BC-ADM

Disclosures

- Melody Hartzler is a speaker for NovoNordisk, Medtronic Diabetes, and Abbott Diabetes. She is the owner of PharmToTable, LLC.

Objectives

- Define the common causes of inflammation
- Explore the inflammation-autoimmune connection
- Discuss successful approaches to manage inflammation
- Apply knowledge to patient cases

Inflammation is Vital

- Inflammation is an adaptive response to provide protection against infection
- Acute inflammatory response:
  - Delivery of plasma and leukocytes to site of infection or injury
    - Production of inflammatory mediators
  - Neutrophils travel to affected tissue to kill invading agents
  - Resolution and repair phase

"Whatever the cause of the inflammatory response, its 'purpose' is to remove or sequester the source of the disturbance, to allow the host to adapt to the abnormal conditions and, ultimately, to restore functionality and homeostasis to the tissue."

Medzhitov R. *Nature*. 2008;454(7203):428-435.

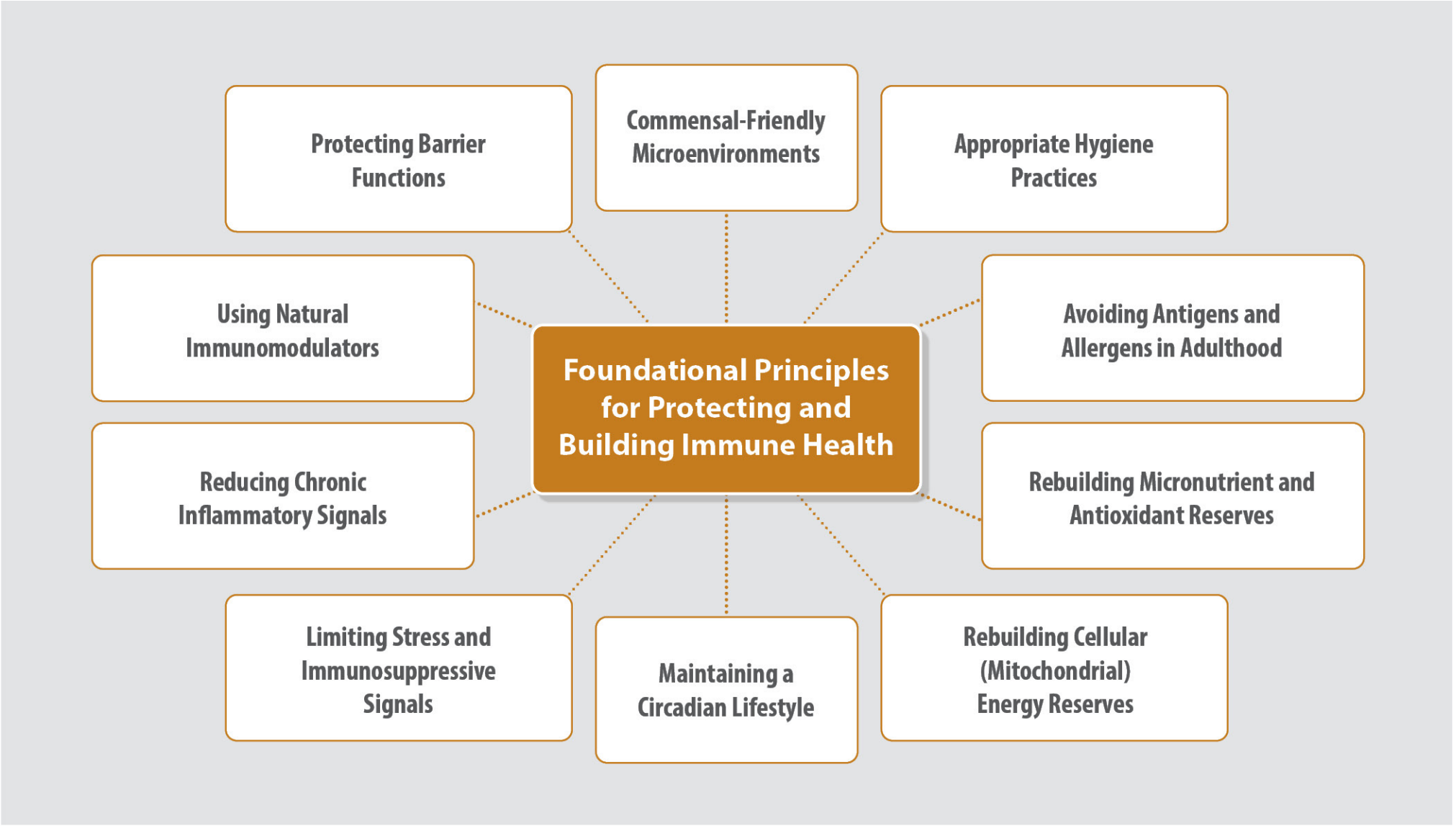
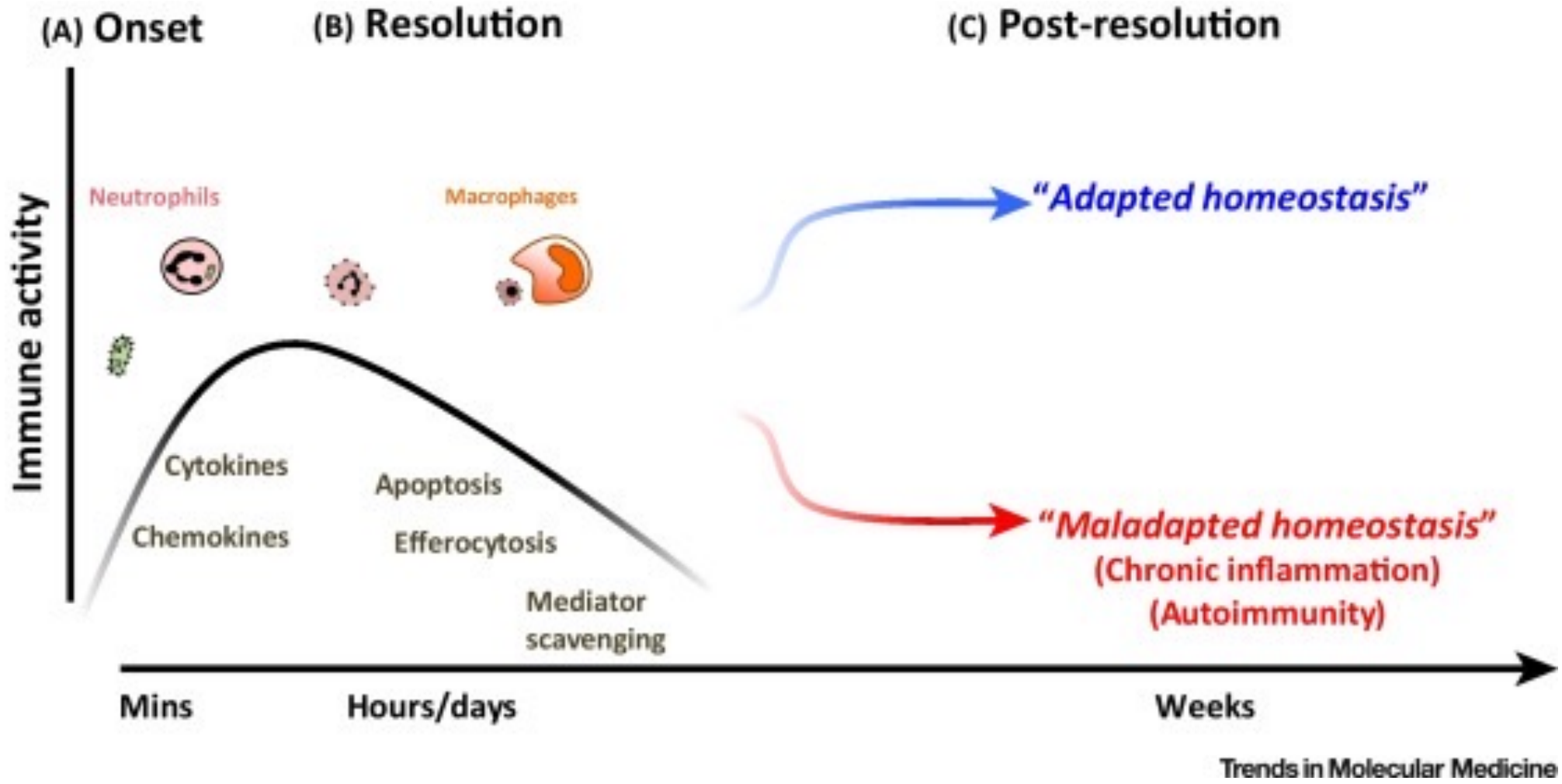
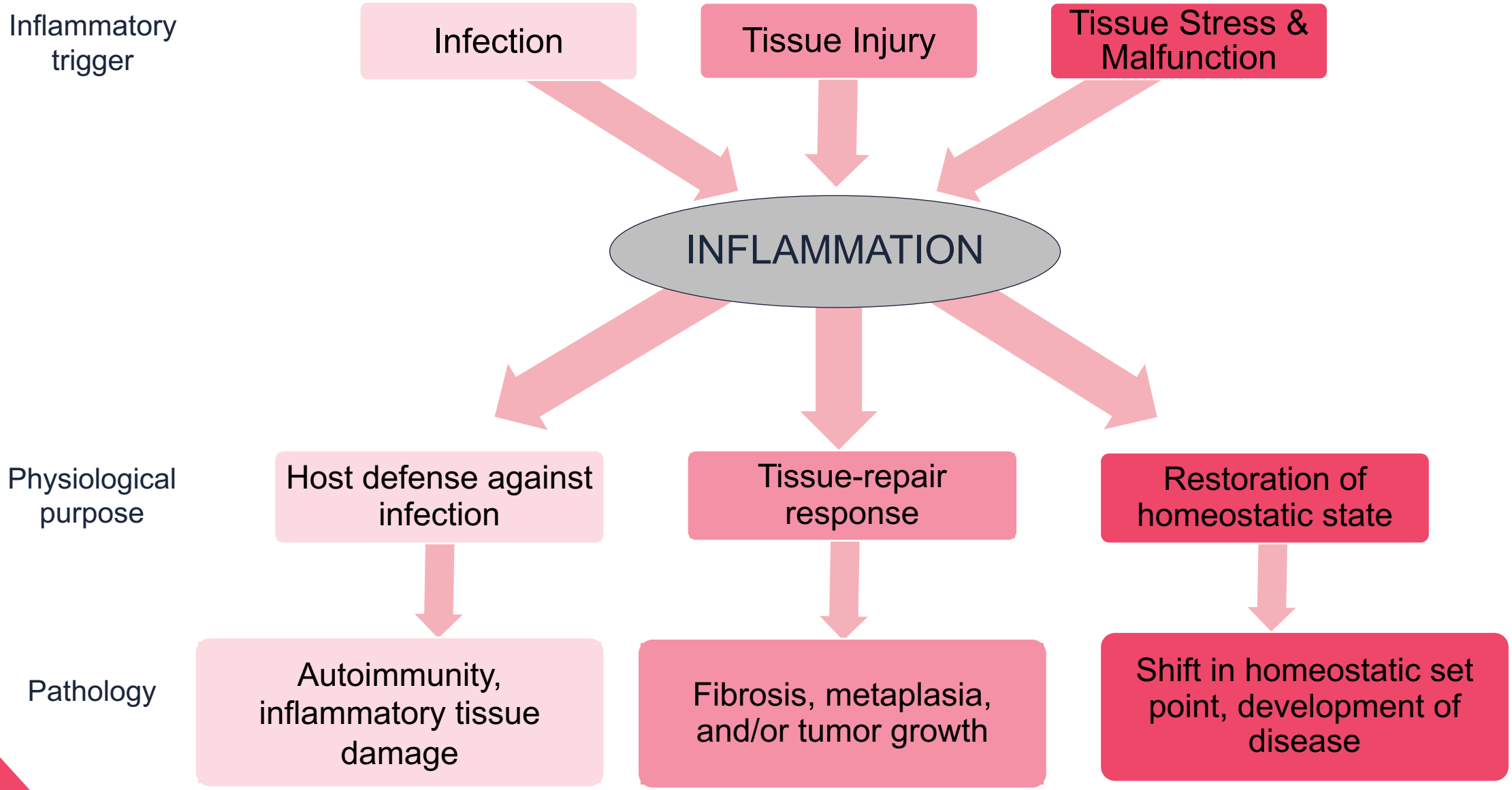


Figure 3: Ten Foundational Principles for Protecting and Building Immune Health.



Feehan KT, et al. *Trends Mol Med*. 2019;25(3):198-214.



Adapted from Medzhitov R. *Nature*. 2008;454(7203):428-435.

Mediators of Inflammation

- Alter the functionality of tissues and organs
  - Adipokines
    - Adiponectin
    - Leptin
    - Resistin
    - Visfatin
  - Inflammasome & DAMPs
  - NK cells

Scrivo R, et al. *Autoimmun Rev*. 2011;10(7):369-374.

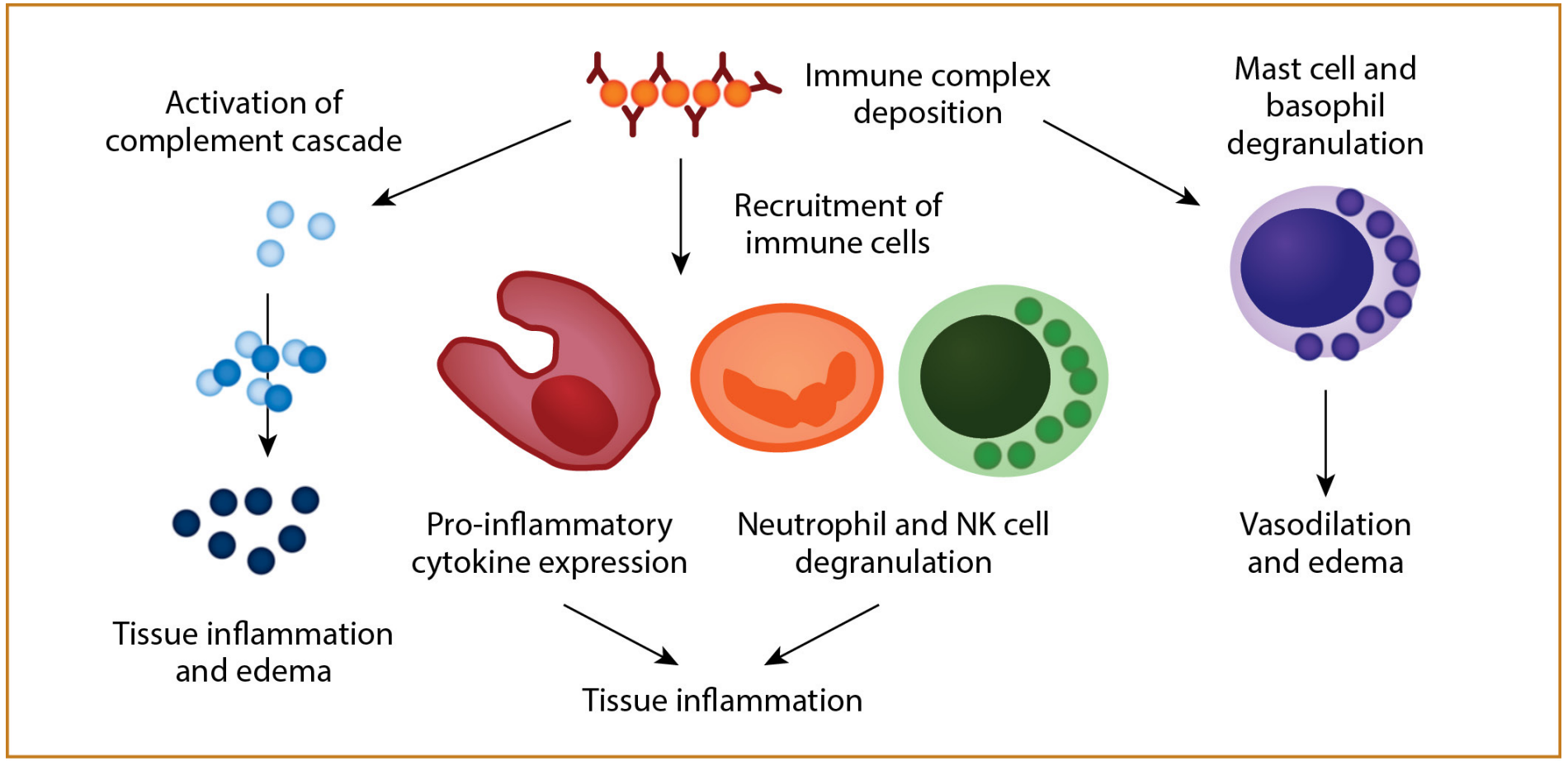


Figure 22: Immune Complex-Mediated Inflammation. Immune complex deposition result in complement activation, which in turn mediates local inflammation and oedema. This results in the recruitment of immune cells, including macrophages, neutrophils, and NK cells, which further contribute to inflammation and tissue damage through inflammatory cytokine expression. Mast cell and basophil degranulation further amplifying tissue edema and mediates vasodilation. Adapted from: Smith EMD, Lythgoe H, Hedrich CM. Vasculitis in Juvenile-Onset Systemic Lupus Erythematosus. *Front Pediatr*. 2019;7:149.

