The Effect of Whole Diet on Inflammation: A Close Look at How C-reactive protein Levels are Affected

William Joshu
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Abstract

Background: Research has shown that increased levels of C-reactive protein (CRP) are found in patients with heart disease, diabetes, and Alzheimer disease. In fact, some studies demonstrate that CRP may even have causal effects. The purpose of this systematic review is to look at the effects of whole diet on serum CRP levels. By simply changing what foods we eat, or what foods we don’t eat, is it possible to reduce our risk of these diseases?

Method: An exhaustive search of available medical literature was conducted using Medline-OVID, CINAHL, and Google Scholar using the keywords: C-reactive protein, diet, food habits, inflammation, anti-inflammatory, and cytokines. Inclusion and exclusion criteria were applied. The bibliographies of the articles were further searched for relevant sources. Relevant articles were assessed for quality using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE).

Results: Six studies met inclusion criteria and were included in this systematic review. A randomized, single blinded-controlled trial with 180 patients with metabolic syndrome demonstrated a statically significant drop in CRP levels in participants who were instructed to eat a Mediterranean-style diet compared to the control group. A second randomized study with 66 patients with moderate to severe rheumatoid arthritis (RA) demonstrated that patients who ate a gluten-free, vegan diet had statistically lower CRP levels than individuals who ate a non-vegan diet. A cross-sectional study of 732 women demonstrated that women who ate a more “prudent” diet compared to a more “western” one had statistically significant lower levels of CRP. A second cross-sectional study of 3042 men and women demonstrated that a greater adherence to a Mediterranean diet showed statistically significant decreases in serum CRP levels. A third cross-sectional study of 5089 patients demonstrated that levels of CRP were positively associated with consumption of fats and processed meats and inversely associated with ingestion of whole grains and fruit. An interventional study with 24 participants with moderate to severe RA demonstrated that there was no statistically significant drop in CRP levels in participants who consumed a very low-fat, vegan diet.

Conclusion: Serum levels of CRP appear to have a correlation to diet. A recommendation can be made to put all patients on a Mediterranean style diet regardless of health status, as it is a simple, low-cost, self-administered, and safe intervention. Furthermore, it can be recommended that patients with RA be placed on a vegan diet. Another consideration is if patients with RA are non-compliant with a vegan diet, then a recommendation that they try a Mediterranean style diet is reasonable.

Degree Type
Capstone Project

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Keywords
C-reactive protein, diet, heart disease, diabetes, Alzheimer disease
Subject Categories
Medicine and Health Sciences

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A Clinical Graduate Project Submitted to the Faculty of the School of Physician Assistant Studies Pacific University Hillsboro, OR

For the Masters of Science Degree, August 10, 201
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**Conclusion:** Serum levels of CRP appear to have a correlation to diet. A recommendation can be made to put all patients on a Mediterranean style diet regardless of health status, as it is a simple, low-cost, self-administered, and safe intervention. Furthermore, it can be recommended that patients with RA be placed on a vegan diet. Another consideration is if patients with RA are non-compliant with a vegan diet, then a recommendation that they try a Mediterranean style diet is reasonable.

**Keywords:** C-reactive protein, diet, heart disease, diabetes, Alzheimer disease
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List of Abbreviations

CRP   C-reactive protein
RA   Rheumatoid arthritis
DM     Diabetes mellitus
AD     Alzheimer disease
IL-6   Interleukin-6
MI     Myocardial infarction
CVA   Cerebrovascular accident
CHD   Coronary heart disease
BMI   Body mass index
MESA Multi-ethnic study of atherosclerosis
sE-selectin Soluble E-selectin
LDL   Low density lipoprotein
HDL   High density lipoprotein
TG     Triglycerides
BP     Blood pressure
TNF   Tumor necrosis factor
HTN   Hypertension
ESR   Erythrocyte sedimentation rate
WHO   World Health Organization
FFQ   Food frequency questionnaire
The Effect of Whole Diet on Inflammation: A Close Look at How C-reactive protein Levels are Affected

BACKGROUND

Currently heart disease is the leading cause of death in the United States, killing about 600,000 people yearly. As of 2004, the World Health Organization (WHO) estimated that 347 million people worldwide were suffering from diabetes mellitus (DM) and projected that deaths related to diabetes would increase by two thirds between 2008 and 2030. There are currently 5.4 million Americans suffering with Alzheimer disease (AD). AD is the sixth leading cause of death in the United States, and, currently, there are no known ways to prevent, slow, or cure AD.

