A LITERATURE REVIEW: CHRONIC INFLAMATION AND NUTRITIONAL STATUS

By

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Abstract

This paper reviewed the mechanisms of systemic inflammation and the nutritional status of the individuals who suffer from chronic diseases including rheumatoid arthritis, systemic lupus erythematous, chronic obstructive pulmonary disease, irritable bowel diseases include ulcerative colitis and Crohn's disease, asthma, and atherosclerosis. Treatment modalities such as diet regimens will also be discussed. The Anti-Inflammatory diet, Mediterranean Diet, and the Dash diet will be discussed. Nutritional status and inflammation go hand in hand according to the findings available today. There is still more research required to completely understand the mechanisms that occur in inflammation.

Key words:
Nutrition, nutritional status, inflammation, chronic inflammation, malnutrition, health, Mediterranean diet, dash diet, anti-inflammatory,

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Introduction

In 2012, chronic disease had been surveyed to affect approximately 117 million adult Americans[1]. In 2010, 48% of the leading causes of death were from heart disease and cancer[1], both of which are chronic diseases that have inflammation within their pathology. Within the chronic disease spectrum, especially cardiovascular disease, obesity, cancer, systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), inflammatory bowel diseases, and sepsis, inflammation plays a large role[2]. Inflammation is also crucial for the healing of wounds. During occurrences of subclinical low to high inflammation response, found in chronic disease, nutritional status plays a sizable part based on the status of the patient ranging from at risk of being malnourished, malnourished, to excessive energy intake[3,4,5]. The purpose of this paper is to investigate the connection between chronic inflammation and nutritional status with a focus on diet modalities such as the Anti-Inflammatory diet, Mediterranean diet, and Dash diet to modify the inflammatory response.

Table 1. Chronic Diseases Associated with Inflammation[2]
• **Cardiovascular disease (specifically Atherosclerosis)**
• **Cancer**
• **Pulmonary Diseases (specifically Chronic Obstruction Pulmonary Disease and Asthma)**
• **Inflammatory Bowel Diseases (specifically Ulcerative Colitis and Crohn's Disease)**
• **Obesity**

- **Autoimmune Diseases (specifically Systemic Lupus Erythematosus)**
- **Rheumatoid Arthritis**

INFLAMMATION

There are two types of inflammation: acute and chronic inflammation; these are interconnected. In 2010, Wong et. al. indicated that the main difference between acute and chronic inflammation is the life span of the inflammation[6]. Acute inflammation is characteristic of wound healing, responding to bacteria or pathogens, and returning the body to homeostasis[2]. Acute inflammation is necessary and can last between a few minutes to several days[7]. Chronic inflammation can occur for years[7]. There are three stages of inflammation which are the inflammatory phase, the complement phase, and the resolution phase[2]. Chronic inflammation occurs because the final stage, resolution stage cannot begin due to "failure to remove [the] inflammatory stimulus"[2] meaning the inflammatory response becomes stuck in the complement phase. Inflammation occurs within exudate and cellular areas. The cellular component of chronic inflammation involves monocytes, macrophages, cytokines, neutrophils, dendritic cells, fibrocytes, and T-cells[2].

As seen in Table 2, these cellular components have important functions in promoting or ending inflammation. After the tissue becomes damaged, the first responders to the tissue site are neutrophils and macrophages. Mast cells are activated by neuropeptides and cytokines[8]. Mast cells then chemically attract other pro-inflammatory mediators such as tumor necrosis factor-α

(TNF- α), cytokines (specifically interleukin (IL)- 1β and IL-6), histamines, prostaglandins, and leukotrienes[2]. Monocytes and neutrophils remove necrotic tissue, bacteria, and debris via phagocytosis. In the last stage of inflammation anti-inflammatory cells enter the site such as transforming growth factor (TGF-β), IL-10, neutrophils, and fibroblasts to complete healing[2]. This physiologic response is typical in acute inflammatory processes. In chronic or systemic inflammatory processes, the initial inflammatory trigger is unknown[9].

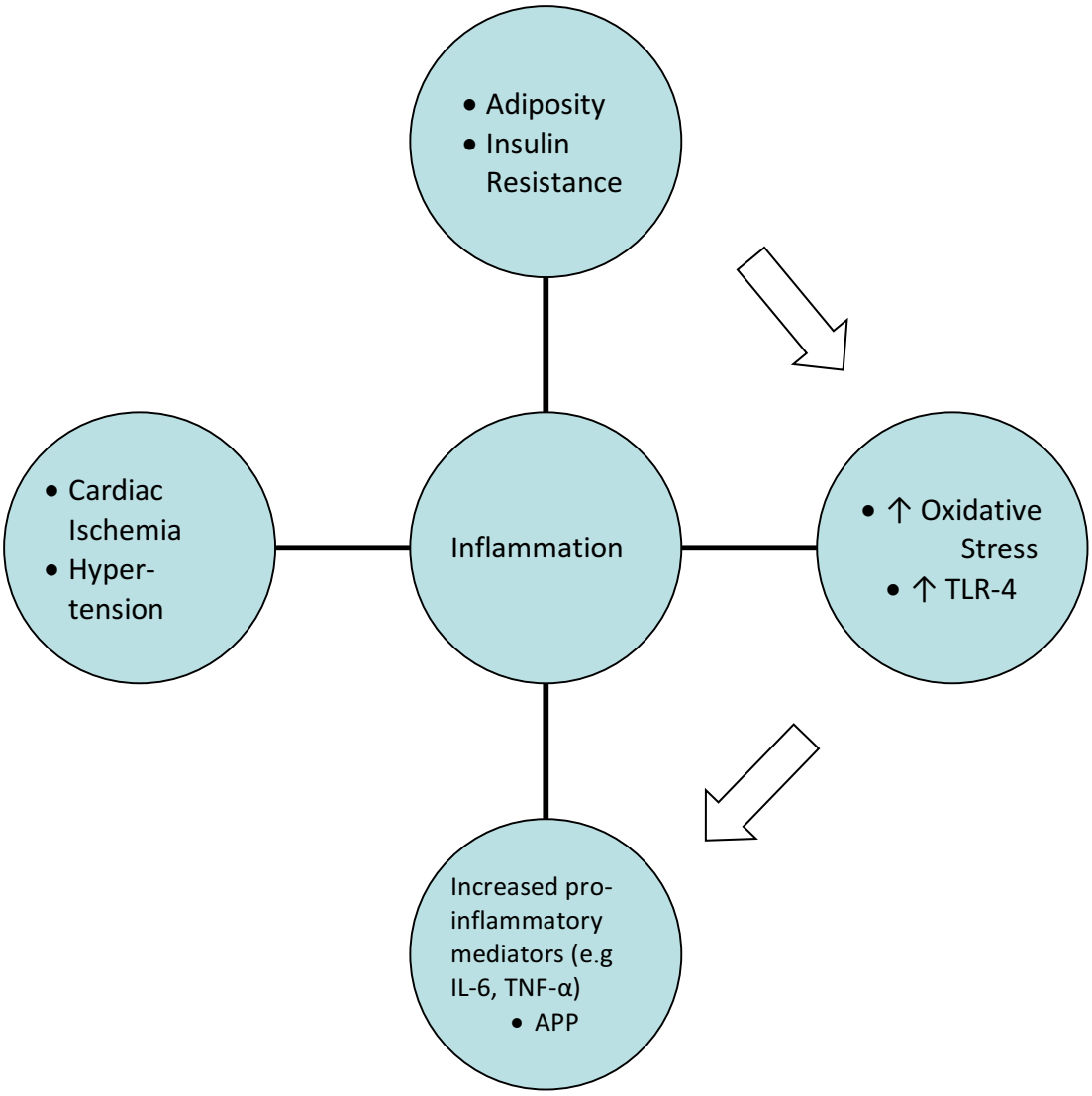
Table 2. Cellular Components of inflammation adapted from Chronic Inflammation[2]

Cellular Component	Function in inflammation
Monocytes	Circulate to area of inflammation and become macrophages or dendritic cells associated with the tissue site to replenish tissue, phagocytosis, antigen representation which leads to an immune response, production of pro and anti-inflammatory cytokines
Macrophages	Watchdog for the immune system, tissue remodeling, inflammation remodeling
Neutrophils	First responders to the inflammation site, activated by chemotaxic receptors, may aide to lead to resolution phase or build up may lead to chronic inflammation
Dendritic Cells	Regulate TH2-immunity
Fibrocytes	Unknown.
Treg (T) Cells	Limit extent and period of inflammatory response.

