Research Project

The effects of a Mediterranean diet, low-carbohydrate diet, and very-low-carbohydrate diet on c-reactive protein levels

Submitted by

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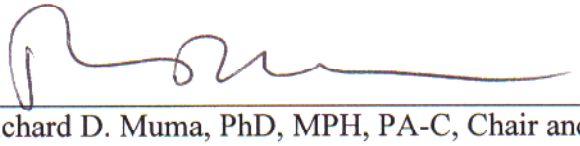
We hereby recommend that the research project prepared under our supervision by Jacqueline A. Stanley entitled The effects of a Mediterranean, low-carbohydrate diet, and very-low-carbohydrate diet on c-reactive protein levels be accepted as partial fulfillment for the degree of Master of Physician Assistant.

Approved:



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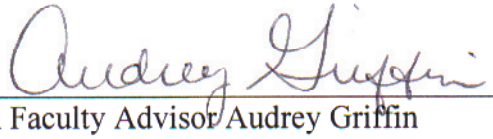

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Introduction: Obesity is associated with high plasma c-reactive proten (CRP) levels, an independent risk factor for cardiovascular disease. The Mediterranean diet (MD), low-carbohydrate diets (LCD), and very-low-carbohydrate diets (VLCD) are gaining popularity and have been studied for their effects on CRP. **Purpose:** The goal of this study is to compare the effects of the MD, LCD, and VLCD on CRP levels. **Method:** A systematic evidence-based literature review was conducted comparing these diets. Medline, PubMed, and FirstSearch databases were searched using the MeSH terms c-reactive protein, low-carbohydrate diet, Mediterranean diet, ketogenic diet, and inflammatory markers. **Results:** Twelve studies examined either of the three diets and their effects on CRP. Each diet has similar effects on CRP in obese individuals. Four studies examined the MD while the other eight a LCD or VLCD. Half of the articles for the MD showed significant decrease in CRP whereas the other half revealed no significant change in CRP. Four LCD and two VLCD articles showed significant reduction in CRP while one LCD and one VLCD study revealed no change. **Conclusion:** An A grade of recommendation can be made that all three diets effectively lower CRP levels when weight loss is observed. Healthy individuals with normal BMI do not achieve a reduction in CRP with adherence to these three diets.

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Introduction

Obesity is on the rise in the United States population, and severe obesity is commonly associated with high plasma c-reactive protein levels[1]. Adipose tissue has been found to secrete cytokines, which, in turn stimulate the production of c-reactive protein (CRP), a marker for inflammation[2]. Knowing this, it makes sense that these overweight individuals have higher plasma CRP levels than normal, healthy individuals. Therefore, with obesity becoming an increasing concern in the US population, it is necessary to further investigate the role of c-reactive protein and the beneficial or adverse effects of elevated CRP levels.

What is CRP?

C-reactive protein is a nonspecific plasma protein produced in the acute response to any sort of systemic inflammation, infection, or damage to tissues. Not only is it a marker of inflammation, but, when present it appears to further stimulate the inflammatory response[3]. CRP is produced by hepatocytes[4] as well as in local endothelium[3]. Its production is stimulated by the release of interleukin-1, tumor necrosis factor, and interleukin-6, all of which are released acutely in response to inflammation[4, 5] by adipose tissue[2] as well as locally in the endothelium[4]. Although plasma CRP is not a marker that is specific to cardiovascular or arterial inflammation, it is a very sensitive indicator of generalized systemic inflammation[4, 6, 7]. In particular, high-sensitivity c-reactive protein is the best and most clinically useful measurement of inflammation[3, 8].

C-reactive protein is measured in the plasma and its baseline concentration is very stable in the general population at a "normal level" for each individual. The half-life of CRP while in plasma is 19 hours and this half-life remains constant under all conditions

and in the presence of any disease state[4]. As of yet, no seasonal variance in plasma levels of CRP has been recognized. The levels of c-reactive protein in plasma are also unaffected by majority of drugs unless the drug acts on the cytokines stimulating CRP release from hepatocytes[4]. However, liver damage can decrease plasma CRP concentrations due to the inability of damaged hepatocytes, or liver cells, to produce it.