Current research is showing the importance of biomarkers of inflammation, mainly C-reactive protein (CRP), in connection with both heart disease and type II DM. The role of CRP is to help activate the complement system (part of the innate immune system). CRP is an acute phase plasma protein, synthesized by the liver, which is evidenced by several hundredfold increases in response to tissue injury. This extreme production by the liver gives credence to the importance of CRP’s role in the body’s response to injury. Similarly, a lack of CRP in the body at times of health indirectly indicates this same principle. CRP is most commonly used to monitor progress and response to therapy in patients with conditions such as infection and inflammatory disease. One reason that CRP is so widely used is that levels do not seem to be influenced by the body’s natural circadian rhythm. Also, CRP is easily and accurately measured in a laboratory and is easy for clinicians to get results.

One study found that elevated levels of CRP help predict the development of type II DM even after adjustment for obesity, clinical risk factors, and fasting insulin levels. In that
same study, interleukin 6 (IL-6) was also found to be a predictor of developing type II DM but in lower magnitude. While some studies\textsuperscript{9,10} have shown a positive correlation between obesity and elevated levels of CRP, other studies\textsuperscript{11,12} have found that CRP levels remain a predictor of developing type II DM independent of obesity, which suggests an independent role in CRP in the developing of type II DM.

Furthermore, inflammation plays a key role in the development of atherosclerotic disease.\textsuperscript{13,14} In particular, inflammation plays a key role in the pathogenesis and evolution of the atheroma in atherosclerosis, but also in the disruption of the atherosclerotic plaque, which can lead to a myocardial infarction (MI), cerebrovascular accident (CVA), stroke, angina, or gangrene.\textsuperscript{13,15}

In addition to an increased risk for type II DM and coronary heart disease (CHD), elevated CRP levels are now beginning to show neurochemical changes linked to the development of cognitive impairment later in life even evidenced in some middle-aged adults who are cognitively intact.\textsuperscript{16} Another study\textsuperscript{17} showed that decreases in executive functioning, including psychomotor speed and attention, were associated with elevated levels of CRP, but that memory and linguistic skills were not associated with the elevated levels. In addition to CRP, elevated levels of interleukin-6 (IL-6) have been shown to have negative effects on cognitive function.\textsuperscript{18} Studies\textsuperscript{19,20} also have shown a that patients with AD have increased levels of inflammatory biomarkers, including IL-6, in serum and cerebrospinal fluid (CSF).

In a time in which more people are suffering and dying from CHD, DM, and cognitive decline, research continues to look at possible causes, and diet may have an important role. A practitioner's goal should be to prevent these debilitating illnesses. With these markers of inflammation being linked to type II DM, CHD, and cognitive decline, what
can be done? The purpose of this review is to look at the effects of the food we eat in correlation with levels of CRP.

METHODS

An exhaustive search of available medical literature was conducted using Medline-OVID, CINAHL, and Google Scholar using the keywords: C-Reactive protein, diet, inflammation, anti-inflammatory, and cytokines. The search was then narrowed to include only English language articles and studies performed only on humans. Articles were included only if they examined whole diet, not individual components of diet, and articles must have diet as the central component of intervention. Articles were excluded if they did not evaluate levels of CRP or if they demanded monetary compensation in order to obtain them. The bibliographies of articles were further searched for relevant sources. Relevant articles were assessed for quality using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE).

RESULTS

Six studies met inclusion criteria and were included in this systematic review including: two randomized control trials, three observations studies, and one interventional study. (See Figure 1)

Esposito et al

In this randomized control trial, investigators assessed the effects of the Mediterranean diet on endothelial function and vascular inflammatory markers in patients with metabolic syndrome.

In total 220 participants were assessed for eligibility. After inclusion and exclusion criteria were applied, 180 participants were randomized using a computer-generated random number sequence. Allocation was concealed in sealed study folders that were held in a
central, secured location until after informed consent was obtained. Staff members who were involved in the intervention group were not blinded, thus the study was partially blinded. The laboratory staff members were blinded. In order to be included in the study, participants had to meet three of the following five criteria: abdominal adiposity (waist circumference >102 cm in men or >88 cm in women), low levels of serum high-density lipoprotein cholesterol (<40mg/dL in men or <50mg/dL in women), hypertriglyceridemia (triglycerides levels of 150mg/dL or greater), elevated blood pressure (130/85 or greater), and impaired glucose homeostasis (fasting plasma glucose concentrations of 100mg/dL or greater). Participants were excluded if they had history of CVD, psychiatric problems, alcohol abuse, smoking, or if they took any medication.22