Cytokines	Released by monocytes, neutrophils, and mast cells to create a pro or anti-inflammatory environment[10]

Black et al. [11] found that the initial trigger can occur from stress or from a malfunction in the tissue as noted by Medzhitov et al[9]. This dysfunctional tissue has been seen in specific studies related to cardiovascular disease, Type II diabetes, obesity, and stress[7,9,11,12,13]. A defect in the tissue may occur from cardiac ischemia, vessels may be broken due to hypertension or a flesh wound, and overactive adipose tissue[7, 13]. An increase in adipose tissue leads to decreased insulin sensitivity as well as increased oxidative stress[13]. This decreased sensitivity leads to increased pro-inflammatory mediated reactions with toll like receptor 4 (TLR-4)[13,14]. Toll like receptor 4 has been associated with the release of inflammation related mediators, cardiovascular disease, obesity, allergic response, autoimmune disorders, and inflammatory bowel diseases[15]. When TLR-4 releases pro-inflammatory cytokines it has been shown to have a deteriorating effect on blood vessels which also sends pro-inflammatory mediators to heal the area, as seen in the study by Bhagat and Vallance[14]. Oxidative stress is known to increase cell death and decrease cell tissue proliferation creating an unhealthy cellular environment[13]. This unhealthy cellular environment puts an additional strain on the homeostatic environment[7,13].

Figure 1. Contributors to Inflammation 2,9,11



Black and fellow researchers investigated the role of the liver, endothelium, and adipocytes in acute phase response caused by psychological stress[11]. This led Black et al. to identify the liver, endothelium, and adipocytes as the key producers of the inflammatory cytokine IL-6; which is linked to acute phase response (APR) and chronic inflammation[11]. Increased levels of IL-6 are linked to pro and anti-inflammatory properties[9,11,13,14,15]. Acute phase response (APR) is basically the term for the reactions that occur in order to heal during acute inflammation[11]. Acute phase protein(APP), and C-reactive Protein (CRP), which are involved in

APR can lead to insulin resistance, type II diabetes, and metabolic syndrome furthering this cycle of inflammation[11]. There are several studies that have investigated the effect of psychological and physiological stressors and insulin resistance[11, 16]. There is data showing that high stress both mentally and environmentally, led to insulin resistance, which headed the physiologic response to an inflammatory cascade involving glucose [11,17]. This was evidenced by increased lab values of substance p, mast cells, corticosteroid releasing factor, catecholamine, glucagon, and renin which induce the APR in human and animal studies[11,16].

Medzhitov et al. have coined the phrase para-inflammation to describe a "state" of inflammation in the body; specifically, an adaptive response to tissue strain or defect that has not yet become chronic inflammation[9]. During para-inflammation the body is fighting for homeostasis while combating inflammatory processes. This is determined by Medzhitov et al. by tissue grade, or level of dead cells found within the tissue that may indicate inflammation[9]. When the body remains in this state for a lengthy period of time, the para-inflammatory state develops into chronic inflammation[9]. This is typical of chronic diseases such as obesity, Type 2 diabetes, atherosclerosis, asthma, and neurodegenerative diseases[9]. This level of para-inflammation is related to increased adiposity as the body is trying to reach a homeostatic level during inflammation[9].

As mentioned earlier, IL-6 has a pro and anti-inflammatory effect on inflammation. IL-6 is released by multiple mediators including mast cells, macrophages, and neutrophils[2]. Mast cells are immature immune cells that circulate within the blood stream until they reach the area of inflammation[2]. Residential cells within the damaged tissue are the first to sense and mediate an

inflammatory response[7]. Residential cells include macrophages, mast cells, and dendritic cells[7]. These cells mature in the localized tissue when activated during the inflammatory response. It is here that mast cell function can vary depending on the tissue requiring action. Vasoactive peptides such as substance p help to degranulate mast cells[9]. These vasoactive peptides can be released during episodes of severe muscle wasting or protein break down also known as a malnourished status[9].

NUTRITIONAL STATUS AND INFLAMMATION

Nutritional status is fundamentally the assessment of nutrient levels, diet, and how well the body is able to metabolically function[18, 19, 20]. Many studies have linked decreased nutritional status (at risk of malnutrition and malnutrition) to worsening chronic disease symptoms and increased mortality [3,4, 5, 18]. Malnutrition incorporates both under and over-nutrition and is considered a contributor to poor consequences in serious disease[21]. Poor nutritional status has been shown to have an effect on specific inflammatory diseases, specifically rheumatoid arthritis (RA), inflammatory bowel diseases such as ulcerative colitis (UC) and Crohn's disease (CD), systemic lupus erythematosus (SLE), atherosclerosis, chronic obstructive pulmonary disease (COPD), obesity, and sepsis.

Nutrition and inflammation incorporates many factors other than the risk of malnutrition or malnutrition status. There is also cachexia to consider which is common in systemic inflammation[21]. Cachexia is wasting of the body due to increased catabolism due to chronic

illness, this can have severe consequences on the ability of the body to fight inflammation[21]. Cachexia has been associated with having an effect on metabolic balance: "insulin resistance, increased lipolysis, increased lipid oxidation, increased protein turnover, and loss of body fat and muscle[21]." A majority of what cachexia effects contributes to inflammatory processes that are most likely already occurring[21].

Obesity, can be considered an inflammatory disease due to the over active adipose tissue creating an inflammatory cascade, which has been discussed earlier [7,13]. Obesity and malnutrition is common across the globe[21]. Obesity alone is associated with increased risk factors such as hypertension, Type II diabetes, cardiovascular disease, dyslipidemia, coronary heart disease, and respiratory disorders[22]. Obesity combined with malnutrition in critical care patents has been seen to change the outcomes of mortality in patients who suffer from sepsis, kidney injury, end stage renal disease, and acute organ failure [22]. Robinson et al. noted, in obese patients, in critical illness without malnutrition, there has been a shielding response from inflammation, however, when malnutrition is added to the formula, there is increased mortality[22]. This is interesting because it questions the inflammatory effect of the excess adipose tissue during adequate nutritional status and critical illness. This is a clear indicator that poor nutritional status may have an effect on inflammation.