Sources of Chronic Inflammation

Diet	Chronic infections	Obesity	Dysbiosis
Sedentary lifestyle	Chronic stress	Sleep disturbance	Environmental toxins

Furman, D, et al. *Nat Med* 25, 1822–1832 (2019).

Infections as Autoimmune Triggers

Infectious Agent	Autoimmune Association	Gram stain
Borrelia	RA, sarcoidosis, schizophrenia, dementia	gram neg stain bc LPS
Chlamydophila pneumoniae	arthritis, myocarditis, Guillain-Barre, Alzheimer's, CFS, COPD, MS, Tourette syndrome	gram negative
Enterovirus	ALS, CFS, Type 1 Diabetes, Guillain-barre, schizophrenia	gram negative
Giardia lamblia	MS, ALS, Parkinson's, CFS, arthritis, uveitis	gram negative
Helicobacter pylori	immune thrombocytopenia, psoriasis, sarcoidosis	gram negative
Herpesvirus	dermatomyositis, SLE, RA, Sjogren's, MS, chronic fatigue	
Norovirus	Crohn's	
Parvovirus B19	RA, SLE, vasculitis	
Streptococcus	Tourette syndrome	gram positive
Toxoplasma gondii	Alzheimer's, Parkinson's, Tourette syndrome, antiphospholipid syndrome, systemic sclerosis, IBD	

Torres-Aguilar H, et al. *Curr Opin Rheumatol*. 2019;31(5):525-531.

Autoimmune vs. Autoinflammatory Spectrum

- Fundamental understanding of autoimmune mechanisms is focused mainly on lack of self-tolerance
- Newer research suggests
  - Many conditions may be more property defined as “autoinflammatory” since they are primarily mediated by cells or processes within the innate immune system and lack distinctive auto-reactive antibodies or T-cells
- Driven by core signaling components of the innate immune system

Guilliams, T. Supporting immune function a lifestyle and nutrient approach. (2nd edition) 2022

Integrative Approaches to Combat Inflammation

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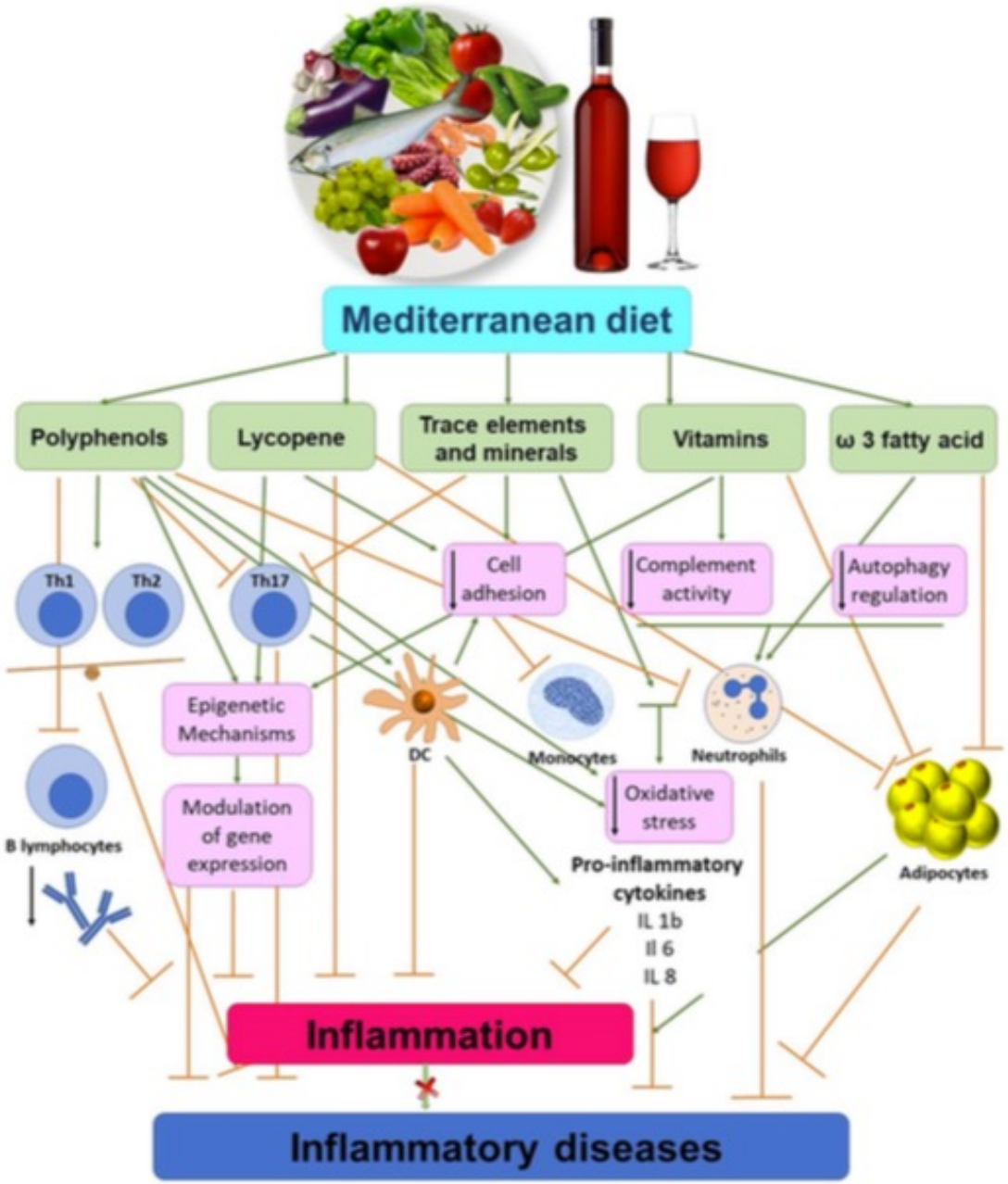
How to Combat Inflammation

- **Diet**
- Physical activity
- Weight loss
- Stress management
- Nutraceuticals
  - Macronutrients/Micronutrients
  - Herbal
- Sleep/Circadian rhythms
- Correct dysbiosis

Mediterranean Diet

- Diet includes:
  - Fruits/Vegetables
  - Whole Grains
  - Beans/Nuts/Seeds
  - Deep Sea Fish/Fermented dairy
  - Olive Oil!
  - Red wine
- Individuals who adhered most closely to the traditional Mediterranean diet had 20% lower CRP levels than individuals with the least adherence.[1]
- Individuals with metabolic syndrome experienced a significant drop in levels of CRP and other markers of inflammation after two years on Med diet compared to controls.[2]

1.Chrysohoou C et al. J Am Coll Cardiol. 2004; 44(1):152-8.
2.Esposito K et al. JAMA. 2004; 292(12):1440-6.



Tsigalou C, et al. *Biomedicines*. 2020;8(7):201.

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Paleolithic and Mediterranean Diet Pattern Scores Are Inversely Associated with Biomarkers of Inflammation and Oxidative Balance in Adults[1–3]

Kristine A Whalen,[4] Marjorie L McCullough,[7] W Dana Flanders,[4–6] Terryl J Hartman,[4,6] Suzanne Judd,[8] and Roberd M Bostick[4,6]*

[4]Department of Epidemiology and [5]Department of Biostatistics and Bioinformatics, Rollins School of Public Health, and [6]Winship Cancer Institute, Emory University, Atlanta, GA; [7]Epidemiology Research Program, American Cancer Society, Atlanta, GA; and [8]Department of Biostatistics, University of Alabama at Birmingham, Birmingham, AL

Abstract

Background: Chronic inflammation and oxidative balance are associated with poor diet quality and risk of cancer and other chronic diseases. A diet–inflammation/oxidative balance association may relate to evolutionary discordance.

Objective: We investigated associations between 2 diet pattern scores, the Paleolithic and the Mediterranean, and circulating concentrations of 2 related biomarkers, high-sensitivity C-reactive protein (hsCRP), an acute inflammatory protein, and F_2-isoprostane, a reliable marker of in vivo lipid peroxidation.

Methods: In a pooled cross-sectional study of 30- to 74-y-old men and women in an elective outpatient colonoscopy population (n = 646), we created diet scores from responses on Willett food-frequency questionnaires and measured

Cross-sectional study of 30- to 74-y-old men and women in an elective outpatient colonoscopy population (n = 646)

Conclusion: These findings suggest that diets that are more Paleolithic- or Mediterranean-like may be associated with lower levels of systemic inflammation and oxidative stress in humans.

Whalen KA, et al. *J Nutr*. 2016;146(6):1217-1226.

Degenerative Neurological and Neuromuscular Disease

Dovepress

CLINICAL TRIAL REPORT

Randomized control trial evaluation of a modified Paleolithic dietary intervention in the treatment of relapsing-remitting multiple sclerosis: a pilot study

This article was published in the following Dove Press journal:
Degenerative Neurological and Neuromuscular Disease
4 January 2017
Number of times this article has been viewed

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Background/objective: A Paleolithic diet may improve fatigue and quality of life in progressive multiple sclerosis (MS) patients, but past research has evaluated the effects of this dietary intervention in combination with other treatments such as exercise. Thus, the purpose of this pilot study was to evaluate a modified Paleolithic dietary intervention (MPDI) in the treatment of fatigue and other symptoms in relapsing-remitting MS (RRMS).

Methods: We measured the effects of a MPDI in 17 individuals with RRMS. Of 34 subjects randomly assigned to control (maintain usual diet) and intervention (MPDI) groups, nine subjects (one man) completed the control group and eight subjects (one man) completed the MPDI.

Results: Significant improvements were seen in Fatigue Severity Scale score and also in Multiple Sclerosis Quality of Life-54 and time to complete (dominant hand) 9-Hole Peg Test from baseline in MPDI subjects compared to controls. Increased vitamin K serum levels were also observed in MPDI subjects postprotocol compared to controls.

Conclusion: A Paleolithic diet may be useful in the treatment and management of MS, by reducing perceived fatigue, increasing mental and physical quality of life, increasing exercise capacity, and improving hand and leg function. By increasing vitamin K serum levels, the MPDI may also reduce inflammation.

Keywords: diet therapy, nutrition therapy, gluten-free, quality of life, fatigue, complementary medicine, alternative medicine

Conclusion: A Paleolithic diet may be useful in the treatment and management of MS, by reducing perceived fatigue, increasing mental and physical quality of life, increasing exercise capacity, and improving hand and leg function. By increasing vitamin K serum levels, the MPDI may also reduce inflammation.

Irish AK, et al. *Degener Neurol Neuromuscul Dis*. 2017;7:1-18.

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Mediterranean Diet in Autoimmune Conditions RA & SLE

Systematic Review | Published: 18 December 2017

The effects of the Mediterranean diet on rheumatoid arthritis prevention and treatment: a systematic review of human prospective studies

Casuarina Forsyth, Matina Kouvari, Nathan M. D'Cunha, Ekavi N. Georgousopoulou, Demosthenes B. Panagiotakos, Duane D. Mellor, Jane Kellett & Nenad Naumovski

Rheumatology International **38**, 737–747 (2018) | Cite this article

6557 Accesses | **68** Citations | **112** Altmetric | Metrics

Abstract

Rheumatoid arthritis is a progressive autoimmune disease characterised by severely swollen and painful joints. To compliment pharmacotherapy, people living with rheumatoid arthritis often turn to dietary interventions such as the Mediterranean diet. The aim of the present systematic review is to discuss the effects of the Mediterranean diet on the management and prevention of rheumatoid arthritis in human prospective studies. Four studies met the inclusion criteria, including two intervention studies reporting improvement in the pain visual analogue scale ($p < 0.05$) and a decrease in the health assessment questionnaire for rheumatoid arthritis score ($p < 0.05$) in the Mediterranean diet groups. Only one study reported a reduction in the 28 joint count disease activity score for rheumatoid arthritis for the Mediterranean diet group ($p < 0.05$). This review has identified beneficial effects of the Mediterranean diet in reducing pain and increasing physical function in people living with rheumatoid arthritis. However, there is currently insufficient evidence to support widespread recommendation of the Mediterranean diet for prevention of rheumatoid arthritis.

RHEUMATOLOGY

Rheumatology 2021;60:160–169
doi:10.1093/rheumatology/keaa210
Advance Access publication 28 June 2020

Original article

Beneficial effect of Mediterranean diet on disease activity and cardiovascular risk in systemic lupus erythematosus patients: a cross-sectional study

Gabriela Pocovi-Gerardino[1], María Correa-Rodríguez[1,2], José-Luis Callejas-Rubio[1,3], Raquel Ríos-Fernández[1,3], María Martín-Amada[4], María-Gracia Cruz-Caparros[5], Blanca Rueda-Medina[1,*] Norberto Ortego-Centeno[1,3,6,*]

Abstract

Objective. To analyse the influence of the Mediterranean diet (Med Diet) on SLE activity, damage accrual and cardiovascular disease risk markers.

Methods. A cross-sectional study was conducted on 280 patients with SLE [46.9 (12.85) years]. Med Diet adherence was assessed through a 14-item questionnaire on food consumption frequency and habits (total score from 0 to 14 points; higher score is greater adherence to the Med Diet). CRP, homocysteine, SLEDAI-2K (SLE disease activity), and SLICC/ACR and SDI (damage accrual) were measured. Obesity, diabetes mellitus, hypertension and blood lipids, among others, were considered cardiovascular disease risk factors.

Results. Greater adherence to the Med Diet was significantly associated with better anthropometric profiles, fewer cardiovascular disease risk factors, and lower disease activity and damage accrual scores ($P \leq 0.001$ for SLEDAI and SDI). An inverse relationship between the Med Diet score and SLEDAI ($P \geq 0.001$; $\beta = -0.380$), SDI ($P \leq 0.001$; $\beta = -0.740$) and hsCRP ($P = 0.039$; $\beta = -0.055$) was observed. The odds ratio for having active SLE (SLEDAI ≥ 5) or the presence of damage (SDI ≥ 1) was lower among patients whose Med Diet score was higher ($P \leq 0.001$). Finally, greater consumption of Med Diet foods (olive oil, fruits, vegetables, fish, etc.) and abstaining from red meat and meat products, sugars and pastries was associated with less SLE clinical activity and damage.