Investigators randomly assigned the 180 participants into either the control or the interventional diet group. At the beginning of the trial, both groups were prognostically balanced. The interventional diet group, the group following the Mediterranean style diet, was given education on how to reduce dietary calories, goal setting, and self-monitoring using food diaries. Dietary advice was also provided. Participants in the interventional group were instructed to eat the following: 50-60% carbohydrates, 15-20% protein, total fat, <30%, saturated fat <10%, cholesterol consumption, <300mg/day, consume 250-300 g of fruit/day, 125-150 g of vegetables/day, 25-50 g of walnuts/day, 400 g of whole grains/day, and increase how much olive oil they consumed daily. Participants in the control diet were given oral and written information about healthy food choices. The control diet consisted of: 50-60% carbohydrates, 15-20% protein, and total fat <30%. Participants in both groups had monthly follow-ups for the first year and bimonthly meetings in the second year. Compliance
was measured by how often participants attended the meetings. All participants were encouraged to increase their level of physical activity. The study lasted 24 months.\textsuperscript{22}

Blood was collected at baseline. Endothelial function was assessed using L-arginin test. Investigators measured the following inflammatory biomarkers: hs-CRP, IL-6, IL-7, and IL-18.\textsuperscript{22}

At the conclusion of the 24 months, sixteen participants, 8 from the interventional group and 8 from the control group, had dropped out. Participants in the interventional diet group had decreased body weight, BMI, blood pressure (BP), glucose levels, total cholesterol, and triglycerides. Also, participants in the interventional group had statistically significantly decreased IL-6, IL-7, IL-18, and hs-CRP when compared to the control group. Of the original 90 participants in the interventional group, only 40 could be classified as still having metabolic syndrome at the conclusion of the study. Conversely, 78 participants in the control group, at the conclusion of the 24-month study, could still be classified as having metabolic syndrome. This calculates to a relative risk of 0.51 and a number-needed-to-treat of 3.\textsuperscript{22}

The only limitation of this study discussed by the authors was whether individual components of the diet account for the results or if the results are due to the diet as a whole.\textsuperscript{22}

\textbf{Elkan et al}

In this randomized control trial,\textsuperscript{23} investigators measured the effects of a vegan diet in patients with RA, on blood lipids, oxidized low-density lipoprotein (oxLDL), and natural atheroprotective antibodies against phosphorylcholine (anti-PCs). Participants were invited to enroll in the studies if they were between 20-69 years old, had RA for 2-10 years, had never tried dietary intervention, and had active disease. Participants were excluded if they
had a current malignancy; CV, pulmonary, or renal disease; and DM. In total, 66 patients were admitted into the study. Patients who were on anti-inflammatory, oral glucocorticoids, or anti-rheumatic medications were allowed to continue. At the start of the trial, the two groups were not prognostically balanced. The vegan group had a total of 30 participants, of which 18 were on glucocorticoids. However, out of the 28 patients in the non-vegan group, only nine were on glucocorticoids.

Patients were randomly assigned to either a gluten-free vegan diet or a non-vegan diet. The study lasted 1 year. Thirty-eight patients were entered into the gluten-free vegan diet, which consisted of 10% protein, 60% carbohydrates, and 30% fats. It contained vegetables, nuts, and fruit, and no animal products. Twenty-eight patients were assigned to the non-vegan diet. This diet was described as 10-15% protein, 55-60% carbohydrates, and saturated fat was limited to <10%. Five or more daily servings of fruits and vegetables were suggested while increasing starch and complex, whole-grain carbohydrates when possible. Each group received instructions and education pertaining to their corresponding diet. Follow-ups for each group took place at 3, 6, 9, and 12 months. Blood samples were collected at baseline, 3 months, and at 1 year. ESR, CRP, hemoglobin, WBC, serum albumin, total cholesterol, low density lipoprotein (LDL), high density lipoprotein (HDL), and triglycerides (TG) were measured. Disease activity was assessed using the Disease Activity Score in 28 joints (DAS28).²³

Of the 38 participants who started in the gluten-free, vegan diet, 30 completed three months with an additional 8 dropping out before the completion of the 12-month study. All twenty-eight participants in the non-vegan diet completed at least three months. Results showed that the participants in the vegan group lost more weight (p<.001) and reduced their
BMI (p<.001). The non-vegan group also lost weight and reduced their BMI but both reductions were seen as non-significant changes. CRP levels in the vegan group dropped dramatically from baseline to 12 months (p=.008). CRP levels did also decrease in the non-vegan group, but it was not seen as significant (p=.28).23

One limitation, as discussed by the authors, was the small number of participants (n=66). Second limitation discussed was compliance. Compliance was monitored by regularly scheduled follow-ups and dietary records. Third limitation was allowing the changes in anti-rheumatic medication during the trial (two patients in the vegan group and one in the non-vegan group started anti-rheumatic therapy during the study period), but was determined too limited to have an impact on the results.23

Lopez-Garcia et al

In this cross-sectional study,24 the investigators examined different diets on markers of inflammation and endothelial dysfunction. The subjects of the study were from the Nurses’ Health Study cohort. The trial enrolled 732 women who met the following eligibility criteria: free from coronary vascular disease (CVD), cancer, or DM.24