One must also consider the effect of a poor diet on inflammatory processes because food can have an impact on the inflammatory response [23]. Poor diet, also known as the Western-style diet, in this paper reflects the consumption of refined or processed carbohydrates, increased saturated fatty acids, increased trans fatty acids, high omega (ω) -3/omega (ω)- 6 ratios, and absent in fruits and vegetables that contain flavonoids, carotenoids, and fiber [24]. When there are

increased refined carbohydrates in the diet, there is a spike in blood sugar and insulin which can lead to hyperglycemia[25]. According to Giugliano, this increased need for glucose metabolism leads to a large release of free radicals[25]. These free radicals can cause oxidative stress known to produce damage within the tissues and activates transcription factors, which in turn activate pro-inflammatory cytokines [25,26]. When there are increased saturated fatty acids in the diet, increased TLR-4 activation on the adipose tissue occurs[24,27]. TLR-4 then activates nuclear factor κB which is a part of cytokine regulation, production, and main molecular activator of inflammation[24,28]. This additionally leads to inflammatory events[24].

Trans fatty acids have been associated with increased levels of TNF receptor 1 and 2 [24,29]. Lopez et al., also identified a positive correlation with intake of saturated and trans fatty acids and TNF, along with decreased endothelial function[29]. The decreased endothelial function is related to symptoms of atherosclerosis, another inflammatory disorder[29]. A single meal with high number and poor quality of fat can influence the acute inflammatory response[29]. This was seen in the review done by Margioris, which separated factors that influence the inflammatory response relative to diet into nutrient dependent and independent. This is shown below in Table 3. The ω-3/ω-6 ratio of 1:7 as seen in the Mediterranean diet has been seen to reduce 9% of cardiovascular mortality, 6% of cancer related cases, and 13% reduction in the incidence of Parkinson's and Alzheimer's[24].

Table 3. Factors that Influence Postprandial Inflammation[23]	
Nutrient Independent	**Nutrient Dependent**
Obesity	Caloric Value (of meal)
Sedentary lifestyle	Glycemic Index
Diabetes mellitus	Lipid Profile (of meal) or processed carbohydrates

Fruits and vegetables have shown to have an inverse correlation to CRP levels as evidenced by Galland[24]. When fruits and vegetables have been added to the dietary regimen of individuals not accustom to eating fruits and vegetables, over a 6-week period, there was a significant decrease in the levels of CRP[24].

Rheumatoid Arthritis (RA)

RA is known to be a chronic, autoimmune, systemic inflammatory disorder that does not only attack the joints but different body systems as well[30]. There have been several studies that have related adequate intake to improving nutritional status of RA patients and other studies that have disproven this conclusion [19,20,31,32]. A cross sectional observational study done by Hejazi et al. recently assessed dietary intake and disease activity in Iranian women with RA[19]. Ninety women who suffer from RA were randomly recruited between the ages of 20-70. Randomly

selected individuals who suffered from other diseases such as diabetes, nephrotic syndrome, liver disease, gastrointestinal disorders and Cushing's syndrome, or were prescribed β-blockers, oral contraceptives and angiotensin converting enzyme inhibitors drugs were excluded from the study. The results showed a positive correlation between activity of RA and malnutrition based on CRP and food frequency questionaires[19].

In the RA patient population, muscle wasting and body mass loss is very common [19]. According to Rall et.al, this has been theorized to occur due to the overproduction of TNF-α and IL-1 during inflammation[33]. When the muscle is lost in RA patients, the space is taken up by adipose tissue, thereby making anthropometric data unusable to correlate with nutritional status because they gain more fat mass. Limitations of the Hejazi et al. study include the lack of use of a bio impedance analysis to determine anthropometric changes as well as the location of the study. During the examinations in the Hejazi et al study, the patient disease activity score, global assessment of pain using visual analog scale, and CRP were tested[19]. The other tests also taken were fasting blood glucose, serum antioxidant total, malondialdehyde concentration and dietary recalls were used to assess nutritional status[19].

The results of the Hejzai et al. study showed a negative association between the disease activity and caloric intake, but there was no statistical significance[19]. Of the patient population studied 24% of the women suffered from malnutrition and inflammation defined by Hejazi et. al as a low serum albumin level below 3.4 g/dl, decreased caloric consumption evident by twenty-four-hour recall, and declining body composition values[19]. Of these women, there was a positive

correlation between malnutrition and disease severity. Based on Dietary Reference Intakes (DRI) calculated from the 24-hour recall food frequency questionnaire, the patients had inadequate intakes of calcium, folic acid, zinc, magnesium, and vitamin B6[19]. Decreased magnesium, B6, zinc, and folic acid been associated with increased inflammation and oxidative stress[124,34,35,36]. The medications the patients used may have an effect on the DRIs caused by increased catabolism and may have worsening effects on the inflammatory processes of RA. The following medications that may cause such an impact are corticosteroids, methotrexate, sulfasalazine, and $_{D}$-penicillamine[19]. The data from this study may have also been effected by decreased ambulation due to pain, therefore potentially causing decreased intake from patients with RA who were required to feed themselves.

Unfortunately, in the Hejazi et al. study there was not a healthy control group to compare the data to. The standard Iranian diet is very different to the Western diet and the deficiencies that occur in the Iranian diet. For instance, the nutrient deficiencies found in the Hejazi et al. study such as folic acid, are very unlikely to be seen deficient in the western diet because it is enriched in most processed foods. In the study conducted by Gómez and colleagues, individuals with class IV RA or end stage RA, showed no improvements in poor nutritional status even with adequate intake[20]. In the Gómez et al. study, there were only 18 individuals who had been evaluated based on stage 4 RA making it not relevant to a greater scale until it is evaluated on with more individuals[20].

Inflammatory Bowel Disorders (IBD)

Chronic inflammation within the gastrointestinal (GI) tract occurs in inflammatory bowel disorders such as Crohn's disease and ulcerative colitis (UC). Crohn's disease can affect any portion of the GI tract whereas UC imparts inflammation only to the lining of the colon[37]. Malnutrition is common in this population, making this a high risk population that can have nutritional deficiencies occur rapidly[38]. There is evidence that supports the link between nutritional status and inflammation from chronic disease [37,38].

An analytical cross sectional study completed by Kalantari and colleagues, evaluated the nutritional status of patients in Iran diagnosed with moderate to severe ulcerative colitis [38]. Over a five months' time, 99 patients were evaluated between the ages of 14 and 80. Patients with diseases such as diabetes or cancer were excluded from the study.

Body mass index, serum albumin, serum iron, hemoglobin, folic acid, vitamins A, B12, D and E vitamins, partial thromboplastin time, international normalized ratio, IgA, and minerals Ca, P, Mg, Zinc, Cu, K levels were evaluated as well as the severity of disease using the Montreal classification system. Study results showed (Table 4) that patients that were at increased risk for malnutrition had moderate to severe UC and were typically older. The malnourished diagnosis was given based on a nutritional risk index (NRI) that takes serum albumin and current or usual body weight in to account.

Patients with a calculated NRI of 83.5 to 97.4 were considered to be malnourished[38]. Patients who suffered from moderate to severe cases of UC had a statistically significant higher amount of serum potassium levels than those who had mild cases of UC. The significance of

this, is that it created a marker which indicated severe UC which often correlated with decreased nutritional status. This may relate to malnutrition however there is not enough data to support this claim. This study in particular had a small sample size of mild cases of UC and was not able to compare the data to healthy individuals. Inflammatory biomarkers were not taken in this study. However, there was evidence that connected severity of disease to increased malnutrition risk[38].