Conclusion. Greater adherence to the Med Diet seems to exert a beneficial effect on disease activity and cardiovascular risk in SLE patients. To confirm these findings, further longitudinal studies would be of interest.

Key words: autoimmune, lupus, Mediterranean diet, inflammation, cardiovascular disease, atherosclerosis, systemic lupus erythematosus

Forsyth C, et al. *Rheumatol Int*. 2018;38(5):737-747.
Pocovi-Gerardino G, et al. *Rheumatology (Oxford)*. 2021;60(1):160-169.

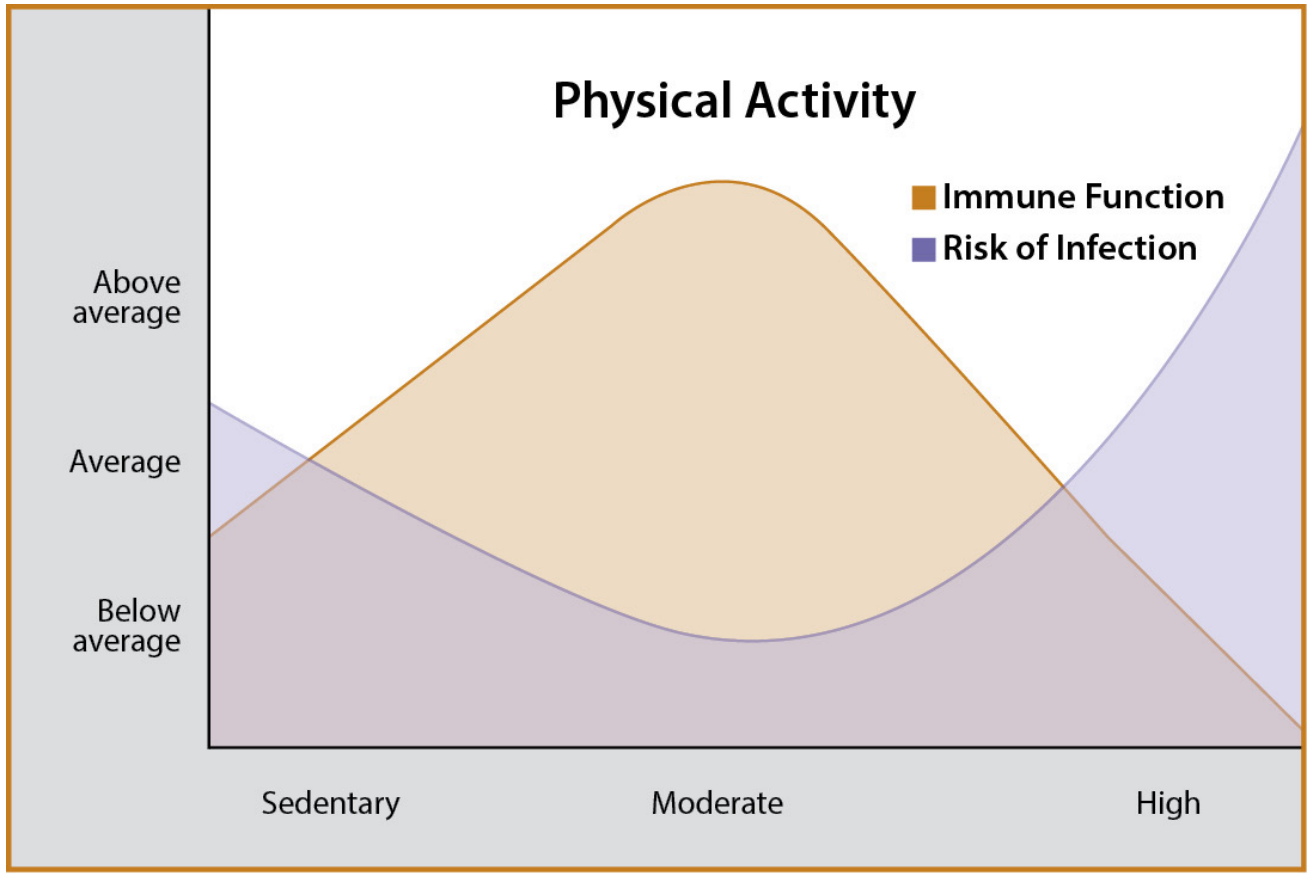
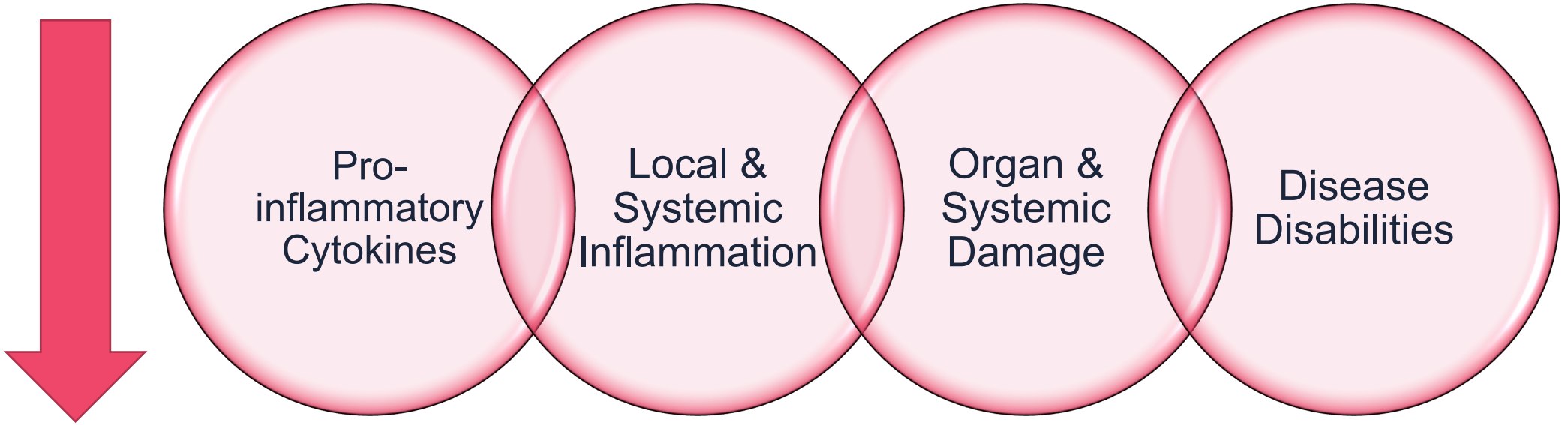


Figure 27: General Impact of Physical Activity (Exercise) on Immune Function and Risk of Infection. Note that sedentary behavior diminishes immune function and increases the risk of infection; an effect that can be reversed with moderate physical activity. Excessive physical activity is a potent immune-suppressant and can greatly increase risk for infection.

Exercise Puts the Breaks on Autoimmune Conditions



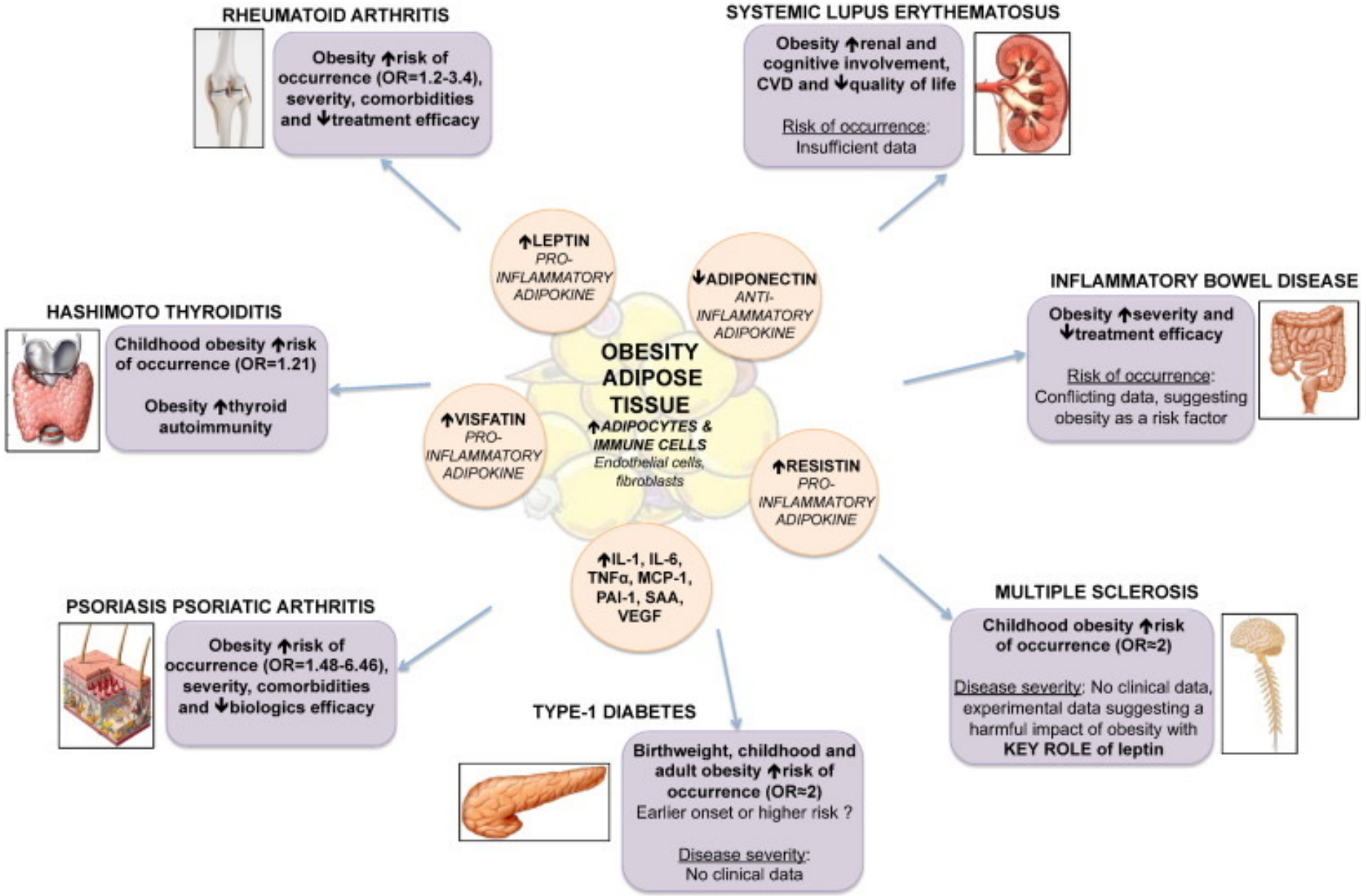
Perandini LA. *Autoimmunity reviews*. 2012;12(2):218-224

Obesity

- A state of chronic or low-grade systemic inflammation
- Metaflammation: obesity-related chronic low-grade inflammation and subsequent altered metabolism
- White adipose tissue secretes adipokines and cytokines
- Obesity associated with:
  - ↑ Th17, IL-1β, IL-18, B cells, antibody production
  - ↓ Treg
  - Microbiome alterations
  - Vitamin D deficiency
  - Autoantibodies

PROMOTE AUTOIMMUNE DISEASE

Versini M, et al. *Autoimmun Rev*. 2014;13(9):981-1000.
Kawai T, et al. *Am J Physiol Cell Physiol*. 2021;320(3):C375-C391.



Versini M et al. *Autoimmun Rev*. 2014;13(9):981-1000

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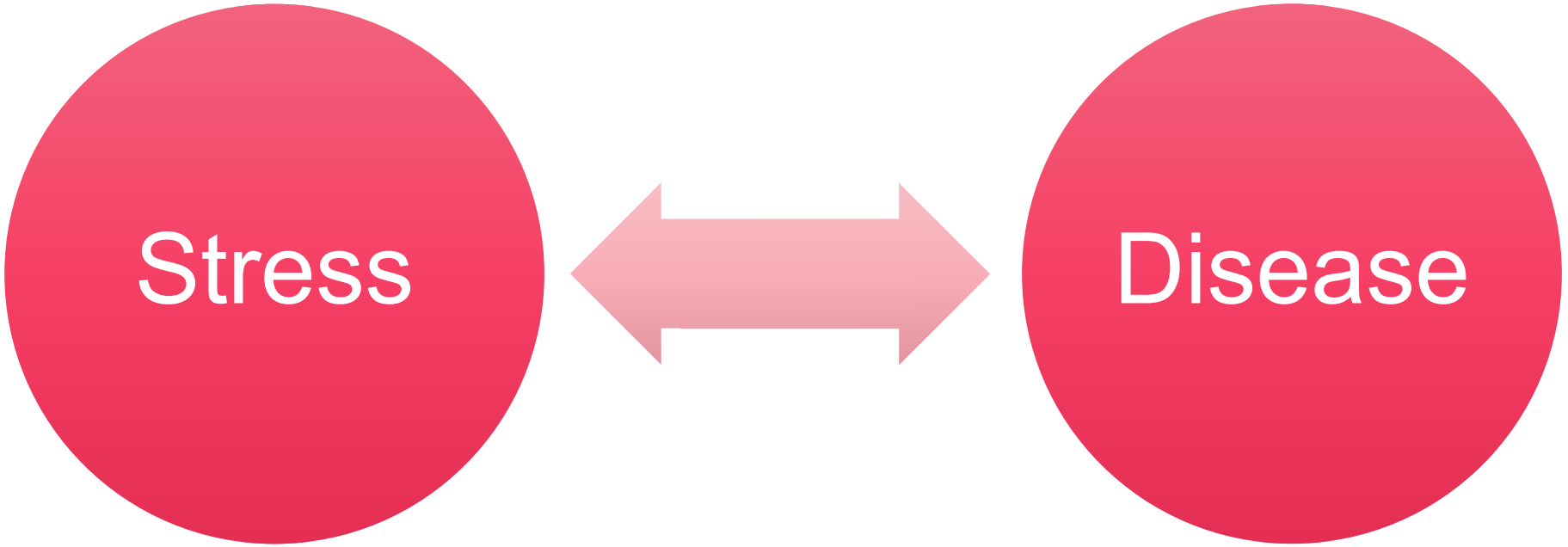
Weight Loss

- ↓ in inflammatory markers
  - (CRP, TNF-a, IL-6 and leptin)[1]
- ↑ in anti-inflammatory marker (adiponectin)[1]
- A number of studies suggest that weight loss may be a useful preventative and adjunctive therapy for the treatment of psoriasis or psoriatic arthritis.[2]
  - Most studies reviewed here were very low calorie diets 1,000-1,500 kcal per day.
  - Gastric bypass surgery appears to be beneficial in select patients.

1.Forsythe LK et al. *Nutr Res Rev*. 2008;21(2):117-133.
2.Debbaneh M et al. *J Am Acad Dermatol*. 2014;71(1):133-140.

Stress



Stress Management

- Close relationship between HPA axis, SNS, and immune system
- Stress triggers the release of neuroendocrine hormones leading to immune dysregulation

A formidable amount of evidence supports the **association and role of stress in influencing various aspects of autoimmune diseases** including for instance disease onset and exacerbations. The **active management of stress** through various psychological techniques **demonstrates significant benefits on disease outcomes**. Thus, given the interrelation between these two factors, **clinical physicians should encourage patients with autoimmune disease to seek stress management practices as part of their daily routines.**

Stojanovich L, et al. *Autoimmun Rev*. 2008;7(3):209-213.
Sharif K, et al. *Autoimmun Rev*. 2018;17(10):967-983.