In 1986 and 1990, a food frequency questionnaire (FFQ) was mailed to all the participants. The FFQ included questions on 116 food items, and quantified portions using natural portions or standard weight and volume. For each food item, participants were asked to indicate the how often they consumed the food over the past year by checking frequency categories, nine total choices, which ranged from “almost never” to “>= 6 times/day.” The selected frequency category for each food item was converted to a value in number of servings per day. Certain considerations were taken for particular single food items such as, but not limited to, pizza, soup, coffee, and eggs. Calculations of averages of food were done
in 1986 and 1990. Investigators also assessed cigarette smoking, body weight, body mass index (BMI), and physical activity.\textsuperscript{24}

Blood was collected between 1989-1990. For collection, participants were sent home phlebotomy kits in order to provide the sample. Of these samples, 97\% were returned to investigators within 26 hours of being drawn. Samples were centrifuged and kept frozen with liquid nitrogen until analysis. The following markers were measured: CRP, IL-6, E-selectin, soluble intracellular adhesion molecule-1 (sICAM-1), and soluble vascular cell adhesion molecule-1 (sVCAM-1).\textsuperscript{24}

Based on FFQ, investigators found two major dietary patterns. Pattern 1 was called the prudent pattern. This pattern was characterized by higher intake of fruits, legumes, vegetables, whole grains, fish, and poultry. Pattern 2 was called the Western pattern. This pattern was characterized by a higher intake of red meat, processed meat, refined grains, sweets, desserts, French fries, and high-fat dairy products. Each pattern was further broken down into quintiles, ranging from 1 to 5. Participants in quintile 5 were said to have the strictest adherence to the respected pattern.\textsuperscript{24}

Investigators found that age-adjusted CRP levels and E-selectin levels decreased with increasing quintile of the prudent patterns. (See Table 5) On the other hand, CRP, IL-6, E-selectin, sICAM-1, and sVCAM-1 showed increasing trends with increasing quintiles of the Western pattern. The same was true even after adjustment for BMI, physical activity, smoking status, and average alcohol consumption. Within the prudent pattern group, subjects in the highest quintile were more physically active, smoked less, had lower intake of saturated fat and trans fatty acids with higher intake in polyunsaturated fat, folate, and fiber when compared to subjects in the lowest quintile. Within the Western pattern group, subjects
in the highest quintile when compared to the lowest quintile had higher BMI, were more likely to smoke, less likely to exercise, had higher intake of saturated fats and trans fatty acids with lower intakes of folate and fiber.\textsuperscript{24}

One limitation, as discussed by the authors, was the study design being cross-sectional, which means that they cannot infer causality. Second limitation was the degree of error in the measurement of food consumption; however, the authors claim that the use of repeated measurement enabled them to reduce within-person random error. The third limitation was the factor analysis approach involved several arbitrary decisions. The final limitation discussed by the authors was that the study population, mostly white, highly educated women from the United States of America does not accurately reflect the general population.\textsuperscript{24}

**Nettleton et al**

In this cross-sectional study,\textsuperscript{25} investigators looked at the relations between dietary patterns and biochemical markers of inflammation and endothelial activation. Participants in the study were taken from the Multi-Ethnic Study of Atherosclerosis (MESA). There were 5089 total participants included from the MESA study in line with the following exclusion criteria: those currently taking oral steroids or currently taking anti-inflammatory asthma medication, those with DM, and those who did not provide sufficient and plausible dietary information.\textsuperscript{25}

Investigators measured the following markers: CRP, IL-6, homocysteine, sICAM-1, and s E-selectin. Samples were collected at baseline, were stored and all processed in the same way, and were analyzed using the same machines.\textsuperscript{25}
Diet assessment of the previous year was done at baseline using a 120-item FFQ that included food and beverages. Serving size was recorded using the terms “small,” “medium,” and “large.” Frequency of consumption was also recorded using averages per day, week, or month. Frequency options ranged from “rare or never” to “/>=2 times/day” for foods and “/>=6 times/day” for beverages. In total, 630 participants were excluded due to unreliable dietary data.25

Investigators formed 47 food groups based on questions from the FFQ on the basis of similar nutrient characteristics or hypothesized biologic effects. Investigators also collected data on demographics, education, medications, smoking history, and physical activity. Height, weight, waist circumference, and BMI were also collected.25

Four main dietary patterns were discerned. Dietary patterns were named according to the most dominant food groups in each of the 4 factor patterns.

1 Pattern 1: fats and processed meats (greatest amount of “fats and oils,” “high-fat and processed meats,” “fried potatoes,” “salty snacks,” and “desserts.”)