Table 4. Nutritional Risk and Patient age, disease duration, and ulcerative colitis status[38]

Variables	Nutritional Risk Index	
	Non Malnourished	Moderate to Severe Malnourished Risk
Age (years)	25.7 – 49.5	26.2 – 45.2
Disease duration (month)	3 – 10.4	3 -10
UC Mild	12 (100)	0
UC Moderate to Severe	78 (89.7)	9 (10.3)

In another study by Valentini et al., the nutritional status of 144 patients with CD and UC, who were classified to be in clinical remission, were assessed by typical nutritional status measures including subjective global assessment (SGA), BMI, serum albumin, trance elements, bioelectrical impedance analysis, and anthropometry as well as body composition analysis and muscle strength[39]. The study results reveals that most patients had been classified as well-

nourished based on lab values and body mass index. However, in all patients, body cell mass (BCM) and handgrip strength were decreased. The lower values for BCM and handgrip strength correlated with increased CRP levels. Since decreased BCM is associated with energy expenditure and metabolism, and CRP levels were elevated, this reflects the possible link between decreased nutritional status and inflammation[40].

In the same study by Valentini, it is interesting to note that in the patients that were identified to be malnourished in comparison to healthy counterparts, the body composition values of malnourished CD were different than the anthropometric values of UC[39]. Malnourished CD patients showed a decreased BMI and fat mass value, while the malnourished UC patients showed decreased BCM and increased CRP. This may be due to the small sample size of malnourished patients as only 23.7% of patients (n = 22) with CD were malnourished and 33.3% (n =16) of patients with UC were malnourished. This spurs the question of what causes those differences when these are both technically inflammatory diseases of the bowel?

According to the authors this was most likely due to increased malabsorption problems in CD whereas malnourished patients with UC showed greater deterioration of muscle function[39]. This is reflective in the data; CD showed decreased BMI values while UC showed decreased BCM[39]. Increased pro-inflammatory mediators in UC, such as IL-6 and CRP have been seen to cause sarcopenia in elderly individuals[21]. However, this was seen in patients between the ages of 18 through 70 years. This may be reflective of the lack of weight gained after weight loss in patients suffering from CD[41].

In another study by Reimund and associates, 40 participants (25 women and 15 men) with CD focused on the connection between the inflammatory properties of CD, nutritional status, and immune mediator cells including hemoglobin concentration, erythrocyte sedimentation rate (ESR), fibrinogen, α1-acylglycoprotein, blood neopterin, IL-2 receptors, TNF-α, and IL-1β[42]. These patients were compared to 26 healthy controls[42]. In this study disease severity and age varied with ages ranging between 12-33 years old. Reimund et al. determined patient nutritional status of nutritional risk or malnourished based on two abnormal values out of the three anthropometric parameters: body weight, triceps skinfold thickness (TSF), or arm muscle circumference (AMC). Table 5 reflects that patients with worsening symptoms of CD, anthropometric measurements decreased and had and increased percent of malnourished patients.

Table 5. Anthropometric Parameters from Reimund study[42]

	Controls	**CD (Whole group)**	**Discrete CD**	**Moderate CD**	**Severe CD**	**p[b]**
Weight	63.2	55.7	62.7	54.7	52.35	0.0007
TSF	1.5	0.93	1.48	0.91	0.63	0.0001
MAC	26.7	23.8	26.55	23.3	22.6	0.0001
2/3 Items	4/26	18/40	1/7	4/15	13/18	0.0006
BMI	21/6	19.75	21.8	19.8	18.5	0.003

Inflammatory biomarker data CRP, Prognostic Inflammatory Nutritional Index, and TNF-α also showed a positive correlation with severity of CD. (see Table 6). These numbers gradually increased as the disease severity worsened. Statistical results of multivariate analysis showed a statistically significant negative correlation between MAC, TSF, serum albumin, and transthyretin (TTR). This shows a possible relationship between inflammatory cytokines, hepatic transport proteins, and body composition. "Biochemical nutritional markers were positively linked to each other and to anthropometric parameters, with a strong correlation between Vitamin A on one hand, and TTR and retinol binding protein (RBP) on the other[42]."

These binding proteins are important contributors to maintain homeostasis in the body. When there are high levels of RBP, as seen in the Reimund et al. study (seeTable 6), these levels appear related to insulin resistance and hyperinflammation[42,43]. The cofactor Vitamin A has many functions, one of which involves immune regulation[44]. There is an interaction that occurs between inflammation, immune components, and hepatic transport proteins such as albumin, pre-albumin and RBP that are more influenced by the inflammatory response than nutritional status. Reimund and colleagues recommend that the clinical focus should be on modifying the patient's nutritional status by targeting nutritional deficiencies, protein energy malnutrition, and decreasing the inflammatory response[42].

Table 6. Biological Parameters in Reimund et al. study[42]

	Controls	***CD (Whole group)***	***Discrete CD***	***Moderate CD***	***Severe CD***	***P***
RBP	*47 (13)*	*38 (17)*	*41 (15)*	*39 (19)*	*32 (15)*	*0.0032**
Albumin	*46 (4)*	*35 (6)*	*42 (2.7)*	*37 (35)*	*30 (46)*	*0.0001**
IGF	*29 (11)*	*19 (6)*	*25 (5)*	*23 (6)*	*18 (6)*	*0.12*
Vitamin A	*0.7 (0.3)*	*0.4 (0.2)*	*0.7 (0.8)*	*0.5 (0.2)*	*0.4 (0.2)*	*0.09*
CRP	*5 (2)*	*28 (26)*	*5 (0.8)*	*27 (27)*	*57 (49)*	*0.0001**
Fibrinogen	*2.8 (0.8)*	*4.3 (1.5)*	*3.3 (1)*	*4 (0.9)*	*4.8 (1.4)*	*0.0001**
TNF-α	*7.7 (2.5)*	*15.2 (14.4)*	*7.1 (2.2)*	*9.8 (8.6)*	*19.2 (15)*	*0.0001**

**reflects statistical significance*

Nutritional Status and Systemic Lupus Erythematosus (SLE)

In all cases of SLE, multiple body systems are affected as SLE is a chronic autoimmune disorder where the body's own immune system attacks various organs; SLE can present differently depending on the patient. In some patients there are major anthropometric changes such as decreased body weight or changes in body composition due to anti-inflammatory drug intake[45]. This may also present in a SLE cachexic related way[45]. Many patients are treated with steroid medications to help decrease inflammation, but these can cause other nutritional deficiencies such as decreased calcium and magnesium. It is common for individuals who suffer

from SLE to have abnormal nutritional status such as inadequate intake, mild to severe malnutrition risk, or malnourished as seen in [45,46,47] studies.

SLE is an autoimmune inflammatory disease, the catabolism of pro-inflammatory cytokines and tissue lead to increased levels of oxidative stress within the body. Oxidative stress has been shown to affect the activity of SLE[48]. Poor nutritional status in a SLE patient does directly affect the oxidative stress in the body, therefore worsening symptoms of SLE[48]. This was shown in another study by Abou-Raya, the results showed that inflammation, stress, and nutritional status have an effect on SLE based on malondialdehyde serum levels and prostaglandin F2α[48]. Malondialdehyde serum levels are associated with oxidative stress and prostaglandin F2α levels are associated with inflammation response[48]. More studies need to be done in order to determine evidence linking poor nutritional status and inflammatory biomarkers in the SLE patient population.