Impacts of Yoga

- Yoga has a buffering action on stress-mediated immune response, stimulates the parasympathetic nervous system, and maintains cardio-vagal tone
- 8 weeks of yoga-based mind body intervention in active RA patients:
  - ↓ levels of ESR and CRP
  - downregulation of pro-inflammatory cytokines (IL-6, IL-17A, TNF-alpha)
  - upregulation of anti-inflammatory cytokines (TGF-beta)

Gautam S, et al. *Restor Neurol Neurosci*. 2019;37(1):41-59.

Sleep

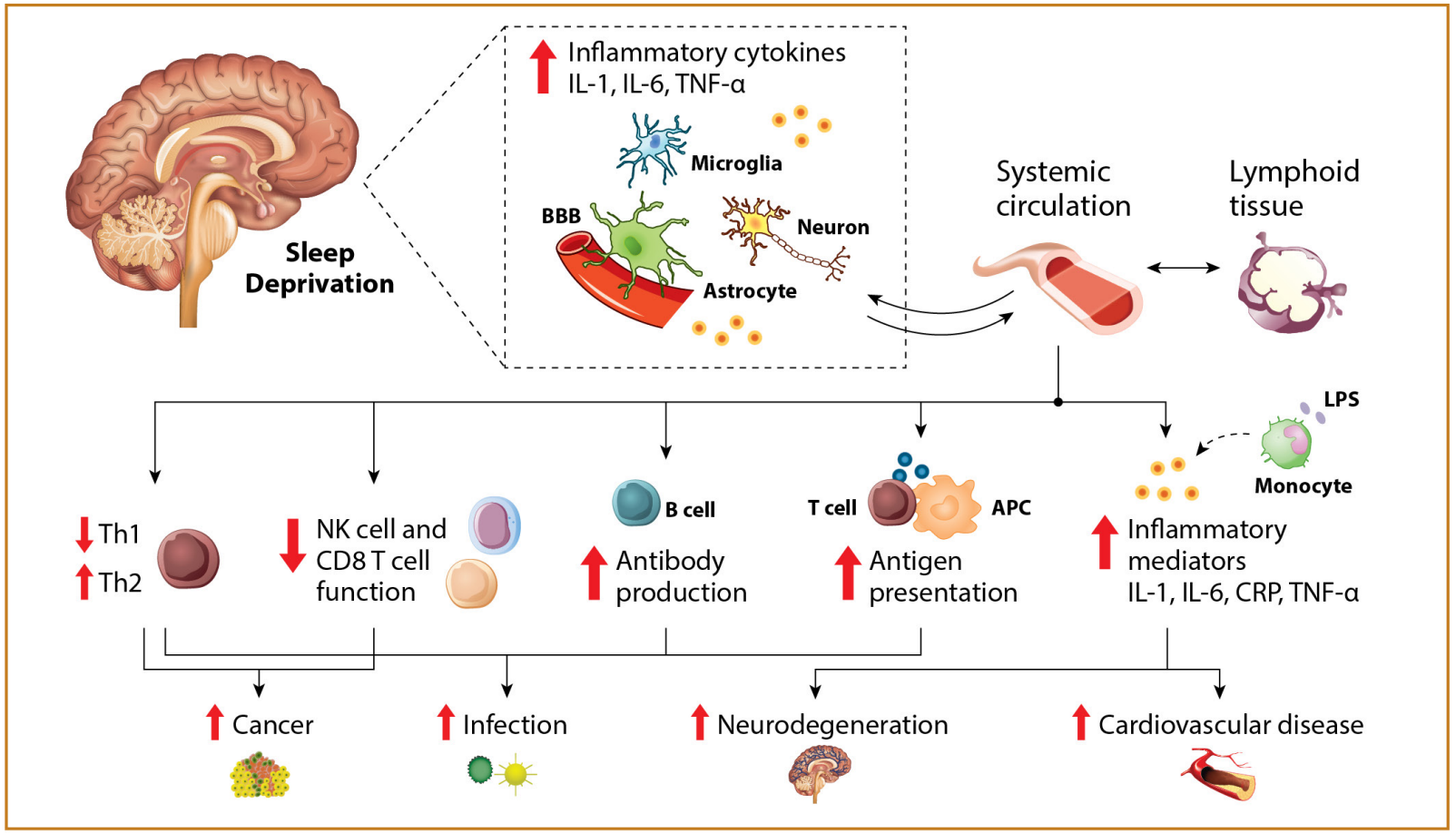
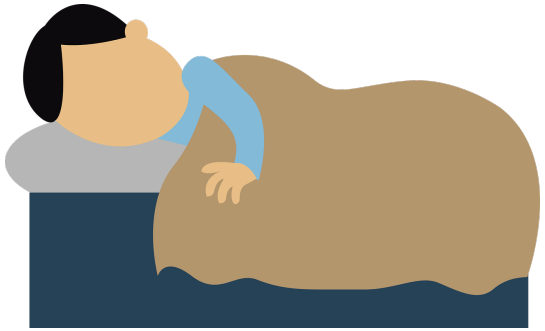


Figure 30: The Effects of Sleep Deprivation on Immune Dysfunction. Sleep deprivation, as induced experimentally or in the context of habitual short sleep, has been found to be associated with alterations in the circulating numbers and/or activity of total leukocytes and specific cell subsets, elevation of systemic and tissue (e.g., brain) pro-inflammatory markers including cytokines (e.g., interleukins [IL], tumor necrosis factor [TNF]-α), chemokines and acute phase proteins (such as C reactive Protein [CRP]), altered antigen presentation (reduced dendritic cells, altered pattern of activating cytokines, etc.), lowered Th1 response, higher Th2 response, and reduced antibody production. Furthermore, altered monocytes responsiveness to immunological challenges such as lipopolysaccharide (LPS) may contribute to sleep deprivation-associated immune modulation. Hypothesized links between immune dysregulation by sleep deprivation and the risk for immune-related diseases, such as infectious, cardiovascular, metabolic, and neurodegenerative and neoplastic diseases, are shown. Figure adapted from: Garbarino, S., Lanteri, P., Bragazzi, N.L. *et al.* Role of sleep deprivation in immune-related disease risk and outcomes. *Commun Biol* 4, 1304 (2021).

Sleep



- **Poor sleep increases risk of autoimmune conditions[1]**
  - Subclinical autoimmune hypothyroidism was diagnosed in 7.7% shift workers and in 3.8% day-time workers. (p=0.03.)
  - Altered anti-TPO autoantibodies were found in 13.6% shift workers and in 8.6% day-time workers (p=0.05)
- **Shift-work increases cytokines[2]**
  - Night shift work compromises host defense by creating cytokine conditions that initially impede anti-viral immunity (lower TNF-α) and may promote autoimmunity (mistimed rise in IL-6).
- **Sleep disturbance and sleep duration impact inflammation**
  - Sleep disturbance associated with ↑ levels of CRP (ES 0.12; 95% CI 0.05 – 0.19) and IL-6 (ES 0.20; 95% CI 0.08 – 0.31).
  - Shorter sleep duration, but not the extreme of short sleep, associated with ↑ levels of CRP
  - Short sleep was defined as < 7 hrs/night, and long sleep was defined as > 8 hrs/night.

1. Magrini A et al. *Int J Immunopathol Pharmacol*. 2006;19(4 Suppl):31-36.
2. Liu PY et al. *Neurobiol Sleep Circadian Rhythms*. 2021;10:100063
3. Irwin MR, et al. *Biol Psychiatry*. 2016;80(1):40-52.

Treatment Considerations: 4 vs 5R

Remove	• Food sensitivities, alcohol, aspirin, NSAIDS from the diet. • Use antimicrobials for dysbiosis, infection, and/or parasites.
Replace	• Digestive support to improved nutrient absorption and metabolism • May include digestive enzymes, or agents that promote improved motility and regular bowel movements.
Reinoculate	• Provide an environment where good bacteria can thrive and where bad ones cannot • Use pre- and probiotics.
Repair	• Support of the cellular repair process by providing specific nutritional support for the regeneration of the GI protective barrier • GI mucosa with healing nutrients and botanicals
Rebalance	• Lifestyle factors that influence the gut bacteria such as stress, sleep, exercise and relationships and assure ongoing gut health.

Jones DS, et al. Textbook of Functional Medicine 2010.

Consider Other Pathologies

- Mold/Lyme
  - Binders
  - Herbals
  - Support lymphatic & liver

Serum-Derived Bovine Immunoglobulin (SBI IGG)

- It works by binding antigens on bacteria, fungi, or toxic substances and preventing them from leaking through tight junctions between cells in the GI tract causing inflammation
- Several case reports/series of patients achieving clinical remission of IBD conditions (Crohn's/UC) with SBI IGG.
- Dose 5-10 grams/day

EnteraGam® [product information]. Ankeny, IA: Entera Health, Inc.; October 2020.
Wilson D, et al. Clin Med Insights Gastroenterol. 2013;6:CGast.S13200.

SBI IGG

Restores homeostasis of the gut barrier

Intestinal barrier function

- Improving gut permeability
- Preventing antigenic translocation across tight junctions

Nutrient absorption

- IgG normalizes gut bacteria improving nutrient utilization

Impact on immune balance (IgG)

- Activates complement (serum system that can destroy viruses and bacteria to protect from infection)
- Protects tissues
- Allows direct binding to microbial cells and interferes with their ability to enter or damage the intestinal cells
- ↓ intestinal mucosal damage
- ↓ inflammatory cell infiltration
- ↓ expression of inflammatory cytokines

EnteraGam® [product information]. Ankeny, IA: Entera Health, Inc.; October 2020.
Wilson D, et al. Clin Med Insights Gastroenterol. 2013;6:CGast.S13200.

SBI improves clinical management of IBD patients who are not fully managed on traditional therapies.

Shafran I, et al. *Therap Adv Gastroenterol*. 2015;8(6):331-339.

Therapeutic Advances in Gastroenterology *Original Research*

Management of inflammatory bowel disease with oral serum-derived bovine immunoglobulin

Ther Adv Gastroenterol
2015, Vol. 8(6) 331–339
DOI: 10.1177/1756283X15593693

Ira Shafran, Patricia Burgunder, David Wei, Hayley E. Young, Gerald Klein and Bruce P. Burnett

Abstract

Introduction: The clinical effect of oral serum-derived bovine immunoglobulin/protein isolate (SBI) on symptom and disease management in patients with inflammatory bowel disease (IBD) is reported in this retrospective case series.

Methods: A single-center, retrospective chart review of IBD patients [$N = 45$; Crohn's disease (CD), $n = 38$ and ulcerative colitis (UC), $n = 7$] with limited to no response to traditional pharmaceutical therapies in controlling symptoms was performed after providing SBI (5 g/day) for nutritional support. Patients were contacted at least monthly to assess response to SBI for symptom management measured by a Likert scale (0 = none; 1 = minimal; 2 = moderate; 3 = significant; 4 = complete). Analysis of variance (ANOVA) was performed on response to therapy based on patient characteristics (age, gender, race) and IBD diagnosis. A multivariate ordered logistical regression model was performed to determine the odds ratio in overall disease management between week 1 and week 12. Finally, the overall group response and percent improvement to SBI was determined over 12 weeks.

Results: The odds ratio from the regression model demonstrated that IBD patients were 2.8 times more likely to report clinical improvement in symptom scores with the addition of SBI to their therapeutic regimens [95% confidence interval (CI) 1.266–6.016, $p = 0.011$]. Disease management was not significantly associated with age, gender, race or disease state. The percentage of patients reporting a response to SBI therapy at week 1 was 49% which increased to 76% after 12 weeks with the fraction of responders gaining significant symptom improvement doubling during the same time period (9% *versus* 20%). Overall, this group of IBD patients showed increased, steady response to SBI therapy between week 1 and 12 with no reported side effects.

Conclusion: These results suggest that SBI improves clinical management of IBD patients who are not fully managed on traditional therapies. SBI should be considered for the nutritional support of IBD regardless of disease activity, location, phenotype, duration, or complexity.

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Ira Shafran, MD, PA

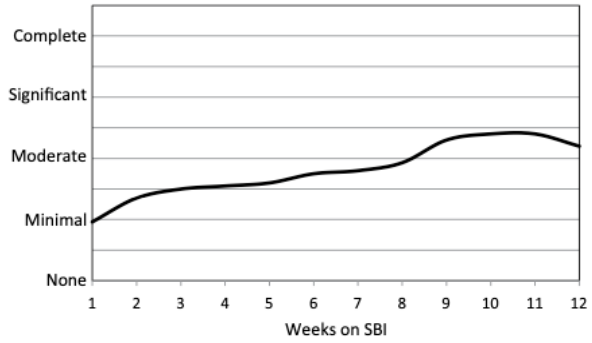

Figure 1. Average reported improved response of all inflammatory bowel disease patients ($N = 45$).

$p = 0.011$] (Table 3). This finding was significant compared with the null hypothesis corresponding to an odds ratio of 1 in which patients would have equal likelihood of reporting the same or worse disease management at 12 weeks as they did at baseline. This model also showed that response to SBI addition was not associated with age, gender, race or diagnosis.

To retrospectively capture the overall pattern of reported clinical management for the entire cohort during the time period used in the statistical analysis, average patient-reported symptom

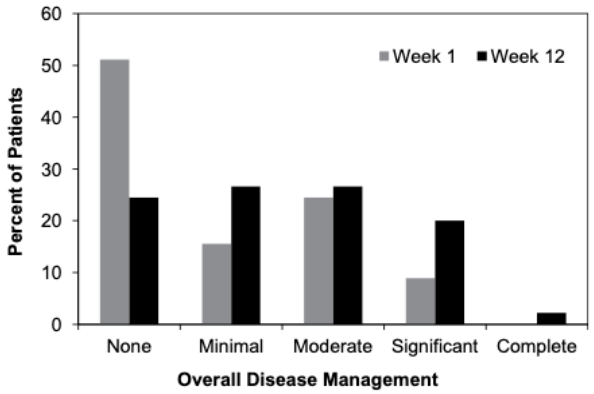

Figure 2. Per cent change in disease management at week 1 *versus* week 12.

The overall response to the addition of SBI in IBD patients suggests that the longer patients are on therapy, the better their outcomes. It is possible that addition of SBI with other therapies used concomitantly resulted in further or even synergistic benefit in these patients. Further clinical research is needed to assess SBI's effects in combination with other treatments for IBD.

Discussion

The longer they used it, the more response was reported. Needs further clinical trial to determine optimal patient populations and length of therapy.

Shafran I, et al. *Therap Adv Gastroenterol*. 2015;8(6):331-339.