2 Pattern 2: vegetables and fish (greatest amount of various vegetable groups (“dark-yellow,” “cruciferous,” “other vegetables”), “fish,” and “soups.”)

3 Pattern 3: beans, tomatoes, and refined grains (greatest amounts of “legumes,” “tomatoes,” “refined bread, rice, and pasta,” “high-fat cheeses and cheese and cream sauces,” and “avocados and guacamole.”)

4 Pattern 4: whole grains and fruit (greatest amount of “whole-grain bread, rice, and pasta,” “fruit,” “seeds, nuts, and peanut butter,” “green leafy vegetables,” and “low-fat milk”).25
Investigators discovered that concentrations of CRP, IL-6, and homocysteine were positively associated with the fats and processed meats pattern and inversely associated with the whole grains and fruit pattern. Also, Pattern 2 (vegetables and fish) was inversely related to IL-6. The relation between the dietary pattern and CRP remained true after adjustment for waist circumference.25

One limitation discussed by the authors was the assumptions that were made when constructing the food groups e.g. mixed food dishes and soups. Another limitation was the way in which information was collected from participants, the food frequency questionnaires. The authors’ acknowledged that is was very subjective, but thought that by using food groups it helped reduced subjectability.25

**ATTICA Study**

In this cross-sectional study,26 investigators evaluated the effects of a Mediterranean diet on plasma levels of CRP, white blood cell count, IL-6, tumor necrosis factor (TNF)-alpha, amyloid A, fibrinogen, and homocysteine. The study was conducted in Attica, a province in Greece. The time frame was from May 2001 to December 2002, and included 3042 participants, which were randomly selected. Exclusion criteria included: history of CVD, atherosclerotic disease, chronic viral infections, an active cold or flu, acute respiratory infections, dental problems, or any surgery in the past week.26

Each participant’s diet was evaluated using an FFQ, which measured daily or weekly intake of food items. The following is what the researchers considered the Mediterranean diet: daily consumption of non-refined cereals and products, fruits (4-6 servings/d), vegetables (2-3 servings/d), olive oil, and non-fat or low-fat dairy products (1-2 servings/d); weekly consumption of fish, poultry, potatoes, olives, pulses, nuts (4-6 servings/week), eggs,
sweets (1-3 servings/week), red meat and meat products (4-5 servings/month); moderate consumption of red wine (1-2 glasses/day); moderate fat consumption; and a high monounsaturated to saturated fat ratio.26

Using the Mediterranean pattern described, researchers calculated each participant’s Mediterranean diet score. This score is a number between 0-55 that represents the participant’s adherence or non-adherence to the diet. The higher the number, the more adherent the participant was. In addition to diet, researchers also gathered information on annual income, education level, smoking status, and physical activity. Blood samples were collected and processed and analyzed in similar manners.26

Researchers found that participants who were in the highest tertile of the diet score (diet score between 36-55) had, on average, 20% lower CRP, 17% lower IL-6, 15% lower homocysteine, 14% lower white blood cell counts, and 6% lower fibrinogen levels when compared to those in the lowest tertile. This was still true even after adjusting for age, gender, smoking, physical activity, financial and education status, BMI, hypertension (HTN), DM, hypercholesterolemia, family history or CHD.26

One limitation of the study, as discussed by the authors, was misreporting of food items consumed, especially alcohol consumption. Another limitation was that the researchers did not complete the dietary analysis for each nutrient component.26

McDougall et al

In this single-blinded dietary intervention study,27 the researchers evaluated the effects of a very low-fat, vegan diet on patients with RA. The study included 24 participants all with either moderate or severe arthritis and was conducted over 4 weeks. None of the participants were on a vegan or dairy-free diet prior to beginning the study, all were on stable
doses of medication, and all were free of CVD, DM, HTN, cancer and other serious chronic
diseases.  

At baseline, blood was collected, and a rheumatologist assigned each patient a
composite score based on joint swelling and tenderness by examining each participant. The
lower the score the less severe the joint involvement. Laboratory test included: CRP,
erythrocyte sedimentation rate (ESR), and RA factor.  

Each participant’s dietary intake was evaluated using a 4-day record and a weekly
food-monitoring checklist. A dietitian provided guidance to each participant. Each week, for
4 weeks, a meeting was held to teach the participants about a low-fat, vegan diet. The diet
contained no animal products (milk, meat, cheese, eggs, etc.) or added oils and fats. Menus
and recipes were provided to each patient and assistance with shopping and meal planning
was given.  

At the conclusion of the study, blood was collected again, and ESR, CRP, and RA
factor were again measured. Investigators found that there was no significant change in CRP
levels. Baseline CRP was 2.08 +/- 1.8 mg/dL. At the conclusion of the 4 weeks study, CRP
levels were 1.74 +/- 1.7 mg/dL p>0.05. ESR remained unchanged, and the RA factor showed
a non-significant change. Despite no laboratory evidence, investigators did find that
participants had a decrease in pain, joint tenderness, swelling, and morning stiffness and an
increase in functionality.  