Borges et al. evaluated the nutritional status and food intake in 170 ambulatory women between the ages of 18-60 with SLE patients cross-sectionally[46]. Nutritional status was determined using the SGA and BMI, while dietary intake was determined from food frequency questionnaires and 24-hour diet recalls. The results showed that 91% of the study participants were well nourished, however 62% of the women were either overweight or obese. An increased number of adipocytes can increase the inflammatory response by activating TLR-4 receptor sites which then activate NFκB that activate an inflammatory cascade[24,25]. This leads to worsening symptoms or comorbidities of dyslipidemia, cardiovascular disease, and insulin resistance[46]. Insulin resistance was not measured within the study.

Additionally, a diet high in saturated or trans fatty acids, oils that were unspecified, and deficient in fruit, vegetable, calcium, and iron was found in a majority of all patients [46]. Decreased iron intake has been associated with increased inflammation in obese patients [49]. It has also been previously noted in this paper that increased saturated and trans fat has a positive correlation with pro-inflammatory markers [24,27,29]. In the Borges et al. study, none of the patients consumed fruits and vegetables. This is interesting because fruits and vegetables are known to have an inverse correlation with the inflammatory markers CRP and IL-6 [24]. This means that increased fruit and vegetable intake may help lower inflammatory status. The decreased serum calcium value may be affected by medications, specifically with RA patients it is often associated with long term corticosteroid use[46]. The data may also be skewed because a large portion of the data was based on patient memory (food frequency questionnaires and 24-hour recalls) which may be less telling than actual serum values. According to Borges et al., there was no association of iron or B12 anemia with the decreased values in this study.

In another study by Noriega et al., anthropometric data such as BMI and nutritional status were assessed for 28 study participants[45]. Nutritional status was determined by SGA and NRI. Of these patients, 35% (n = 10) were considered to be at severe nutritional risk based on NRI[45]. The study did not go in to detail about the results of the SGA scores which would have helped to determine if the SLE patients where adequately nourished, moderately malnourished, or severely malnourished. The study investigators determined from this small study that hospital risk increased for patients with a moderate to high NRI number. A limitation of this study is that the anthropometric and SGA data were not given in order to determine a correlation between NRI

and SGA. In a similar study by Abou-Raya et al. who evaluated the association between SLE disease severity, nutritional status, and compared disease/nutrition outcome related to diet. In this study, 121 patient's nutritional status was assessed using BMI data and the SGA. Dietary intake was assessed using food frequency quesitionaires[47]. Study results showed that a majority of the cohort were overweight and most diets were lacking in fruits, vegetables, and dairy products[47] while most diets were high in fat and oil based foods. Patients with SLE have severe pain which may lead some individuals to eat more high inflammatory comfort food rather than healthy fruits and vegetables[47].

Atherosclerosis

Atherosclerosis is the buildup of plaque made up of foam cells and macrophages within the arteries[50]. This plaque formation occurs from various factors including genetics and lifestyle choices such as diet and exercise[50]. As the plaque continues to build up, the artery lumen becomes smaller and smaller, restricting oxygenated blood flow to the extremities[50]. At the core of atherosclerosis is inflammation[50]. The initial attractor of foam cells and macrophages is thought to be lymphocytes and macrophages[50]. Atherosclerosis has been linked to higher levels of inflammatory biomarkers such as acute phase proteins, TNF-α, CRP, and serum amyloid A[50]. There is also a connection with obesity and atherosclerosis and inflammatory biomarkers. Increased energy intake and saturated fats, which then turns into fat is stored as fat, raises total

cholesterol and LDL-C levels within the bloodstream, which creates an inflammatory atmosphere[50].

People with atherosclerosis are generally overweight or obese, this was shown in the study by Jarosz et al.[51]. This study evaluated the effect of weight on nutritional status in patients who have been diagnosed with atherosclerosis. Less than two percent of the group studied, which were of Polish descent, were underweight based on BMI and arm circumference. The other 98% were overweight and obese. This study did not give a standard measure of unit to determine malnourished status; malnourishment in this study was based on biochemical data such as lymphocyte count and serum albumin[51]. These labs are markers of inflammation not nutritional status. Based on anthropometric data, a very small percentage of patients were considered to be adequately nourished according to Jarosz et al. The results of the Jarosz et al. study showed the overweight and obese patients lost weight, had deficient serum albumin values, and the male population studied were found to have a decreased erythrocyte and leukocyte count. The data given from the Jarosz et al. study did not identify any changes in dietary intake. This study did not give a standard measure of unit to determine malnourished status and malnourishment in this study was based on biochemical data lymphocyte count and albumin[51].

There is another evaluation tool for measuring nutritional status and it is called the CONUT score which stands for controlling nutritional status[3]. This number is calculated based on serum albumin, lymphocyte count, and total cholesterol. This ties in factors from immune response, calorie depletion, and protein intake. The CONUT score has been demonstrated to be a useful predictor of risk assessment in cancer and cardiovascular diseases [3,52]. This is a different

way to measure nutritional status because it reduces the significance of the serum albumin value[52]. This is beneficial because serum albumin levels can be affected by factors other than nutritional status, such as fluid status, liver damage, and infection[52]. When poor nutritional status and cardiovascular disease meet, the CONUT score, TNF-α, and length of prognosis help to determine patient outcomes as evident in the study by Nakagomi et al.[3].

Table 7. Nakagomi Study Results[3]

	Univariate			Multivariate		
	Hazard Ratio (HR)	**95% Confidence Interval (C.I)**	***P* value**	**HR**	**95% C.I**	***P* value**
CONUT	44.55	10.76- 184.37	<0.001	11.97	2.21-64.67	0.004
CRP	15.27	5.99 -38.50	<0.001	2.12	0.51-8.88	0.304
AGE ≥ 70	3.26	1.73 -6.14	<0.001	1.69	0.44-6.45	0.442
Monocyte TNF-α	29.46	9.10-95.32	<0.001	14.10	2.55-77.92	0.002
BMI ≤ 21 kg/m^2	7.07	3.56-14.04	<0.001	1.41	0.42-4.75	0.584

Researchers found a positive correlation between TNF-α, CRP, and CONUT score as Cardiac Heart Failure progressed[3]. Out of the 114 participants, a low CONUT score equaled poor outcomes such as a repeat cardiac event, cardiac failure leading to death, and worsening symptoms[3]. Fat loss and muscle wasting from cardiac cachexia, seen in this study are linked to inflammatory pathways including the catabolizing pro-inflammatory mediators include TNF-α, IL-6, and IL-1[3]. These are all seen in high ratios in patients with CHF that have cardiac cachexia

or malnourished status thus again reflecting a possible link between inflammatory status and nutritional status.

Carotid intima-media thickness (CIMT) was measured in the study by Nakagomi et. al[3]. The CIMT was compared with the inflammatory values CRP and TNF-α. These figures showed a positive correlation, while serum albumin was negatively correlated with CIMT. As the CIMT numbers increased, this was paralleled by inflammatory biomarkers. The CONUT score, that was used to determine nutritional status was also shown to be related to the CIMT. This is helpful to target the pathophysiology of atherosclerosis and identify future treatments for atherosclerosis and CHF, since atherosclerosis is often an early indicator of CHF[3]. There may also be a connection between inflammation and hunger as in the Nakagomi study, ghrelin and leptin levels were abnormal possibly because of the high ratio of TNF-α.