High Dose Probiotics

Open

Treatment of Relapsing Mild-to-Moderate Ulcerative Colitis With the Probiotic VSL#3 as Adjunctive to a Standard Pharmaceutical Treatment: A Double-Blind, Randomized, Placebo-Controlled Study

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OBJECTIVES: **VSL#3 is a high-potency probiotic mixture that has been used successfully in the treatment of pouchitis. The primary end point of the study was to assess the effects of supplementation with VSL#3 in patients affected by relapsing ulcerative colitis (UC) who are already under treatment with 5-aminosalicylic acid (ASA) and/or immunosuppressants at stable doses.**

METHODS: **A total of 144 consecutive patients were randomly treated for 8 weeks with VSL#3 at a dose of 3,600 billion CFU/day (71 patients) or with placebo (73 patients).**

RESULTS: **In all, 65 patients in the VSL#3 group and 66 patients in the placebo group completed the study. The decrease in ulcerative colitis disease activity index (UCDAI) scores of 50% or more was higher in the VSL#3 group than in the placebo group (63.1 vs. 40.8; per protocol (PP) $P=0.010$, confidence interval $(CI)_{95\%}$ 0.51–0.74; intention to treat (ITT) $P=0.031$, $CI_{95\%}$ 0.47–0.69). Significant results with VSL#3 were recorded in an improvement of three points or more in the UCDAI score (60.5% vs. 41.4%; PP $P=0.017$, $CI_{95\%}$ 0.51–0.74; ITT $P=0.046$, $CI_{95\%}$ 0.47–0.69) and in rectal bleeding (PP $P=0.014$, $CI_{95\%}$ 0.46–0.70; ITT $P=0.036$, $CI_{95\%}$ 0.41–0.65), whereas stool frequency (PP $P=0.202$, $CI_{95\%}$ 0.39–0.63; ITT $P=0.229$, $CI_{95\%}$ 0.35–0.57), physician's rate of disease activity (PP $P=0.088$, $CI_{95\%}$ 0.34–0.58; ITT $P=0.168$, $CI_{95\%}$ 0.31–0.53), and endoscopic scores (PP $P=0.086$, $CI_{95\%}$ 0.74–0.92; ITT $P=0.366$, $CI_{95\%}$ 0.66–0.86) did not show statistical differences. Remission was higher in the VSL#3 group than in the placebo group (47.7% vs. 32.4%; PP $P=0.069$, $CI_{95\%}$ 0.36–0.60; ITT $P=0.132$, $CI_{95\%}$ 0.33–0.56). Eight patients on VSL#3 (11.2%) and nine patients on placebo (12.3%) reported mild side effects.**

CONCLUSIONS: **VSL#3 supplementation is safe and able to reduce UCDAI scores in patients affected by relapsing mild-to-moderate UC who are under treatment with 5-ASA and/or immunosuppressants. Moreover, VSL#3 improves rectal bleeding and seems to reinduce remission in relapsing UC patients after 8 weeks of treatment, although these parameters do not reach statistical significance.**

Am J Gastroenterol 2010; 105:2218–2227; doi:10.1038/ajg.2010.218; published online 1 June 2010

Systematic review with meta-analysis: the efficacy of probiotics in inflammatory bowel disease

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Summary

Background: Ulcerative colitis (UC) and Crohn's disease (CD) are inflammatory bowel diseases (IBD). Evidence implicates disturbances of the gastrointestinal microbiota in their pathogenesis.

Aim: To perform a systematic review and meta-analysis to examine the efficacy of probiotics in IBD.

Methods: MEDLINE, EMBASE, and the Cochrane Controlled Trials Register were searched (until November 2016). Eligible randomised controlled trials (RCTs) recruited adults with UC or CD, and compared probiotics with 5-aminosalicylates (5-ASAs) or placebo. Dichotomous symptom data were pooled to obtain a relative risk (RR) of failure to achieve remission in active IBD, or RR of relapse of disease activity in quiescent IBD, with 95% confidence intervals (CIs).

Results: The search identified 12 253 citations. Twenty-two RCTs were eligible. There was no benefit of probiotics over placebo in inducing remission in active UC (RR of failure to achieve remission=0.86; 95% CI=0.68-1.08). However, when only trials of VSL#3 were considered there appeared to be a benefit (RR=0.74; 95% CI=0.63-0.87). Probiotics appeared equivalent to 5-ASAs in preventing UC relapse (RR=1.02; 95% CI=0.85-1.23). There was no benefit of probiotics in inducing remission of active CD, in preventing relapse of quiescent CD, or in preventing relapse of CD after surgically induced remission.

Conclusions: VSL#3 may be effective in inducing remission in active UC. Probiotics may be as effective as 5-ASAs in preventing relapse of quiescent UC. The efficacy of probiotics in CD remains uncertain, and more evidence from RCTs is required before their utility is known.

Tursi A, et al. *Am J Gastroenterol*. 2010;105(10):2218-2227.
Derwa Y, et al. *Aliment Pharmacol Ther*. 2017;46(4):389-400.

RESEARCH ARTICLE

Assessing the efficacy and safety of fecal microbiota transplantation and probiotic VSL#3 for active ulcerative colitis: A systematic review and meta-analysis

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Competing interests: The authors have declared that no competing interests exist.

Abstract

Background

Fecal microbiota transplantation is an effective treatment for many gastrointestinal diseases, such as *Clostridium difficile* infection and inflammatory bowel disease, especially ulcerative colitis. Changes in colonic microflora may play an important role in the pathogenesis of ulcerative colitis, and improvements in the intestinal microflora may relieve the disease. Fecal bacterial transplants and oral probiotics are becoming important ways to relieve active ulcerative colitis.

Purpose

This systematic review with meta-analysis compared the efficacy and safety of basic treatment combined with fecal microbiota transplantation or mixed probiotics therapy in relieving mild to moderate ulcerative colitis.

Methods

The PubMed, Embase, and Cochrane libraries (updated September 2019) were searched to identify randomized, placebo-controlled, or head-to-head trials assessing fecal microbiota transplantation or probiotic VSL#3 as induction therapy in active ulcerative colitis. We analyze data using the R program to obtain evidence of direct comparison and to generate intermediate variables for indirect treatment comparisons.

Results

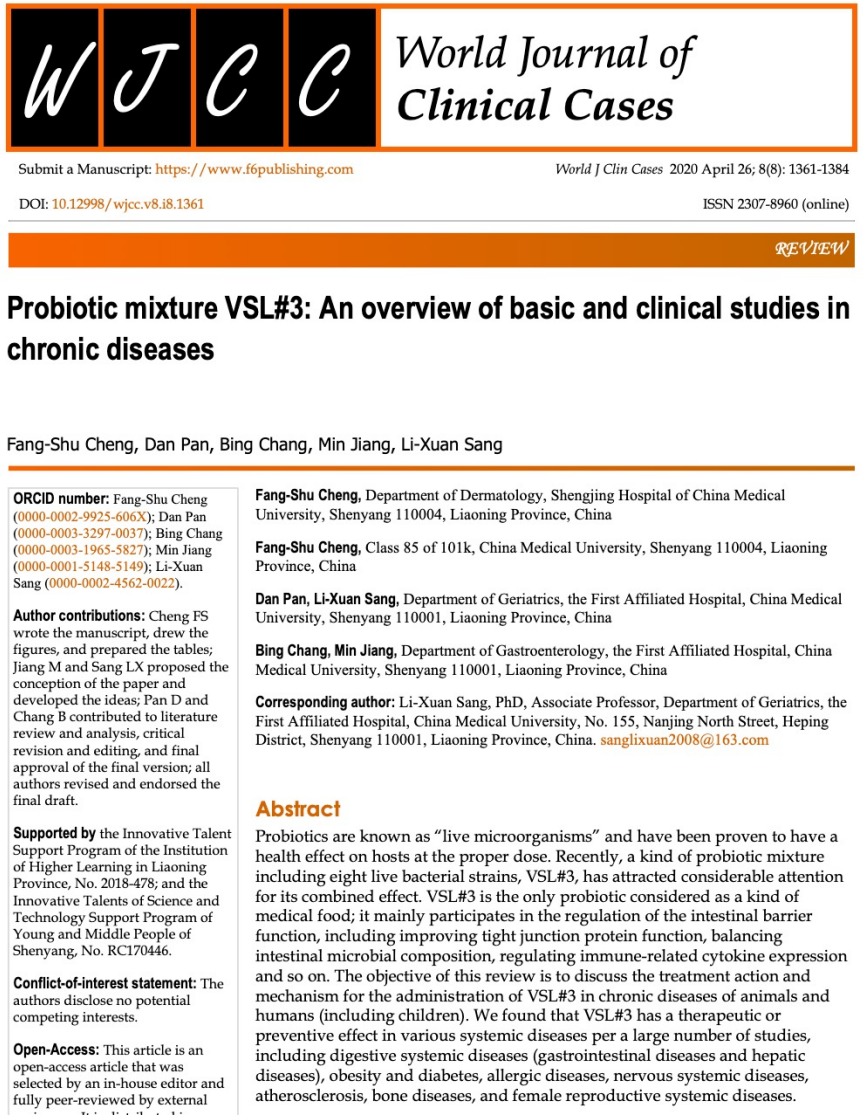
Seven randomized, double-blind, placebo-controlled trials were used as the sources of the induction data. All treatments were superior to placebo. In terms of clinical remission and clinical response to active ulcerative colitis, direct comparisons showed fecal microbiota transplantation (OR = 3.47, 95% CI = 1.93–6.25) (OR = 2.48, 95% CI = 1.18–5.21) and mixed probiotics VSL#3 (OR = 2.40, 95% CI = 1.49–3.88) (OR = 3.09, 95% CI = 1.53–6.25) to have better effects than the placebo. Indirect comparison showed fecal microbiota transplantation and probiotic VSL#3 did not reach statistical significance either in clinical remission (RR = 1.20, 95% CI = 0.70–2.06) or clinical response (RR = 0.95, 95% CI = 0.62–1.45). In terms of safety, fecal microbiota transplantation (OR = 1.15, 95% CI = 0.51–2.61) and VSL #3 (OR = 0.90, 95% CI = 0.33–2.49) showed no statistically significant increase in adverse events compared with the control group. In terms of serious adverse events, there was no statistical difference between the fecal microbiota transplantation group and the control group (OR = 1.29, 95% CI = 0.46–3.57). The probiotics VSL#3 seems more safer than fecal microbiota transplantation, because serious adverse events were not reported in the VSL#3 articles.

Conclusions

Fecal microbiota transplantation or mixed probiotics VSL#3 achieved good results in clinical remission and clinical response in active ulcerative colitis, and there was no increased risk of adverse reactions. There was no statistical difference between the therapeutic effect of fecal microbiota transplantation and that of mixed probiotics VSL#3. However, the use of fecal microbiota transplantation and probiotics still has many unresolved problems in clinical applications, and more randomized controlled trials are required to confirm its efficacy.

Good summary of the evidence!

- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7190945/



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REVIEW

Probiotic mixture VSL#3: An overview of basic and clinical studies in chronic diseases

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Author contributions: Cheng FS wrote the manuscript, drew the figures, and prepared the tables; Jiang M and Sang LX proposed the conception of the paper and developed the ideas; Pan D and Chang B contributed to literature review and analysis, critical revision and editing, and final approval of the final version; all authors revised and endorsed the final draft.

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Abstract

Probiotics are known as "live microorganisms" and have been proven to have a health effect on hosts at the proper dose. Recently, a kind of probiotic mixture including eight live bacterial strains, VSL#3, has attracted considerable attention for its combined effect. VSL#3 is the only probiotic considered as a kind of medical food; it mainly participates in the regulation of the intestinal barrier function, including improving tight junction protein function, balancing intestinal microbial composition, regulating immune-related cytokine expression and so on. The objective of this review is to discuss the treatment action and mechanism for the administration of VSL#3 in chronic diseases of animals and humans (including children). We found that VSL#3 has a therapeutic or preventive effect in various systemic diseases per a large number of studies, including digestive systemic diseases (gastrointestinal diseases and hepatic diseases), obesity and diabetes, allergic diseases, nervous systemic diseases, atherosclerosis, bone diseases, and female reproductive systemic diseases.

Cheng FS, et al. *World J Clin Cases*. 2020;8(8):1361-1384.

Anti-inflammatory Nutraceuticals

FUNCTIONAL MEDICINE
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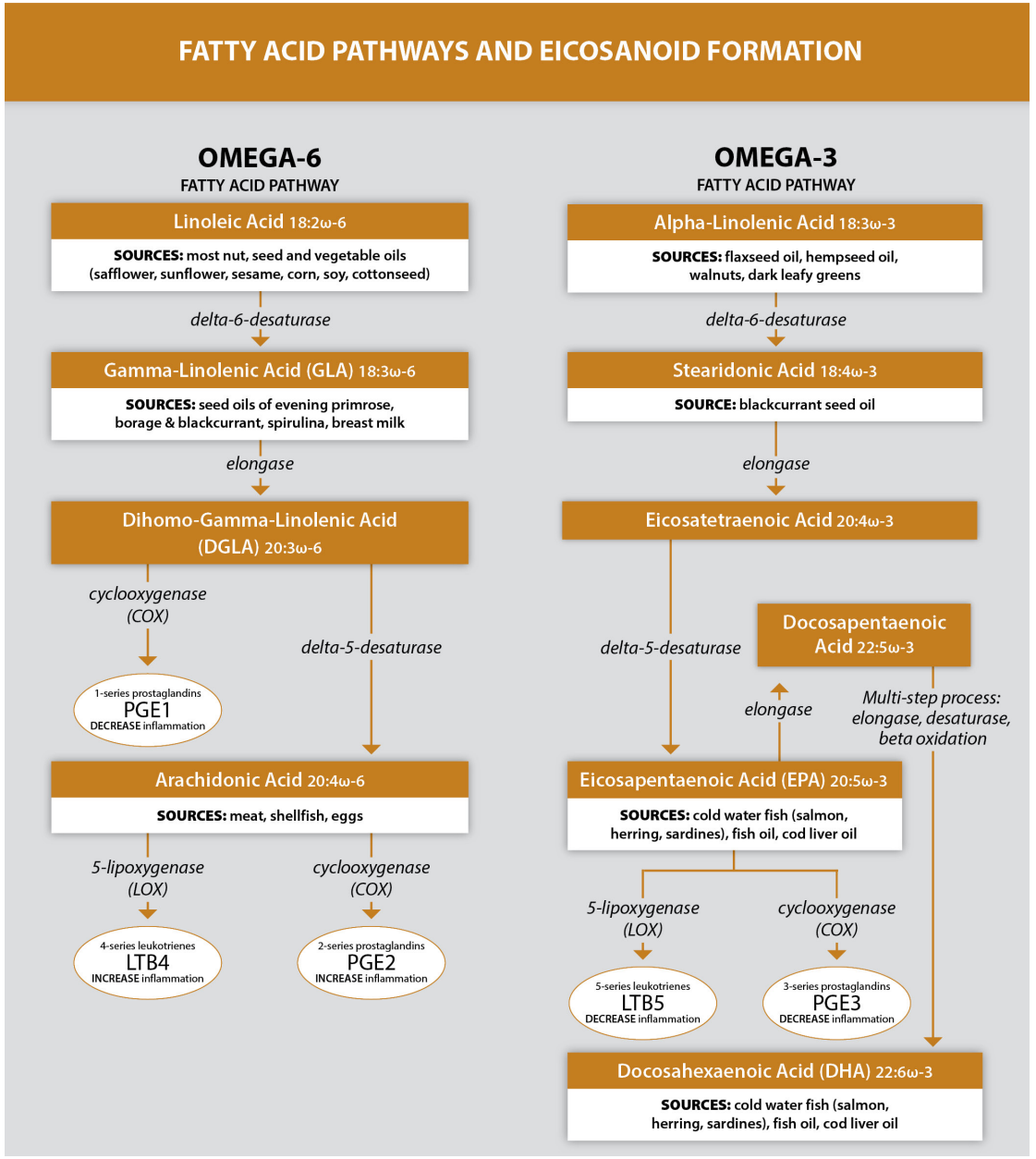
Omega-3 Fatty Acids



Omega Clinical Pearls

- Forms
  - rTG (re-esterified forms, monoglycerides, etyl esters (EE), free fatty acids (FFA), or phospholipids
- Most commonly studied either EE or rTG
- Superior bioavailability with rTG > EE forms
- DHA >EPA ?
  - DHA outperforms EPA in nearly every surrogate marker
  - DHA--> No clinical trials looking at MI, CVD, mortality
  - 1:1 likely a good ratio based on evidence
- Most pharmaceuticals more EPA
- Icosapent ethyl CVOT
- Quality

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2. Bhatt et al. N Engl J Med 2019; 380:11-22

Rheumatol Int (2003) 23: 27–36
DOI 10.1007/s00296-002-0234-7

ORIGINAL ARTICLE

Olaf Adam · Corinna Beringer · Thomas Kless
Christa Lemmen · Alexander Adam · Michael Wiseman
Patrick Adam · Reinhard Klimmek · Wolfgang Forth

Anti-inflammatory effects of a low arachidonic acid diet and fish oil in patients with rheumatoid arthritis

Received: 10 April 2002 / Accepted: 19 July 2002 / Published online: 6 September 2002

Background Patients with rheumatoid arthritis (RA) improve on a vegetarian diet or supplementation with fish oil. We investigated the effects of both dietary measures, alone and in combination, on inflammation, fatty acid composition of erythrocyte lipids, eicosanoids, and cytokine biosynthesis in patients with RA. *Methods* Sixty-eight patients with definitive RA were matched into two groups of 34 subjects each. One group was observed for 8 months on a normal western diet (WD) and the other on an anti-inflammatory diet (AID) providing an arachidonic acid intake of less than 90 mg/day. Patients in both groups were allocated to receive placebo or fish oil capsules (30 mg/kg body weight) for 3 months in a double-blind crossover study with a 2-month washout period between treatments. Clinical examination and routine laboratory findings were evaluated every month, and erythrocyte fatty acids, eicosanoids, and cytokines were evaluated before and after each 3-month experimental period. *Results* Sixty patients on AID & Omega-3 did best! 217%) and lower formation of leukotriene B_4 (34% vs 8%, $P > 0.01$), 11-dehydro-thromboxane B_2 (15% vs 10%, $P < 0.05$), and prostaglandin metabolites (21% vs 16%, $P < 0.003$) were found in AID patients, especially when fish oil was given during months 6–8 of the experiment. *Conclusion* A diet low in arachidonic acid ameliorates clinical signs of inflammation in patients with RA and augments the beneficial effect of fish oil supplementation.