The only limitation discussed by the authors was the lack of a control group.

DISCUSSION

Current research is showing the importance of inflammatory biomarkers, mainly
CRP, in connection with both heart disease and type II DM. Elevated CRP levels are also
beginning to show neurochemical changes linked to the development of cognitive impairment later in life. This systematic review shows a relationship between diet and increased levels of CRP, which may play a promising role in decreasing the incidence of certain chronic diseases.

Two studies\(^\text{26,27}\) have shown, with consistency, that patients on a Mediterranean diet have statistically lower CRP levels compared to patients not on a Mediterranean diet. This was true for patients who were in good health,\(^\text{26}\) as well as those with metabolic syndrome.\(^\text{22}\) One study\(^\text{22}\) found a significant drop in the number of patients with metabolic syndrome after two years on the Mediterranean diet with a number-needed-to-treat (NNT) of 3. (See Esposito et al\(^\text{22}\) in Table 2 and Table 3.) In addition, individuals who consumed diets with higher intakes of fruits, vegetables, legumes, whole grains, fish, and poultry had significantly lower CRP levels compared to individuals to eat diets high in red meat, processed meat, refined grains, sweets, desserts, French fries, and high-fat dairy products.\(^\text{24,25}\) (See Table 4 and 5.)

The use of a vegan diet to decrease CRP levels and symptomatology in RA patients was evaluated by two different studies.\(^\text{23,27}\) The first study\(^\text{23}\) showed that a gluten-free, vegan diet was also shown to have statistically lower CRP levels compared to individuals on a non-vegan diet. In the same study, investigators also proved that a gluten-free, vegan diet lowered BMI, low density lipoprotein (LDL), and increased natural atheroprotective antibodies against phosphorylcholine (anti-PCs) compared to the non-vegan group in which anti-PCs decreased. Conversely, the second study\(^\text{27}\) showed that while there was a decrease in CRP levels in patients who ate a very low-fat, vegan diet that these levels were not statistically significant (See Elkan et al\(^\text{23}\) and McDougall et al\(^\text{27}\) in Table 2).
There are two reasons why these studies may have yielded different results. The first may be partially due to the limitations of the Elkan et al study, in which groups were not prognosically balanced at the start of the trial. The vegan group had a total of 30 participants, of which 18 were on glucocorticoids. However, out of the 28 patients in the non-vegan group, only nine were on glucocorticoids. And the second, in the McDougall et al study which did not show a statistically significant decrease in CRP at the conclusion of the trial, was the short duration of the trial, four weeks. Important to note that although CRP levels did not change, patients on the very low-fat, vegan diet did experience reduction in RA symptoms. Patients saw statistically significant reductions in pain, limitations of functionality, joint tenderness, joint swelling, and morning stiffness in both trials.

In addition to CRP, other markers of inflammation and endothelial dysfunction such E-selectin, IL-6, sICAM-1, sVCAM-1, WBC, fibrinogen, and homocysteine were also evaluated. Also, total cholesterol was measured. The Mediterranean diet and diets high in fruits, vegetables, whole grains, legumes, fish and poultry were associated with lower levels of E-selectin, IL-6, sICAM, sVCAM, and homocysteine. The Mediterranean diet was also associated with lower levels of fibrinogen and WBC count. The Mediterranean, vegan diets, and diets high in fruits, vegetables, whole grains, legumes, fish and poultry were associated were associated with significantly decreased cholesterol.

**Limitations of the Studies**

Limitations of all studies were reviewed and summarized. (See Table 1). To begin, the randomized control trial, Esposito et al had very few limitations. There is a concern for the difficulty of compliance to a diet, such as the Mediterranean diet, but this is a common
issue for any dietary intervention. There was a good sample size, 180 participants, and appropriate randomization. The two groups were prognostically balanced. Proper blinding was maintained, concealment was done, and loss to follow-up was 9% (n=16, 8 from the intervention group and 8 from the control group). A larger population in both groups would have been preferred. No areas for risk of bias could be theorized; therefore this study is of high quality.

The randomized controlled trial Elkan et al study\textsuperscript{23} had only 38 patients assigned to vegan diet group and 28 patients assigned to the non-vegan diet control group. Loss to follow-up was significant, which was evidenced by 42% of the patients in the vegan diet group dropping out before the conclusion of the trial. There was no loss to follow-up in the control group. At the start of the trial, groups were not prognostically balanced at the beginning of the trial in regards to patients using glucocorticoids. The vegan group contained 60% (n=18) of participants were on glucocorticoids at the start of the trial compared to 32% (n=9) in the non-vegan group. This was despite the use of randomization.