In instances of cardiac cachexia, ghrelin has been shown to have an effect on inflammation particularly in studies of CHF patients[53]. In the study by Dixit et al., pro-inflammatory cytokines were inhibited by ghrelin and these patients did not suffer from cardiac cachexia[53]. Whereas in another case, several pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α have been indicated in increasing the symptoms of cardiac cachexia[53,54]. This may indicate that without ghrelin inflammation may increase. Cytokines such as IL-1, IL-6, and TNF have been indicated to alter the GI system in various ways. For example, a change in stomach content movement, an altercation in the release of appetite stimulating hormones that include cholecystokinin, leptin, and insulin from the gut mucosa[55].

Chronic Obstructive Pulmonary Disease (COPD)

COPD is an inflammatory disease that not only effects all parts of the lung, can also effect blood pH, heart, and, skeletal muscle[56]. There are increased pro-inflammatory mediators that are seen in this disease[56]. Nutrition is also a concern because often COPD patients have difficulty maintaining a healthy weight due to the high inflammatory state forcing the body into a catabolic status[57]. Not only that, but COPD patients are often short of breath and fatigue easily making day to day activities difficult to achieve[56,58]. In hospitalized patients, poor nutritional status and high inflammatory biochemical values may be an indicator for increased risk for mortality.

Table 8. COPD Mortality Patient Data[58]

	Survived (n=212)	**Died (n=49)**	**P**
BMI	19.3 - 30.4	17.1 - 28.3	0.0007
Age	56 - 80	63 - 81	0.0005
Women	54	43	0.03
Current Smokers	25	29	0.39
Diabetes	9	16	0.03
Cardiovascular Disease	43	50	0.18
Living Alone	53	51	0.74

One study predicted that patients who were underweight at the time of admission to the hospital have an increased risk of mortality within the next two years, unlike patients who are overweight[58]. Hallin et al. and colleagues studied 261 participants in the Nordic countries (Denmark, Norway, Sweden, and Finland) to examine whether a relationship existed between weight and mortality[58]. The participants involved were recently admitted to the hospital for an acute exacerbation and they all suffered from stage 1 or higher of COPD based on the global initiative for chronic obstructive disease (GOLD) scale. BMI, spirometry, psychological status, and quality of life were also assessed. Out of the participants, 19% died within two years.

Table. 9 Risk Factors for mortality in Hallin et al. study[58]

	Hazard Risk Ratio	**95% Confidence Interval**	**P**
BMI <20 kg/m^2	12.9	2.8-59	0.001
BMI 20-25 kg/m^2	6.5	1.5-28	0.01
BMI 25-30 kg/m^2	1		
BMI >30 kg/m^2	7.7	1.5-40	0.02
Women	0.60	0.31-1.18	0.14
FEV_1 per 10% predicted	0.85	0.67-1.08	0.19
Diabetes	4.2	1.7-10	0.002

The reasons for death were grouped together by the researchers in the following categories: respiratory causes, respiratory insufficiency and pneumonia, cardiovascular diseases,

heart failure, stroke and rupture of aortic aneurysms, malignancy, lymphoma, and others[58]. The patients who passed away had a significant negative correlation between BMI reflective of being underweight and decreased Forced Expiratory Volume in 1 second. The majority of patients who had died, had a BMI of 22.7 ± 5.6 as shown in Table 8. This shows that individuals who had a decreased lung capacity were also underweight and died within two years. People with the lowest death rate were individuals who were overweight. This is interesting because one would think that the increased adipocytes would increase systemic inflammation and force more body catabolism rather than increase survival rate. The disadvantages to this study are the differences between the diets and lifestyles of people who live in Nordic countries, nutritional status was not accounted for, and a small population sample making it difficult to relate it to the western population. It is unclear based on the data given if the patients were continuously losing weight or if they remained underweight for the duration of the study.

However, in another study by Coxson et. al., chronically malnourished patients were studied to determine if any connection may exist between poor nutritional and pulmonary emphysema[59]. This was a small study that only consisted of only 21 patients who suffered from anorexia-nervosa and were compared to healthy individuals that were similar in age and sex. The participants were evaluated based on BMI, smoking history, hemoglobin, white blood differential cell count, serum α1-antitrypsin, spirometry, total lung capacity, residual volume, and CT scans of the aortic arch, the tracheal carina, posterior aspect of the eighth rib, and lung anatomy. The results of the study showed that there was a correlation between BMI and diffusing capacity of the lungs for carbon monoxide (Dl_{CO}).

Table 10. Reression Analysis for Coxson et al. study[59]						
	Mean CT Density			Volume of Gas per Weight of Lung Tissue (mL gas/ g tissue)		
	r	p	r	p	r	p
BMI (kg/m^2)	0.59	<0.001	-0.60	<0.001	0.60	<0.001
DL_{CO}/ VA (%PcorrHGB)	0.20	0.24	-0.27	0.11	0.17	0.33
FEV_1,% P	0.22	0.20	-0.19	0.26	0.22	0.19
FVC, %P	0.32	0.06	-0.31	0.06	0.32	0.06
FEV_1/ FVC	-0.32	0.05	0.36	0.03	-0.30	0.07
TLC, %P	0.21	0.21	-0.20	0.25	0.23	0.18

There was notable tissue loss as the BMI decreased in the anorexic participants. This study's findings are supported by another study done by Pieters et.al in which 24 anorexic women were evaluated by carbon monoxide diffusion capacity[60]. There are other more general reasons why this may have occurred in the anorexic patients. The decrease in lung tissue may have arisen because there is less oxygen required to oxygenate the body. Also, the Coxson et al. study it was difficult to determine if the tissue destruction transpired because of emphysema. The weight of the participants was only measured at the beginning of the study. It is unknown if the participants weight remained stable. Emphysema cannot be diagnosed without a tissue sample

and Coxson et.al only utilized the data from CT scans to determine destroyed lung tissue[59]. However, with decreased nutritional status participants did show decreased tissue and mass loss. Unfortunately, in the study by Coxson, inflammatory markers were not taken to compare with declining nutritional status[59].

However, in another study, Arora et al., set out to determine if a correlation existed between inflammatory status, nutritional status, and severity of COPD[61]. Sixty-six patients with COPD considered to be stable according to GOLD were enrolled with the following outcome measures analyzed: CRP, leptin, and pre-albumin levels, BMI, mid upper arm circumference (MUAC), skin fold thickness, and 6-minute walk test. The patients were grouped into three categories: moderate COPD, severe COPD, and very severe COPD based on FEV1 results. As the severity of COPD increased the following values decreased: BMI, leptin, pre-albumin, MUAC, and walk test. Furthermore, a positive correlation with disease severity and CRP levels was found. These values indicate that as COPD becomes more severe nutritional status declines and inflammation increases[61]. There is evidence that certain dietary factors within fruits and vegetables consistent with a healthy diet have potential beneficial characteristics for people who suffer from COPD[62]. A cross sectional study done over the period of 25 years, on 12,763 men showed improved FEV1 values in the group of men who had increased fruit, vegetable, and fish intake in comparison to a normal diet[62]. Based on the study, it is uncertain what a normal diet consisted of, however it had less fruit and vegetable intake.

Table. 11 Tabar et al. COPD Results[63]

131 patients with COPD studied		
	r	p
BMI	-0.3873	0.000
MAC	-0.2555	0.0039
Malnourished patients likely to have ≥1 exacerbations	0.7041	0.000

In some cases, as nutritional status declines there is an increase in COPD exacerbations[63]. This is evident in the cross-sectional study of 131 patients done by Tabar et al.[63]. Patients who had at least one exacerbation per year were typically of poor nutritional status, while patients who were adequately nourished didn't have any exacerbations[63]. Patients who suffer from COPD and most likely have a decline in nutritional status will lose lean muscle tissue[63]. This will take a toll on physical capacity as well. This is important to know because in some cases, where poor nutritional status is not evident via SGA or other measures, physical capacity helped to determine declining nutritional status[63]. This physical deterioration was correlated with increased CRP levels. There is a link between lung function, nutritional status, systemic inflammation, and physical capacity as seen in the cross sectional study done by Hallin et al.[64].