Keywords Arachidonic acid · Eicosanoids · Fish oil · N-3 fatty acids · Rheumatoid arthritis · Vegetarian diet

Introduction

Rheumatoid arthritis (RA) is an autoimmune disease characterized by flares of arthritis involving small and

- 60 patients with definitive RA
- 2 groups observed x 8 months:
  - Western diet
  - Anti-inflammatory diet (AID) – (< 90 mg of arachidonic acid per day)
- Both groups received placebo or fish oil capsules (30 mg/kg body weight) x 3 months
- **Patients on AID & Omega-3 did best!**
- 70 kg = 30*70 = 2,100 mg of Omega 3

Adam O, et al. *Rheumatol Int*. 2003;23(1):27-36.

FUNCTIONAL MEDICINE
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Polyunsaturated Fatty Acids in RA

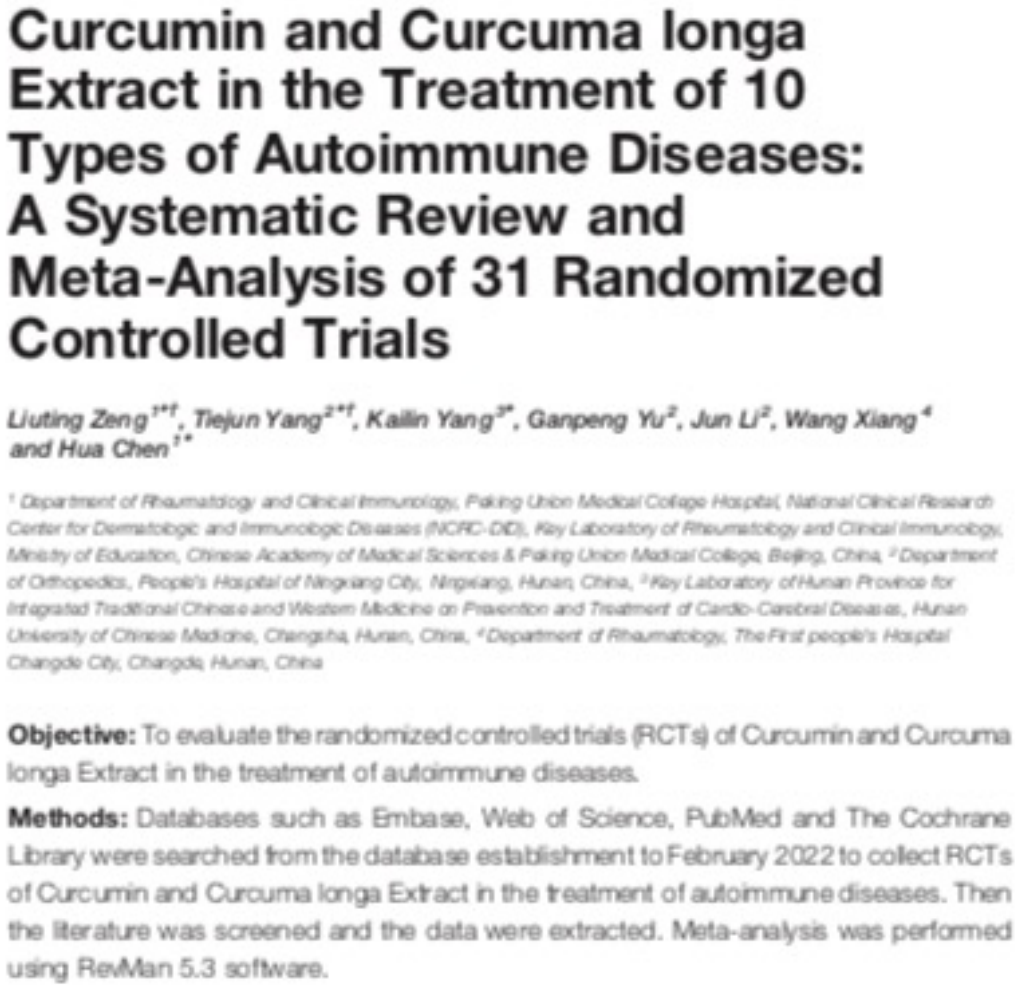
- Doses ~1.6 grams -3.8 EPA / 1.1-2.1 grams DHA
- Improvements in lab markers of inflammation
  - ↓ neutrophil LTB/LTB4
  - ↓ macrophage IL 1
  - ↓ ESR
- Improvements in disease function
  - Morning stiffness
  - Tender Joint Counts (TJC)
  - Mean time to onset of fatigue
- ↓ need for NSAIDS or biologics

Navarini L, et al. *Lipids Health Dis*. 2017;16(1):197.

Turmeric (*Curcuma longa)*

- Curcumin is the main component
  - potent inhibitor of NF- κB, COX-2, LOX
  - reduces inflammatory mediators: IL-6, IL-1β, MCP-1, metalloproteanases
  - strong antioxidant

White CM, et al. Pharmacol Res. 2019 Aug;146:104280.



Curcumin and Curcuma longa Extract in the Treatment of 10 Types of Autoimmune Diseases: A Systematic Review and Meta-Analysis of 31 Randomized Controlled Trials

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Objective: To evaluate the randomized controlled trials (RCTs) of Curcumin and Curcuma longa Extract in the treatment of autoimmune diseases.

Methods: Databases such as Embase, Web of Science, PubMed and The Cochrane Library were searched from the database establishment to February 2022 to collect RCTs of Curcumin and Curcuma longa Extract in the treatment of autoimmune diseases. Then the literature was screened and the data were extracted. Meta-analysis was performed using RevMan 5.3 software.

Rheumatoid arthritis (RA) - Five RCTs

Compared to control, curcumin:

- ↓ DAS28 (P=0.0002)
- ↓ ESR (P<0.0001)
- ↓ CRP (P=0.0003)

Ulcerative colitis (UC) - Nine RCTs

Compared to control, curcumin:

- ↓ clinical activity index (P<0.0001)
- ↓ ESR (P=0.0003)
- ↓ CRP (P=0.03)

Zeng L, et al. *Front Immunol*. 2022;13:896476.

Effects of curcumin supplementation on metabolic parameters, inflammatory factors and obesity values in women with rheumatoid arthritis: A randomized, double-blind, placebo-controlled clinical trial

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Abstract

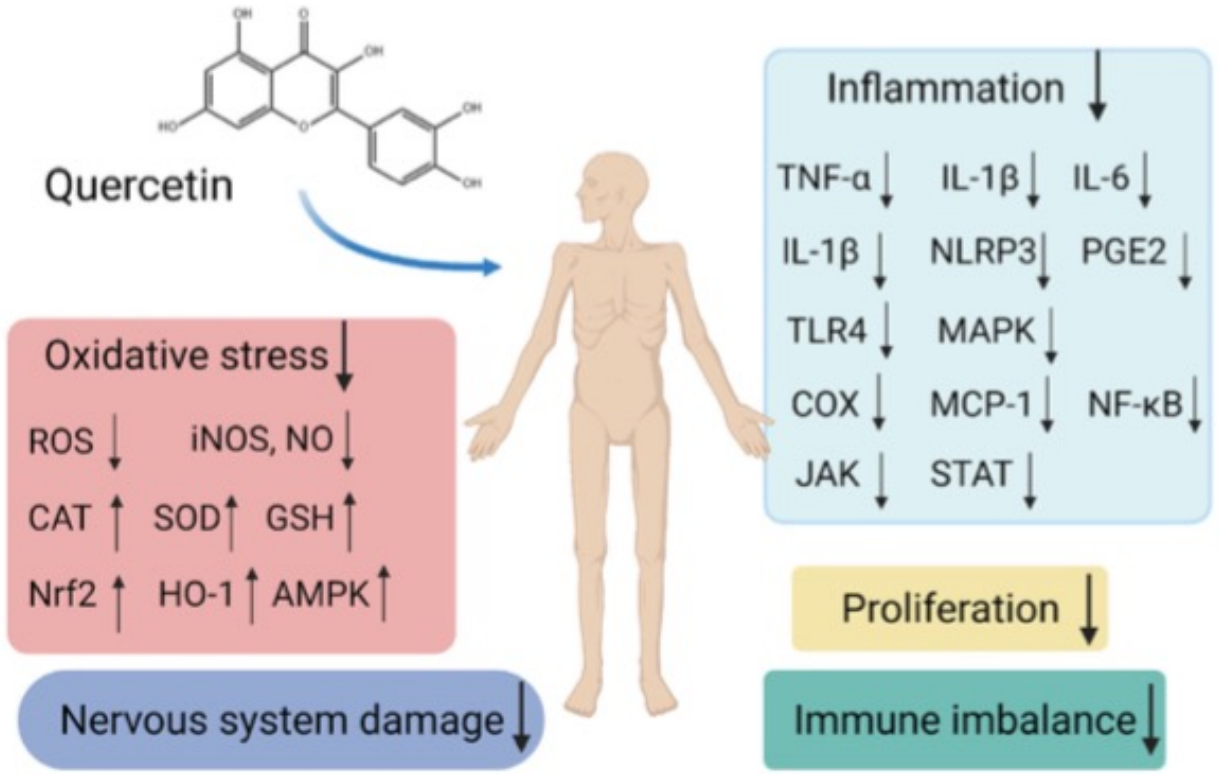
Rheumatoid arthritis (RA) is a chronic inflammatory disease that leads to cartilage damage with mostly accompanied by metabolic disorders. This study aimed to investigate the effects of curcumin supplementation on metabolic parameters (lipid profile and glycemic indices), inflammatory factors, visfatin levels, and obesity values in women with RA. This randomized, double-blind, placebo-controlled clinical trial was conducted on 48 women with RA. The patients were treated with curcumin (500 mg once a day) or placebo for 8 weeks. Fasting blood samples, anthropometric measurements, dietary intakes, and physical activity levels of subjects were collected at baseline and the end of the study. Curcumin supplementation significantly decreased homeostatic model assessment for insulin resistance (HOMA-IR), erythrocyte sedimentation rate, serum levels of high-sensitivity C-reactive protein and triglycerides, weight, body mass index, and waist circumference of patients compared with the placebo at the end of the study ($p < .05$ for all). HOMA-IR and triglyceride levels significantly increased within the placebo group. Changes in fasting blood sugar, insulin, other lipids profile, and visfatin levels were not significant in any of the groups ($p > .05$). These results support the consumption of curcumin, as a part of an integrated approach to modulate metabolic factors, inflammation, and adiposity in women with RA.

- 48 women with moderately active RA
- Curcumin (500 mg/day) or placebo for 8 weeks
- Significant ↓ in ESR and hs-CRP in curcumin group (44.68%, $p < .001$ and 20.93%, $p = .017$, respectively)

Pourhabibi-Zarandi F, et al. *Phytother Res*. 2022;36(4):1797-1806.

Quercetin

- Inhibits pro-inflammatory cytokines (TNF-a, IL-1b, & IL-6); promotes anti-inflammatory cytokines (IL-10)
- Reduces COX, LOX expression
- Stabilizes mast cells



Shen P, et al. *Front Immunol*. 2021;12:689044.

The Effect of Quercetin on Inflammatory Factors and Clinical Symptoms in Women with Rheumatoid Arthritis: A Double-Blind, Randomized Controlled Trial

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Key words: quercetin, rheumatoid arthritis, clinical symptoms, DAS-28, HAQ, hs-TNFα

Objective: Previous studies have shown that the bioflavonoid quercetin has anti-inflammatory and anti-nociceptive effects. We investigated the effect of quercetin supplementation on inflammation, disease severity, and clinical symptoms in women with rheumatoid arthritis (RA).

Methods: The present study was a randomized, double-blind, placebo-controlled clinical trial in which 50 women with RA were allocated into a quercetin (500 mg/day) or placebo group for 8 weeks. Plasma levels of high-sensitivity tumor necrosis factor-α (hs-TNFα), erythrocyte sedimentation rate (ESR), clinical symptoms including early morning stiffness (EMS), morning and after-activity pain, and tender (TSC) and swollen joint counts (SJC) were determined. Disease activity and functional disability were assessed by Disease Activity Score 28 (DAS-28), physician global assessment (PGA), and a health assessment questionnaire (HAQ) at the beginning and end of the study.

Results: Quercetin supplementation for 8 weeks significantly reduced EMS, morning pain, and after-activity pain ($p < 0.05$). DAS-28 and HAQ scores decreased in the quercetin group compared to placebo and the number of patients with active disease significantly decreased in the quercetin group. Plasma hs-TNFα level was significantly reduced in the quercetin group compared to placebo ($p < 0.05$). There were no significant differences in TJC and SJC between groups but TJC significantly decreased in the quercetin group after the intervention. Supplementation had an effect on ESR but it was not significant ($p > 0.05$).

Conclusions: Five hundred milligrams per day quercetin supplementation for 8 weeks resulted in significant improvements in clinical symptoms, disease activity, hs-TNFα, and HAQ in women with RA.

- 50 women with RA
- Quercetin (500 mg/day) or placebo x 8 wks
- Significant reduction in:
  - active disease
  - early morning stiffness, morning pain
  - DAS-28 and HAQ scores
  - hs-TNFa

Javadi F, et al. *J Am Coll Nutr*. 2017;36(1):9-15.

Black Cumin Seed (Nigella sativa)

- Thymoquinone (TQ) - major active chemical component
- Antioxidant, anti-inflammatory and immune-modulatory properties

Gheita AT, et al. *Phytother Res.* 2012;26:1246–8.

The effects of Nigella sativa on thyroid function, serum Vascular Endothelial Growth Factor (VEGF) – 1, Nesfatin-1 and anthropometric features in patients with Hashimoto's thyroiditis: a randomized controlled trial

Mahdieh Abbasalizad Farhangi[1*], Parvin Dehghan[1], Siroos Tajmiri[2] and Mehran Mesgari Abbasi[3]

Abstract

Background: Hashimoto's thyroiditis is an autoimmune disorder and the most common cause of hypothyroidism. The use of Nigella sativa, a potent herbal medicine, continues to increase worldwide as an alternative treatment of several chronic diseases including hyperlipidemia, hypertension and type 2 diabetes mellitus (T2DM). The aim of the current study was to evaluate the effects of Nigella sativa on thyroid function, serum Vascular Endothelial Growth Factor (VEGF) – 1, Nesfatin-1 and anthropometric features in patients with Hashimoto's thyroiditis.