All three cross-sectional studies\textsuperscript{24-26} were all limited due to the respected researchers use of FFQ’s. Through the use of FFQ’s, all the studies were highly vulnerable to recall bias. In addition to recall bias, the use of FFQ’s allows the researchers flexibility when it comes to interpretations of certain food items, e.g. mixed dishes. Although the Lopez-Garcia et al\textsuperscript{24} was conducted over 4 years, researchers failed to measure serum CRP levels at the beginning of the trial, choosing to only collect samples at the conclusion. This trial\textsuperscript{24} also failed to screen patients for current medication use, which may have resulted in biased results.

The McDougall et al study\textsuperscript{27} was a single-blinded interventional study. The first limitation was the extremely small population (n=24). Compliance was high, as evidenced by
22 of the 24 participants completing the four-week trial. A larger study population would be preferred, as would a longer trial length. The use of a control group would also be preferred.

The quality of each study was assessed utilizing the GRADE assessment tool. (See Table 1.) Esposito et al\textsuperscript{22} was of high quality while all the other studies were downgraded to very low\textsuperscript{23-27} due to the limitations identified. Overall, the quality of evidence is a low. Further research examining the role of diet on serum levels of CRP, as well as other biomarkers of inflammation, are needed. The use of blinded, randomized control trials is preferred. Food frequency questionnaires should not be used due to the likelihood of recall bias. Steps should be taken to minimize issues with compliance such as frequent follow-ups and education. Further research is needed to determine the exact role of CRP in CHD, DM, AD, and cognitive decline.

CONCLUSION

Though overall GRADE for this systematic review was low to very low, a recommendation can still be made to put all patients on a Mediterranean style diet regardless of health status as it is a simple, low-cost, self-administered, and safe intervention. This is especially important for patients with metabolic syndrome or any patient at-risk for CHD or type II DM. Placing a patient on a Mediterranean style diet will not only help with cholesterol levels but may also be beneficial to in decreasing cognitive decline later in life. Furthermore, it can be recommended that patients with RA be placed on a vegan diet. Another consideration is if patients with RA are non-compliant with a vegan diet, then a recommendation that they try a Mediterranean style diet is reasonable. Since dietary changes falls under the category of preventative medicine, future research is likely and hopeful, as the link between inflammation and chronic disease needs to be more established.
References


6. The Phenomenon of the Acute Phase Reactant


17. Wersching, H., Dunning, T., Deppe, M., Knecht, S., Lohmann, H., Mohammadi, S.,
et al. (2010). Serum C-reactive protein is linked to cerebral microstructural integrity and cognitive function. *Neurology, 74*(13), 1022-1029.


Table 1

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Limitations</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Inconsistency</th>
<th>Publication bias likely</th>
<th>Quality</th>
<th>Importance</th>
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<tbody>
<tr>
<td>Circulating Levels of CRP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Esposito et al²²</td>
<td>RCT</td>
<td>No serious limitations</td>
<td>No serious indirectness</td>
<td>No serious imprecision</td>
<td>No serious inconsistencies</td>
<td>No bias likely</td>
<td>High</td>
<td>Important</td>
</tr>
<tr>
<td>Elkan et al²³</td>
<td>RCT</td>
<td>Very Serious limitations²⁴</td>
<td>No serious indirectness</td>
<td>Serious imprecision²⁵</td>
<td>No serious inconsistencies</td>
<td>No bias likely</td>
<td>Very low</td>
<td>Important</td>
</tr>
<tr>
<td>Lopez-Garcia et al²⁴</td>
<td>Cross Sectional</td>
<td>Serious limitations²⁶</td>
<td>Very serious indirectness²⁷</td>
<td>No serious imprecision</td>
<td>No serious inconsistencies</td>
<td>No bias likely</td>
<td>Very Low</td>
<td>Important</td>
</tr>
<tr>
<td>Nettleton et al²⁵</td>
<td>Cross-sectional</td>
<td>Serious limitations²⁸</td>
<td>No serious indirectness</td>
<td>No serious imprecision</td>
<td>No serious inconsistencies</td>
<td>No bias likely</td>
<td>Very low</td>
<td>Important</td>
</tr>
<tr>
<td>Chrysohoou et al²⁶</td>
<td>Cross Sectional</td>
<td>Serious limitations²⁹</td>
<td>No serious indirectness</td>
<td>No serious imprecision</td>
<td>No serious inconsistencies</td>
<td>No bias likely</td>
<td>Very low</td>
<td>Important</td>
</tr>
<tr>
<td>McDougal et al²⁷</td>
<td>Interventional</td>
<td>Very Serious limitations³⁰</td>
<td>No serious indirectness</td>
<td>No serious imprecision</td>
<td>No serious inconsistencies</td>
<td>No bias likely</td>
<td>Very Low</td>
<td>Important</td>
</tr>
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</table>