TREATMENT

Anti-Inflammatory Diet

The Anti-inflammatory (AI) diet is designed to silence inflammatory genes that may be activated through diet[28]. As mentioned earlier in the paper, highly processed refined carbohydrates, high fat, and excess calorie consumption can increase internal inflammatory properties[28]. The particular molecular targets of the AI diet are AMP kinase and NF-κB[28]. The AI diet consists of carbohydrate to protein to fat ratio of 40:30:30[28]. This ratio is alleged to aid in insulin and glycemic control[28]. The omega 3 and 6 polyunsaturated fatty acids (PUFA) play a large role in the activation or deactivation of inflammatory properties and eicosanoid development[28]. The omega 6 PUFA, also known as linoleic acid, can be broken down into arachidonic acid which is the main component of eicosanoids leading to cellular inflammation[28]. The omega 3 PUFA has eicosapentaenoic acid (EPA) or docosahexanenoic acid (DHA) which are both anti-inflammatory[28]. The AI diet also incorporates the importance of a varied diet consistent in non-starchy vegetables containing polyphenols such as asparagus, lettuce, broccoli, and cucumber[28]. Polyphenols are known for their chronic disease prevention properties[65]. Polyphenols are involved in biologic mechanisms that involve anti-inflammatory pathways such as COX-1 and COX-2 inhibition, nitrous oxide synthase, NF-κB, and cytokine production[65].

Table 12. Anti-Inflammatory Diet Summary[28]

Carbs : Protein : Fat Ratio	*40:30:30 with caloric restriction*
Omega 3 PUFA	*Increase*

Omega 6 PUFA	*Decrease*
Molecular Targets	*NF-$_K$B , AMP Kinase*
Focus	*Decrease omega 6 FA and stabilize Insulin*
Eicosapentaenoic Acid (EPA) Docosahexaenoic Acid (DHA)	*2-3 g supplementation*
Non-Starchy Vegetables	*Increase*

It is important to identify the factors that can activate NF-κB because the AI diet is supposed to inhibit NF-κB activity[28]. According to Marimotto et al. and Calder oxidative stress and hormones can activate the NF-κB inflammatory switch [65,66]. Oxidative stress may come from excess energy consumption or an increase in adipocyte tissue[28]. "Additional dietary factors include saturated fatty acids, advanced glycosylated end products (AGE), and inflammatory cytokines from nearby cells all acting through specific receptors at the cell surface can also activate NF-κB[28]."

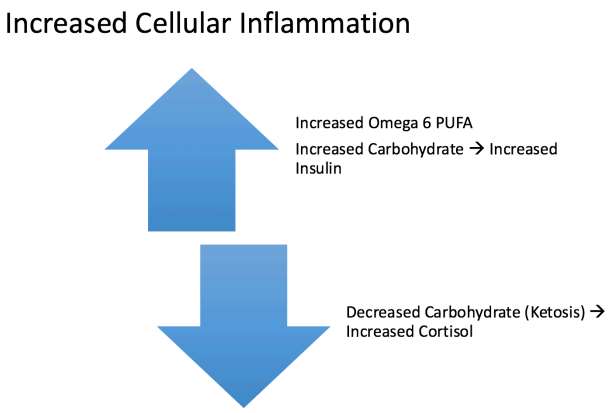
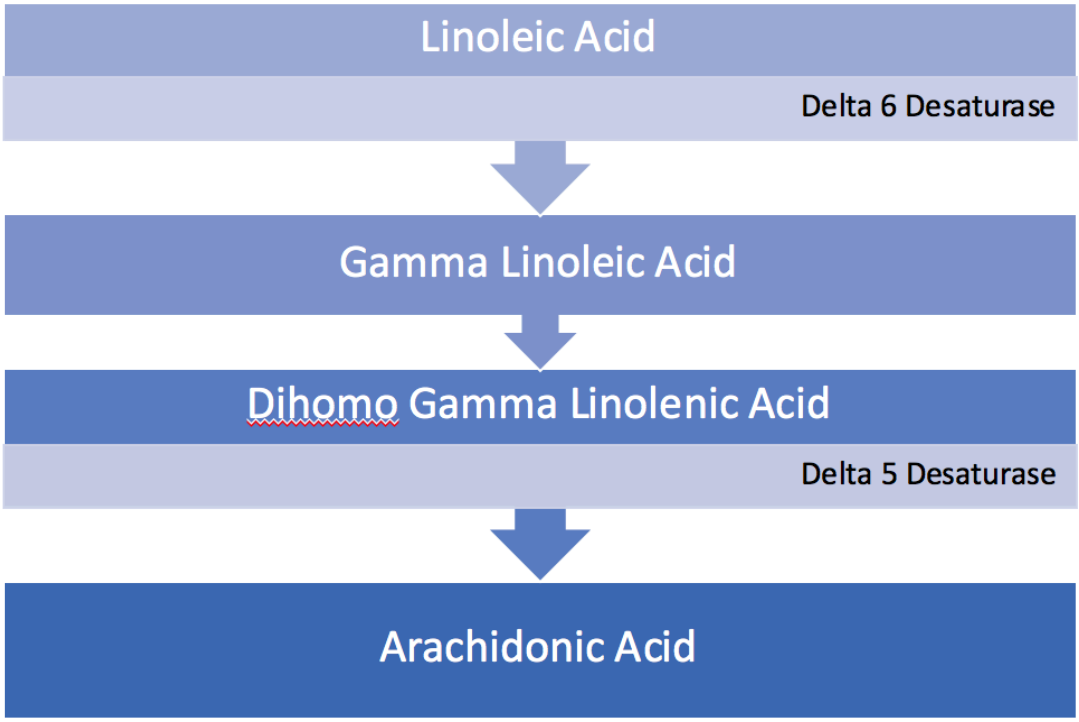


Figure 2. Contributors to Cellular Inflammation [28]

Nuclear factor kappa B is inhibited by polyphenols[28]. The polyphenols found within vegetable and fruit coloring activate the transcription factor PPAR-γ and this inhibits NF-κB. Polyphenols also play a role in the activation of AMP kinase. AMP kinase plays a large role in glucose metabolism and energy regulation[28].

The arachidonic acid can have an impact on the cellular inflammation within the body[28]. The Arachidonic acid (AA) to EPA ratio is actually considered to be a more telling indicator of inflammation than CRP values according to Dr. Sears, the current leader of anti-inflammation dietary research[28]. The typical Western diet contains over 12 times the amount of AA to EPA recommended[28]. This means that there are more omega 6 components within the diet that can be broken down by the enzymes delta 6 desaturase and delta 5 desaturase to become AA. This is shown in Figure. 3. The enzymes in the reaction to convert linoleic acid to AA are influenced by the glycemic load of the meal. The greater the influx of glucose, causing a rise in insulin, the greater the amount of AA will be produced[28]. With increased AA intake, which is pro-inflammatory, an increased intake of EPA is required to even out the inflammatory imbalance[28].

The EPA helps increase the dietary potential of anti-inflammation[28].