Methods: Forty patients with Hashimoto's thyroiditis, aged between 22 and 50 years old, participated in the trial and were randomly allocated into two groups of intervention and control receiving powdered Nigella sativa or placebo daily for 8 weeks. Changes in anthropometric variables, dietary intakes, thyroid status, serum VEGF and Nesfatin-1 concentrations after 8 weeks were measured.

Results: Treatment with Nigella sativa significantly reduced body weight and body mass index (BMI). Serum concentrations of thyroid stimulating hormone (TSH) and anti-thyroid peroxidase (anti-TPO) antibodies decreased while serum T3 concentrations increased in Nigella sativa-treated group after 8 weeks. There was a significant reduction in serum VEGF concentrations in intervention group. None of these changes had been observed in placebo treated group. In stepwise multiple regression model, changes in waist to hip ratio (WHR) and thyroid hormones were significant predictors of changes in serum VEGF and Nesfatin-1 values in Nigella sativa treated group ($P < 0.05$).

Conclusions: Our data showed a potent beneficial effect of powdered Nigella sativa in improving thyroid status and anthropometric variables in patients with Hashimoto's thyroiditis. Moreover, Nigella sativa significantly reduced serum VEGF concentrations in these patients. Considering observed health- promoting effect of this medicinal plant in ameliorating the disease severity, it can be regarded as a useful therapeutic approach in management of Hashimoto's thyroiditis.

- 40 patients with Hashimoto's thyroiditis
- Powdered Nigella sativa or placebo daily for 8 weeks
- Nigella sativa treated group:
  - ↓ TSH and anti-TPO concentrations
  - ↑ T3 increased
  - ↓ VEGF

Farhangi MA, et al. *BMC Complement Altern Med*. 2016;16(1):471.

SHORT COMMUNICATION

Effectiveness of *Nigella sativa* Oil in the Management of Rheumatoid Arthritis Patients: A Placebo Controlled Study

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The constituents of *Nigella sativa* modulate the immune system. The aim of the present work was to study the effectiveness of *Nigella sativa* oil in RA patients. Data from 40 female RA patients diagnosed according to the 2010 ACR/EULAR were analysed and discussed. The patients took two placebo (starch filled) capsules daily for 1 month. This was followed by a month of *Nigella sativa* oil capsules 500 mg twice/day. The disease activity score (DAS-28) significantly decreased after receiving the *Nigella sativa* capsules (4.55 ± 0.82) compared with before and after placebo (4.98 ± 0.79 and 4.99 ± 0.72, respectively) ($p = 0.017$). Similarly, the number of swollen joints and the duration of morning stiffness improved. A marked improvement in the disease activity was shown by both the ACR20 and EULAR response criteria in 42.5% and 30% of the patients, respectively, after intake of Nigella. Supplementation with *Nigella sativa* during DMARD therapy in RA may be considered an affordable potential adjuvant biological therapy.

- 40 female RA patients
- 2 placebo capsules/day for 1 month followed by 500 mg Nigella sativa oil capsules twice/day for 1 month
- ↓ DAS-28, number of swollen joints and morning stiffness after receiving Nigella sativa

Gheita AT, et al. *Phytother Res.* 2012;26:1246–8.

Ginger

- More than 40 antioxidants have been isolated from ginger rhizome
- Phenolic active ingredients such as gingerols and shogaols

Poles J, et al. *J Clin Transl Res*. 2021;7(3):333-376.

- 66 patients with active RA
- 1500 mg ginger daily vs placebo
- ↓ CRP (p = 0.050) and IL-1β (p=0.021)
- ↓ TNF-α levels although not significant (p=0.093)

The effect of ginger supplementation on IL2, TNFα, and IL1β cytokines gene expression levels in patients with active rheumatoid arthritis: A randomized controlled trial

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Abstract

Background: Rheumatoid arthritis (RA) is a chronic autoimmune and inflammatory disease that affects the joints and consequently leads to the destruction of cartilage and bone lesions. Traditionally, ginger has been consumed in treatment of osteoarthritis, joint and muscle pain, neurological diseases, and inflammation of gums, tooth pain, asthma, stroke, diabetes, and constipation. The aim of this study was to determine the effect of ginger on some immunological and inflammatory markers in patients with rheumatoid arthritis.

Methods: In this study, which was performed during 2013-2016, 66 patients with active rheumatoid arthritis who referred to the rheumatology clinic at Shariati hospital were en-rolled. Patients were randomly divided into 2 groups: one group consumed 1.5 gr ginger per day, and the other group took roasted wheat flour (placebo), respectively. To determine the effect of confounding factors on the findings of the study, questionnaires for nutrient intake, physical activity, and medication were filled, and BMI was measured. For each participant, at the beginning and end of the study, Serum hs-CRP and mRNA levels of IL-1β, IL-2 and TNF-α were determined by ELISA and Quantitative Real Time PCR, respectively. Statistical analysis was performed using SPSS software. Significance level was set at $p<0.05$.

Results: Results of the study showed ginger powder supplementation caused a significant decline in CRP ($p=0.050$) and IL-1β mRNA level ($p=0.021$). TNFα mRNA levels reduced in ginger group compared to placebo groupalthough the difference was not significant be-tween the 2 groups ($p=0.093$). Ginger had no effects on IL2 gene expression.

Conclusion: This study showed that ginger reduces inflammatory factors hs-CRP and IL-1β gene expression in patients with active RA and it seems that ginger can improve the inflam-mation in the patients.

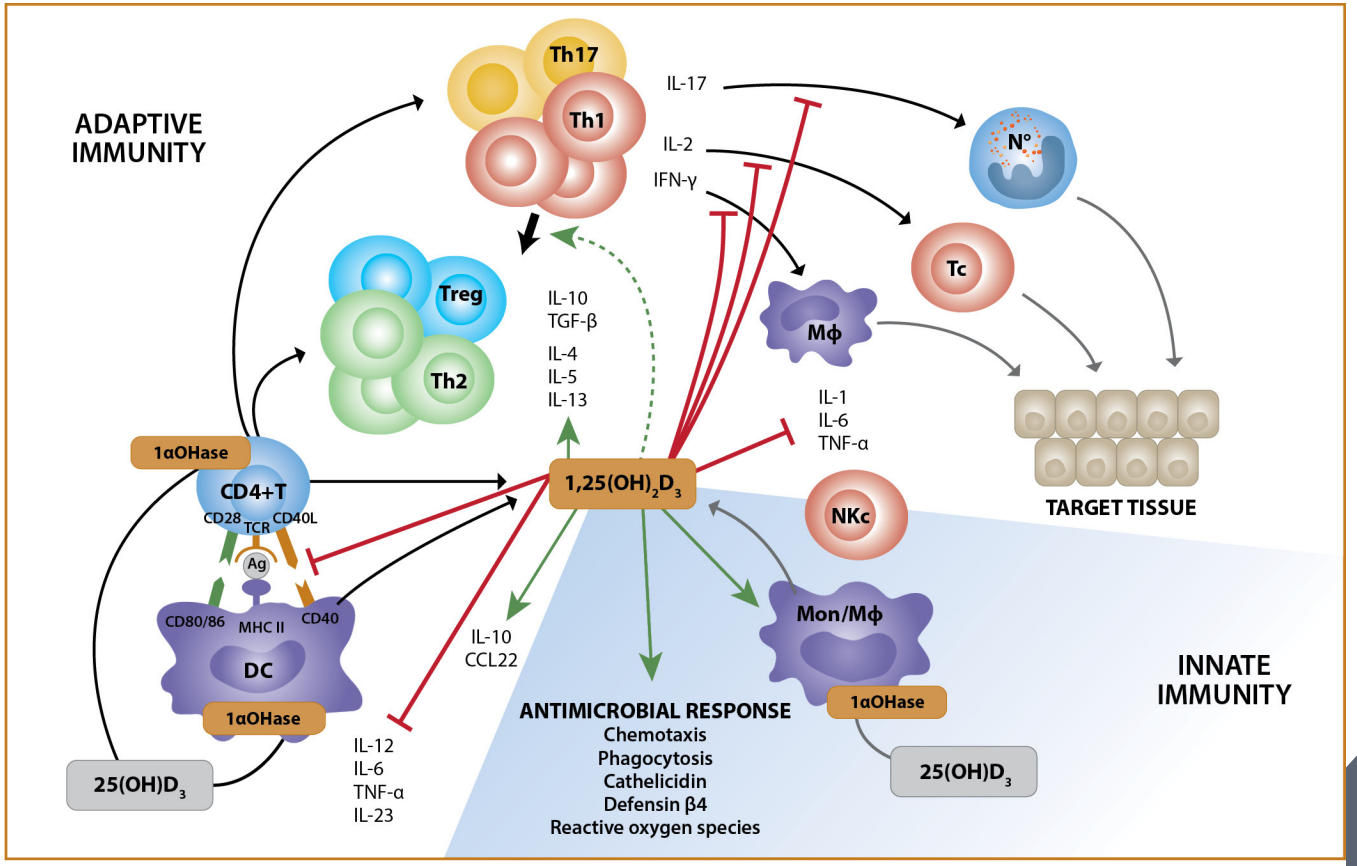
Aryaeian N, et al. *Med J Islam Repub Iran*. 2019;33:154.

Micronutrients

Vitamin D Deficiency & Autoimmunity

- In vitro, vit D regulates genes involved in inflammation and acquired and innate immune responses

- Association between autoimmune disease development and vit D deficiency from decreased sun exposure in northern latitudes



Chandrashekara S, et al. *Rheum Dis*. 2017;20(7):825-831.
Guilliams, T. Supporting immune function a lifestyle and nutrient approach. (2nd edition) 2022

Vitamin D and marine omega 3 fatty acid supplementation and incident autoimmune disease: VITAL randomized controlled trial

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ABSTRACT

OBJECTIVE

To investigate whether vitamin D and marine derived long chain omega 3 fatty acids reduce autoimmune disease risk.

DESIGN

Vitamin D and omega 3 trial (VITAL), a nationwide, randomized, double blind, placebo controlled trial with a two-by-two factorial design.

SETTING

Nationwide in the United States.

PARTICIPANTS

25 871 participants, consisting of 12 786 men ≥50 years and 13 085 women ≥55 years at enrollment.

INTERVENTIONS

Vitamin D (2000 IU/day) or matched placebo, and omega 3 fatty acids (1000 mg/day) or matched placebo. Participants self-reported all incident autoimmune diseases from baseline to a median of 5.3 years of follow-up; these diseases were confirmed by extensive medical record review. Cox proportional hazard models were used to test the effects of vitamin D and omega 3 fatty acids on autoimmune disease incidence.

MAIN OUTCOME MEASURES

The primary endpoint was all incident autoimmune years. For the vitamin D arm, 123 participants in the treatment group and 155 in the placebo group had a confirmed autoimmune disease (hazard ratio 0.78, 95% confidence interval 0.61 to 0.99, P=0.05). In the omega 3 fatty acids arm, 130 participants in the treatment group and 148 in the placebo group had a confirmed autoimmune disease (0.85, 0.67 to 1.08, P=0.19). Compared with the reference arm (vitamin D placebo and omega 3 fatty acid placebo; 88 with confirmed autoimmune disease), 63 participants who received vitamin D and omega 3 fatty acids (0.69, 0.49 to 0.96), 60 who received only vitamin D (0.68, 0.48 to 0.94), and 67 who received only omega 3 fatty acids (0.74, 0.54 to 1.03) had confirmed autoimmune disease.

CONCLUSIONS

Vitamin D supplementation for five years, with or without omega 3 fatty acids, reduced autoimmune disease by 22%, while omega 3 fatty acid supplementation with or without vitamin D reduced the autoimmune disease rate by 15% (not statistically significant). Both treatment arms showed larger effects than the reference arm (vitamin D placebo and omega 3 fatty acid placebo).

STUDY REGISTRATION

ClinicalTrials.gov NCT01351805 and NCT01169259

In this large primary prevention trial, supplementation with vitamin D 2000 IU/day for 5 years, alone or in combination with 1 g/day of omega 3 fatty acids (460 mg EPA & 380 mg DHA acid) led to a lower incidence of confirmed autoimmune disease than placebo

Hahn J. et al. *BMJ* 2022; 376:e066452

Original Article

Vitamin D supplementation reduces thyroid peroxidase antibody levels in patients with autoimmune thyroid disease: An open-labeled randomized controlled trial

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ABSTRACT

Background and Aims: Although Vitamin D deficiency has been linked to autoimmune thyroid disorders (AITD), the impact of Vitamin D supplementation on thyroid autoimmunity is not known. This study aimed to evaluate the impact of Vitamin D supplementation on thyroid autoimmunity (thyroid peroxidase antibody [TPO-Ab] titers) in patients with newly diagnosed AITD in a randomized controlled trial. **Materials and Methods:** One hundred two patients with newly diagnosed AITD (TPO-Ab > 34 kIU/L and/or sonographic evidence of thyroiditis) patients were randomized into Group-1 (intervention group) and Group-2 (control group). Group-1 received cholecalciferol 60,000 IU weekly and calcium 500 mg/day for 8 weeks; Group-2 received calcium 500 mg/day for 8 weeks. Responders were defined as ≥25% fall in TPO-Ab titers. Individuals with at least 3-month follow-up were analyzed. Trial is registered at ctri.nic.in (CTRI/2015/04/005713). **Results:** Data from 100 AITD patients (68 with thyroid stimulating hormone [TSH] ≤10 mIU/L, 32 with TSH > 10 mIU/L), 93% having Vitamin D insufficiency, were analyzed. TPO-Ab titers were highest among patients in the lowest 25-hydroxyvitamin D quartile ($P = 0.084$). At 3 months follow-up, there was significant fall in TPO-Ab in Group-1 (–46.73%) as compared to Group-2 (–16.6%) ($P = 0.028$). Sixty-eight percentage patients in Group-1 were responders compared to 44% in Group-2 ($P = 0.015$). Kaplan–Meier analysis revealed significantly higher response rate in Group-1 ($P = 0.012$). Significantly greater reduction in TPO-Ab titers was observed in AITD with TSH ≤ 10 mIU/L compared to TSH > 10 mIU/L. Cox regression revealed Group-1 followed by TPO-Ab and free tetraiodothyronine levels to be a good predictor of response to therapy ($P = 0.042$, 0.069, and 0.074, respectively). **Conclusion:** Vitamin D supplementation in AITD may have a beneficial effect on autoimmunity as evidence by significant reductions in TPO-Ab titers.

Key words: Autoimmune hypothyroidism, autoimmunity, thyroid peroxidase antibody, thyroiditis, Vitamin D

- 93% of patients had Vitamin D insufficiency
- 60,000 IU Cholecalciferol weekly
- TPO-Ab were highest in those with lowest 25-hydroxy-D levels
- 3 month FU 46% reduction in TPO-Ab vs. 16% in control

Chaudhary S, Dutta D, Kumar M, et al. *Indian J Endocrinol Metab*. 2016;20(3):391-398.

Role of vitamin D supplementation in improving disease activity in rheumatoid arthritis: An exploratory study

S. CHANDRASHEKARA and Anand PATTED

ChanRe Rheumatology and Immunology Center, Bangalore, India

Abstract

Aim: The aim of this exploratory study is to estimate the relationship between vitamin D (vit D) deficiency and active rheumatoid arthritis (RA), and the role of supplementation in improving disease activity.