² Groups were not prognostically balanced at start of trial. The vegan group contained 60% (n=18) of participants were on glucocorticoids at the start of the trial compared to 32% (n=9) in the non-vegan group.
³ Significant loss to volume up (42% in the vegan group) and small sample size (n=66)
²⁴ Study design is vulnerable due to high probability recall bias. Food frequency questionnaires are subjective and allow researchers flexibility with interpretation.
²⁵Serum CRP levels were not measured at baseline. Subjects were not screened for current medication use.
²⁶ Study design is vulnerable due to high probability recall bias. Food frequency questionnaires are subjective and allow researchers flexibility with interpretation.
²⁷Study design is vulnerable due to high probability recall bias. Food frequency questionnaires are subjective and allow researchers flexibility with interpretation.
²⁸ Very low sample size (n=25) and lack of control group
### Table 2

Circulation levels of C-Reactive Protein (CRP)

<table>
<thead>
<tr>
<th>Study</th>
<th>Baseline</th>
<th>4 weeks</th>
<th>3 months</th>
<th>12 months</th>
<th>24 months</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elkan et al&lt;sup&gt;1&lt;/sup&gt;</td>
<td>13 (6-26)</td>
<td>-</td>
<td>11 (5-29)</td>
<td>5 (4-20)</td>
<td>-</td>
<td>.008</td>
</tr>
<tr>
<td>Elkan et al&lt;sup&gt;2&lt;/sup&gt;</td>
<td>22 (5-32)</td>
<td>-</td>
<td>10 (5-33)</td>
<td>12 (4-19)</td>
<td>-</td>
<td>.28</td>
</tr>
<tr>
<td>Esposito et al&lt;sup&gt;1&lt;/sup&gt;</td>
<td>2.8 (.7-5.4)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1.7 (.04-4.9)</td>
<td>.01</td>
</tr>
<tr>
<td>Esposito et al&lt;sup&gt;2&lt;/sup&gt;</td>
<td>2.9 (.5-5.7)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2.8 (.5-5.5)</td>
<td>.12</td>
</tr>
<tr>
<td>McDougall et al&lt;sup&gt;1&lt;/sup&gt;</td>
<td>2.08 +/- 1.8</td>
<td>1.74 +/- 1.7</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>&gt;.05</td>
</tr>
</tbody>
</table>

<sup>H</sup>Vegan diet patients  
<sup>K</sup>Control diet patients  
<sup>1</sup>Non vegan diet patients  
<sup>I</sup>Interventional diet patients  
<sup>L</sup>All patients

### Table 3

Circulating levels of CRP by Tertile of the Mediterranean Diet Score<sup>26</sup>

<table>
<thead>
<tr>
<th>Biomarker of inflammation</th>
<th>1&lt;sup&gt;st&lt;/sup&gt; (0-20)</th>
<th>2&lt;sup&gt;nd&lt;/sup&gt; (21-35)</th>
<th>3&lt;sup&gt;rd&lt;/sup&gt; (36-55)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP</td>
<td>2.0 +/- 1.8</td>
<td>1.8 +/- 2.1</td>
<td>1.6 +/- 1.5</td>
<td>.01</td>
</tr>
</tbody>
</table>

### Table 4

Circulating Levels of CRP across quintiles (Q) of dietary pattern scores<sup>25</sup>

<table>
<thead>
<tr>
<th>Factor</th>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
<th>Q5</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1: Fats and processed meats</td>
<td>1.52 +/- 1.04</td>
<td>1.71 +/- 1.04</td>
<td>1.81 +/- 1.04</td>
<td>1.99 +/- 1.04</td>
<td>2.02 +/- 1.05</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>2: Vegetables and fish</td>
<td>1.75 +/- 1.04</td>
<td>1.90 +/- 1.04</td>
<td>1.82 +/- 1.04</td>
<td>1.81 +/- 1.04</td>
<td>1.73 +/- 1.04</td>
<td>.31</td>
</tr>
<tr>
<td>3: Beans, tomatoes, and refined grains</td>
<td>1.70 +/- 1.04</td>
<td>1.74 +/- 1.04</td>
<td>1.80 +/- 1.04</td>
<td>1.93 +/- 1.04</td>
<td>1.84 +/- 1.04</td>
<td>.09</td>
</tr>
<tr>
<td>4: Whole grains and fruit</td>
<td>1.96 +/- 1.04</td>
<td>1.99 +/- 1.04</td>
<td>1.80 +/- 1.04</td>
<td>1.74 +/- 1.04</td>
<td>1.55 +/- 1.04</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>