There are some areas in which there is clinical evidence that supports the use of the anti-inflammatory diet to aid in treatment. In the study done by Adam et al., 68 patients with RA were split into separate groups; one group consumed an anti-inflammatory diet, another consumed an anti-inflammatory diet with fish oil pills, and the last group consumed a Western diet[67]. The results showed a decrease in inflammation in both of the AI diet groups, while the group that also consumed dietary fish oil showed a greater decrease in inflammation, nearly double at the cellular level. This was made evident by the EPA erythrocyte lipid percentage and decreased leukotriene B_4 levels[67]. Based on the data given from the Adam et al. study there is no indication of how well the patients followed the AI diet on a daily basis[67].

In another study, the AI diet was tested on 40 individuals who struggled with IBD. The results were not nearly as conclusive as the RA study because only eleven consistently remained on the diet for four weeks as evident by diet history journals[68]. All eleven patients had results that led to the decreased intake of an IBD medication which according to Olendzki et al., indicated decreased inflammation[68]. There were not any CRP or inflammatory lab values to base decreased inflammation as a result of the AI diet. More research is required to identify the clinical effectiveness of the AI diet on IBD. Typically, most IBD patients have an individualistic diet regimen due to the individuality of the microbiota living within the gut[69].

Mediterranean Diet

The Mediterranean diet is a form of anti-inflammatory diet that incorporates greater fat intake, up to 40% of total kcals, emphasizes the importance of omega-3 fatty acids, and oleic acid[70]. This is gained through increased fish intake, virgin olive oil use, legumes, complex carbohydrates, wine, feta cheese, yogurt, and decreased red meat intake[70]. Virgin olive oil is a staple in the Mediterranean diet. It is the main fat used to cook with and often used as the dressing or dipping sauce for bread, salad, and pasta[71]. Virgin olive oil contains alpha-tocopherol and phenols unlike processed olive oil that has been stripped of the healthier components[72]. Supplementation of alpha-tocopherol has been related to decreasing oxidative stress and inflammatory lab markers such as LDL, F_2- isoprostanes, TNF, and CRP[72]. The Mediterranean diet leads to high levels of beta-carotene, vitamins B6, B12, C and E, and polyphenols because of

its reliance on fresh fruit and vegetable intake[70]. According to Chrysohoou et al., the Mediterranean diet has shown beneficial effects on blood pressure, BMI, and platelet aggregation due to its ability to help increase high density lipoprotein (HDL) levels and lower total triglyceride amounts[70].

The Mediterranean diet is highly recommended for individuals who are at high risk of cardiovascular disease by the American Stroke Association due to its anti-inflammatory properties[73]. There was a Mediterranean diet trial of 7,447 high risk cardiovascular patients who were grouped into a nut supplemented Mediterranean diet and an olive oil supplemented Mediterranean diet groups[73]. The risk of stroke for the first group went from 5.0 to 3.1 per 1000 persons per year. The second group did not show as great of a decrease, coming in at 4.3 per 1000 persons per year, however, this was still a beneficial change[73]. This is interesting to note because the monounsaturated fat of the olive oil is a big component of the Mediterranean diet. Based on the current research, one would think the greater decrease of stroke risk would have come from the group who supplemented their diet with olive oil. The Women's Health initiative studied the effect of a low fat diet with increased fruit and vegetable intake, increased whole grains, and the results did not show any reduction of stroke risk[73]. This makes an evident point that fat makes a difference on one's overall health risk potential, giving rise to the Mediterranean diet which not only incorporates fat, but incorporates monounsaturated fatty acids and omega-3's[73].

The Mediterranean diet has also been shown to be beneficial to individuals who are obese or diagnosed with metabolic disorders such as diabetes[74]. In a Spanish cohort of 41,440 subjects, men and women were studied over the period of three years, to understand the benefits of the

Mediterranean diet[75]. Anthropometric data such as BMI, were measured once at the beginning and then was reported by subjects at the end of the study. The results showed that people who remained on the Mediterranean diet the best, had the lowest incidence of obesity[75]. The decreased inflammatory properties of the inflammatory diet including beta-carotene, vitamins B6, B12, C and E, and omega 3's help to decrease the inflammatory environment of the patients with diabetes and metabolic disorders, by decreasing weight and producing a more immune protective environment[75].

Dietary Approaches to Stop Hypertension (DASH) Diet

The DASH diet is another recommended treatment or lifestyle change for individuals who are suffering from atherosclerosis, diabetes, hypertension, hyperlipidemia, hyperglycemia, and obesity[76]. The DASH diet utilizes many of the components of the anti-inflammatory diet to provide a protective effect against increasing obesity and metabolic disorders[76]. The main components to the DASH diet are decreased sodium intake of <2,400 mg/d, low glycemic index meals, calorie restricted, low fat dairy products, low in cholesterol, and low in saturated fats[77]. There is also a focus on particular nutrients such as potassium, magnesium, and calcium because of their known benefits to help with cardiovascular function[76]. "The DASH diet's beneficial effects are not limited to decreasing blood pressure and some studies have reported significant improvements in insulin sensitivity, inflammation, oxidative stress, and recognized cardiovascular risk factors including concentrations of fasting glucose and total cholesterol[76,78,79]."

In a randomized cross over design, 44 Type II diabetic patients were placed on an 8-week long control or DASH diet[78]. The differences between the two diets were the amount of PUFA and emphasis of low fat dairy products in the DASH diet. After 8 weeks the participants who were on the DASH diet showed decreases in liver enzymes: alanine aminotransferase, aspartate aminotransferase, decreased fibrinogen, and decreased CRP values[78]. The DASH diet decreased participant CRP values an average of 26.9 units[78]. In comparison to the control diet, which decreased the CRP values 5.1 units. This indicates there is an anti-inflammatory component to the DASH diet that may be beneficial for individuals who are diagnosed with a chronic inflammatory disease.

CONCLUSION

The impact of poor nutritional status on the above chronic inflammatory diseases is evident to increase the inflammatory biomarkers of the disease and lead to increased mortality. Inflammation is a necessary aspect of the body response that is reflective of immune response and health. However, when the body becomes fixed in the resolution phase chronic inflammation occurs. Chronic inflammation is a complex issue that incorporates damage from the cellular level to the buildup of fatty tissue caused by lack of daily movement. Chronic inflammation is a series of reactions that can contribute to a multitude of problems that become a cycle that the body never quite adapts to and is in a constant battle to reach homeostasis. The diseases associated with chronic inflammation are atherosclerosis, obesity, systemic lupus erythematosus, COPD, CD, UC, RA, and cancer. The inflammatory origins of all of these diseases may be different, but

the overall consequence of inflammation remains the same. More research is needed to identify the specific cellular components and how/why they work. There are mechanisms within inflammation that are still not fully understood that may lead to better treatment plans in the future.

In all of the mentioned diets, a consistent component in all of them is the incorporation of fruits, vegetables, and weight loss. Weight loss overall has been shown to reduce fasting blood glucose, total cholesterol, triglycerides, LDL, TNF-α, and IL-8 concentrations[80]. These are all aspects that decrease inflammation. Particularly in people who have created an inflammatory state within their bodies be excessive caloric intake. The goal of treatment would not only to focus on weight loss but also to maintain the weight loss over the course of the life time to maintain a healthier status. This is most notable of the Mediterranean diet as evidenced by the Spanish cohort mentioned previously in the paper. Author's stated the satiety and flavor was increased because of the additional fat[75].

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