Method: A randomized recruitment, consent screening, open-label interventional study was conducted in patients who fulfilled American College of Rheumatology/European League Against Rheumatism 2010 criteria for diagnosing RA and on stable disease-modifying anti-rheumatic drugs (DMARDs) for 3 months. Serum vit D levels and Disease Activity Score of 28 joints/C-reactive protein (DAS28-CRP) disease activity status were estimated at the first visit. Subjects with low vit D levels and DAS28-CRP > 2.6 were supplemented with vit D for 12 weeks, and were assessed for improvement in disease activity and serum vit D levels.

Results: One hundred and fifty RA patients of mean age 49 ± 12.1 years, mean duration of illness 78 ± 63 months, and on treatment with DMARDs for 44 ± 39 months were recruited for the study. Of these, 73 (49%) subjects were found to have DAS28-CRP > 2.6 and serum vit D below 20 ng/mL. The patients received vit D supplement of 60 000 IU/week for 6 weeks, followed by 60 000 IU/month for a total duration of 3 months. Disease activity and vit D status were assessed for 59 (80.8%) patients who reported at the end of 12 weeks of treatment. Mean DAS28-CRP of these patients showed a statistically significant improvement from 3.68 ± 0.93 at baseline to 3.08 ± 1.11 after supplementation ($P = 0.002$). Serum vit D levels improved from 10.05 ± 5.18 to 57.21 ± 24.77 ng/mL ($P < 0.001$) during the period.

Conclusion: Supplementation of vit D in RA patients with persisting disease activity and vit D deficiency contributed to significant improvement in disease activity within a short duration.

Key words: DAS28, rheumatoid arthritis, vit D, vitamin D.

- 150 RA patients
- Vit D 60,000 IU/week for 6 weeks, followed by 60,000 IU/month for a total of 3 months
- Significant improvement in mean DAS28-CRP and vit D levels

Chandrashekara S, et al. *Rheum Dis*. 2017;20(7):825-831.

Zinc

- Essential trace element; plays a role in > 300 enzymatic processes
- Antioxidant & anti-inflammatory effects
- Deficiency may affect up to two billion people worldwide
- Zn levels significantly lower in autoimmune disease patients
- Deficiency associated with:
  - ↑ activation of NF-κB and NF-κB-regulated inflammatory cytokine expression
  - ↑ IL-6, IL-8 and TNF-α levels

1. *Sanna et al. Nutrients*. 2018;10(1):68
2. *Choi et al. Acta Pharmacol Sin* **39**, 1120–1132 (2018).
3. Jarosz et al. *Inflammopharmacology*. 2017;25(1):11-24.

Selenium & Hashimoto's Thyroiditis

- Selenium (Se) is an essential micronutrient with many pleiotropic effects ranging from antioxidant and anti-inflammatory to increasing active thyroid hormone production
- Supports the conversion of peripheral T4 to T3 via outer (5')- ring deiodination of the pro-hormone T4, are selenoproteins and thus this conversion is susceptible to Se deficiency
- For that reason Se-deficient individuals have mildly elevated serum T4 and T4 to T3 ratios, but normal TSH
- Food sources
  - Brazil nuts, oysters, tuna, whole grains, meats, sunflower seeds
- Supplementation:
  - Selenomethionine 200 µg as a single treatment or combined with LT4 reduced the serum levels of anti-thyroid peroxidase antibodies compared with placebo (or placebo plus LT4) in three studies ($p < 0.001$)

1. Liontiris MI, Mazokopakis EE. *Hell J Nucl Med*. 2017;20(1):51-56.
2. Zuuren EJ, et al. *Eur Thyroid J*. 2014;3(1):25-31.

CoQ10

- Mitochondrial enzyme that regulates oxidative phosphorylation while acting as an antioxidant, mitigating ROS production, and pro-inflammatory signaling[1]
- 45 MS patients randomized to receive either 500 mg/day of CoQ10 or placebo for 12 weeks[2]
  - matrix metallopeptidase 9 (MMP-9), [TNF]-α, [IL]-6 levels decreased significantly in treatment group

1. Poles J, et al. *J Clin Transl Res*. 2021;7(3):333-376.
2. Sanoobar M, et al. *Nutr Neurosci*. 2015;18(4):169-176.

CoQ10 in Rheumatoid Arthritis

Effects of Coenzyme Q_{10} Supplementation on Inflammatory Cytokines (TNF-α, IL-6) and Oxidative Stress in Rheumatoid Arthritis Patients: A Randomized Controlled Trial

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[a]*Students' Research Committee, Faculty of Nutrition, Tabriz University of Medical Sciences, Tabriz,* [b]*Department of Rheumatology, Faculty of Medicine, Urmia University of Medical Sciences, Urmia,* [c]*Road Traffic Injury Research Center,* [d]*Department of Community Nutrition, Faculty of Nutrition, Tabriz University of Medical Sciences, Tabriz, Iran*

Received for publication May 31, 2015; accepted August 25, 2015 (ARCMED-D-15-00393).

Backgrounds and Aims. Overproduction of proinflammatory cytokines is a main trait of rheumatoid arthritis. Coenzyme Q_{10} (CoQ_{10}), an endogenous antioxidant, has shown anti-inflammatory effects in some diseases. In this study we aimed to assess the effects of CoQ_{10} supplementation on cytokines generation and oxidative stress in rheumatoid arthritis.

Methods. In this double-blind, randomized controlled clinical trial, 44 patients with rheumatoid arthritis were recruited. Twenty two patients received 100 mg/day capsules of CoQ_{10} and 22 patients took placebo for 2 months. At the beginning and the end of the intervention, 7 mL of fasting blood was taken from patients to measure malondialdehyde (MDA), total antioxidant capacity (TAC), interleukin (IL)-6 and tumor necrosis factor alpha (TNF-α).

Results. At the end of the study, serum MDA significantly decreased in supplemented group (mean difference = −1.47 nmol/mL; 95% confidence interval (CI), −2.52 to −0.43; $p = 0.008$). CoQ_{10} also suppressed overexpression of TNF-α (difference in median was +1.1 in placebo vs. +0.03 in CoQ_{10} group; $p = 0.033$). There was no significant difference in TAC and IL-6 levels between groups.

Conclusions. This study showed beneficial effects of CoQ_{10} supplementation on inflammatory cytokines and oxidative stress in rheumatoid arthritis patients.

Key Words: Coenzyme Q_{10} (CoQ_{10}), Ubiquinol, Inflammatory cytokines, Oxidative stress, Rheumatoid arthritis.

- 100 mg CoQ10/day
- Reduced MDA and reduced expression of TNF-α in 2 months

Abdollahzad H, et al. *Arch Med Res*. 2015;46(7):527-533.

FUNCTIONAL MEDICINE
Continuing Education

Effects of coenzyme Q10 supplementation on matrix metalloproteinases and DAS-28 in patients with rheumatoid arthritis: a randomized, double-blind, placebo-controlled clinical trial

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Received: 23 April 2019 / Revised: 24 July 2019 / Accepted: 30 July 2019 / Published online: 7 August 2019

Abstract

Objectives This study aimed to assess the effect of CoQ10 supplementation on serum matrix metalloproteinases (MMPs) and clinical parameters in rheumatoid arthritis (RA) patients.

Method In this randomized, double-blind, placebo-controlled trial, 54 RA patients who fulfilled the eligibility criteria (18–56 years, diagnosed at least 6 months ago, with DAS-28 > 3.2) were randomly assigned into two groups to receive 100 mg/day CoQ10 ($n = 27$) or placebo ($n = 27$) for 2 months. Serum MMP-1 and MMP-3 levels and clinical status using disease activity score in 28 joints (DAS-28) were assessed before and after supplementation. Data were analyzed using $\chi 2$, independent sample t test, paired t test, Wilcoxon, Mann-Whitney, and analysis of covariance.

Results A significant reduction was observed in both CoQ10 and placebo groups in the medians of serum MMP-1 (0.2 to 0.16, $P < 0.001$), (0.18 to 0.15, $P = 0.001$); swollen joint count (2 to 0, $P < 0.001$), (2 to 0, $P = 0.009$); and the means of DAS-28 (5.01 ± 1.21 to 2.34 ± 0.68, $P < 0.001$), (4.88 ± 0.96 to 4.04 ± 1.36, $P = 0.009$) respectively. Serum MMP-3 level increased significantly in placebo group (2.26 to 2.57, $P = 0.020$), and the MMP-3 changes between groups were significant ($P = 0.027$). Furthermore, significant reductions were only observed in ESR, pain score, and tender joint count in CoQ10 group compared with baseline ($P = 0.001$, $P < 0.001$, and $P < 0.001$, respectively). Significant differences were observed between two groups in DAS-28, pain score, and swollen and tender joint count after the intervention ($P < 0.001$, $P < 0.001$, and $P = 0.012$ and $P < 0.001$, respectively).

Conclusions It seems that CoQ10 may provide a new complementary approach for RA patients.

- 100 mg CoQ10/day
- Significantly reduced swollen joint count, tender joint count, VAS pain score, and DAS-28 compared to placebo after 2 months

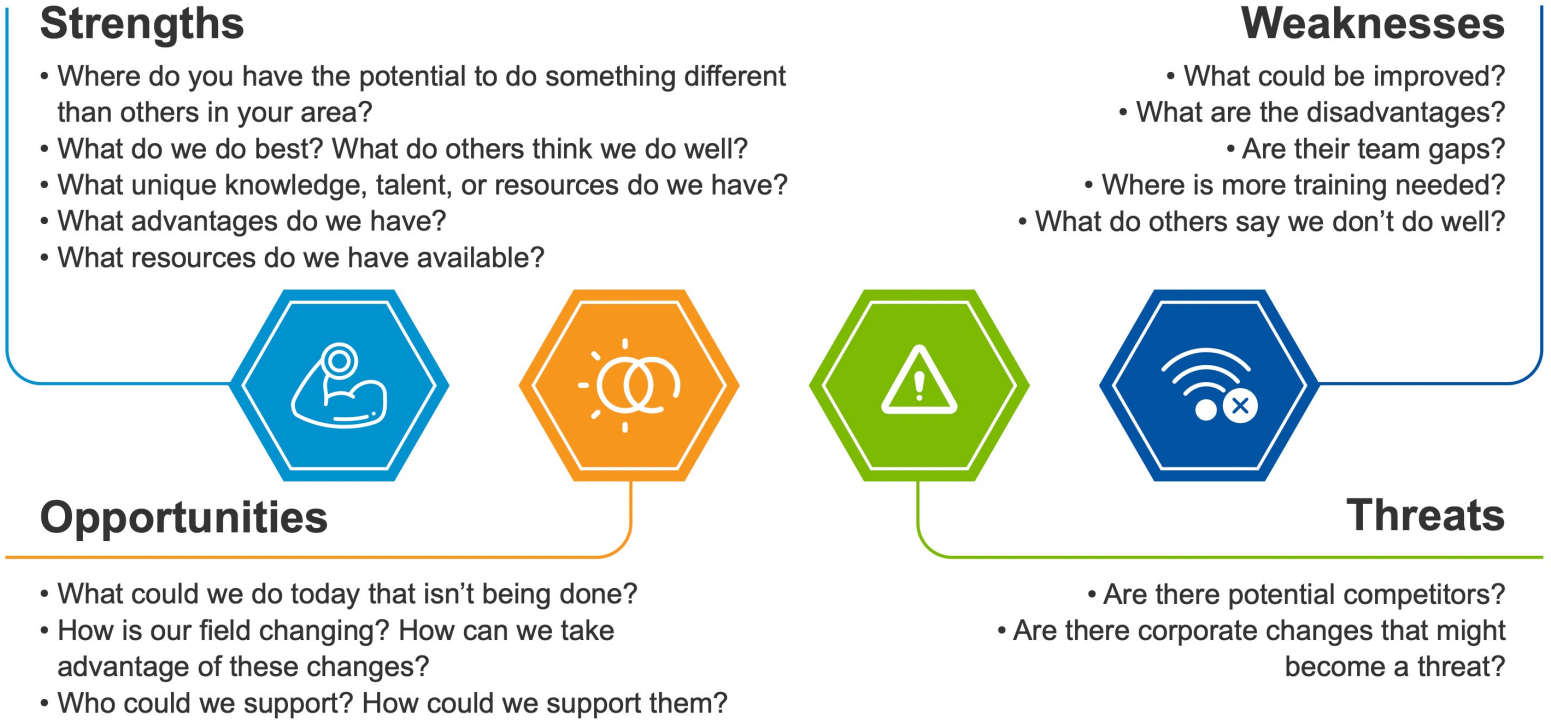
Building Successful Programs

- **Identify opportunities**
  - What is missing in the market (i.e. your niche)?
  - Who is not being cared for?
  - What are your patient's pain points?
  - Identify target audience
- **Defining the service**
  - Outcomes
  - Mission/Vision
- **Set goals**
  - Financial
  - Impact
- **Evaluating staff/workflow**
  - Contracting out vs. training within?
  - Training staff
  - Physical space considerations
- **Developing Resources**
  - Patient handouts
  - Teaching tools
  - Outline content
  - Other tech tools (apps?)
- **Implementation**
  - Delivery (i.e. in person/on-line), asynchronous, group visits?
  - Go-live plan
- **Evaluation**
  - How will you measure success?
  - Patient satisfaction
  - What's next?

1. *Clinical Pharmacist*, CP, May 2015, Vol 7, No 4;7(4):DOI:10.1211/PJ.2015.20068427
2. Gupta V et al. *Pharmacy (Basel)*. 2018;6(4):111. Published 2018 Oct 11.

Business Plans

- Describe Service
- SWOT Analysis
- Marketing Strategy
- Financial Plan



1. *Writing a Business Plan for a New Pharmacy Service 2007: https://aphanet.pharmacist.com/sites/default/files/files/mtm_writing_business_plan.pdf*
2. *A toolkit for establishing clinical pharmacy services developed by the North Carolina Association of Pharmacists. https://ncap.memberclicks.net/assets/docs/NCAP%20Toolkit_FINAL_4May2021.pdf*

Case 1

- JC is a 48 y/o WF that resides in North Dakota. She currently does not take any medications or supplements.
- 6 months ago she started noticing stiffness in both hands in the morning that progressively lasted longer. Now it lasts about 75 min and includes hands and wrists.
- She is taking Naproxen 220-440 mg TID to get through her work day. Her PCP ran labs.
- Lab work
  - CRP: 32 mg/dl (standard CRP)
  - ESR 60 mm/h
  - + Rheumatoid factor

Case 1

- JC visited a rheumatologist and was prescribed oral methotrexate and folic acid and presents to your pharmacy with her first prescription. You start to learn more about her diagnosis. She mentions her provider said if this doesn't help, she will prescribe low dose prednisone. She is nervous about these medications and wants to do what she can to reverse her symptoms without them.

Case 1

- Gather in a group of 4-5 people around you to discuss this case

- Questions for your team:
  - What labs would you recommend?
  - What nutrition protocol would you ask the patient to follow?
  - Would you start any supplements? If so, which ones and what doses?

Case 2

- Your independent pharmacy is ready to develop a new service to 1) improve patient care and 2) increase revenue.
- You want to begin with a simple program for patients with Hashimoto's thyroiditis because you've looked at your fast-moving meds and you dispense levothyroxine in your top ten medications.

Case 2

- Return to your group to discuss…
  - What steps will you take to create a program for these patients?
  - Consider drawing out your SWOT analysis!
  - Who will you target?
  - What kind of service will resonate with that group?
  - What resources will you provide?
  - Who will provide the service?
  - What innovative models of delivery would you consider?
  - What might your clinical protocol look like?

Take-Aways

1. Addressing inflammation is an important piece of reversing symptoms of autoimmune conditions
2. Nutrition, nutrient supplementation, and other core lifestyle interventions can improve autoimmune outcomes
3. You have the potential to build patient programs to improve care for autoimmune patients by addressing root causes