The current means of measuring CRP is by using a highly sensitive latex-enhanced assay technique which has been compared to the original ELISA technique and found to be a valid measurement. This assay can detect CRP at levels as low as 0.007 mg/L which is much lower than previous assays[3] and is referred to as a high-sensitivity CRP assay. Increasing the sensitivity of the assay has allowed for CRP to become a more valuable marker for inflammation as well as cardiovascular disease.

CRP and disease

High levels of plasma CRP are recognized to be an independent risk factor for cardiovascular disease (CVD)[2, 3, 9-13] and play a direct role in atherosclerosis[1, 7, 12, 14]. The American Heart Association and the Center for Disease Control have recognized the importance of CRP as a risk factor for cardiovascular disease and have established a means of classifying risk for cardiovascular disease according to circulating plasma CRP levels. A plasma CRP level of <1.0 mg/L is classified as low risk for CVD. A value of 1.0-3.0 mg/L is considered average risk for CVD while a CRP of >3.0 mg/L in the plasma is considered high risk for CVD[3].

In addition to cardiovascular disease, increased CRP levels are associated with insulin resistance[2, 10, 15, 16] and diabetes[2, 10]. Also, a high body mass index (BMI) has been significantly related to higher levels of c-reactive protein[10, 17] due to the release of

cytokines by adipose tissue, which stimulate CRP production[2]. One study revealed a greater association between CRP and BMI when BMI is greater than 25[18]. CRP is considered to be "one of the strongest predictors of progressive vascular disease and future cardiovascular events in apparently healthy men and women" [9]. With high levels of CRP being recognized as present in so many disease states, it is important to begin evaluating effective treatments for lowering and managing levels of CRP and possibly preventing onset of these diseases.

Treatment of high plasma CRP

Currently, the primary treatment for reducing CRP levels and, thus, reducing cardiovascular risk has been diet induced weight loss[9]. There are few studies examining the effects of diet on CRP levels. The studies that do address diet and CRP are relatively new and the best way to approach elevated levels of CRP is still unknown. However, the Mediterranean diet, a diet recommending increased intakes of foods such as fruits, vegetables, walnuts, whole grains, and olive oil, has been shown to significantly decrease CRP levels and improve endothelial function[16]. The Mediterranean diet has recently been recognized by the American Heart Association to have impressive effects on the progression of cardiovascular disease[16]. Also, low-carbohydrate diets and very-low-carbohydrate diets are gaining popularity and have been examined for their effects on high levels of CRP[1].

Although both the Mediterranean diet and low-carbohydrate diets have been studied separately, a collective analysis of all studies involving the use of these diets to lower CRP levels has not been performed. In this study, the question of interest is: What are the effects of the Mediterranean diet vs. the popular low-carbohydrate or very-low-

carbohydrate diet on CRP levels? Secondly, is there any advantage to adhering to a very-low-carbohydrate diet, rather than a low-carbohydrate diet, to further reduce CRP levels and, does gender effect CRP response to dietary intervention?

A systematic review of the studies examining these three diets and their effects on CRP levels was performed. The outcomes determine which of the three diets is more effective in reducing CRP levels and thus reducing the incidence of cardiovascular disease in patients with elevated levels of plasma CRP.

Goal of study

The initial goal of this study was to determine an appropriate means of dietary treatment for individuals with high levels of CRP and, thus, at high risk for cardiovascular disease, diabetes, etc. A second goal is to make recommendations based on these findings to help improve and/or manage increased levels of CRP and prevent progression of any associated disease state.

This study examines what the current literature reveals about CRP and its usefulness in predicting risk of cardiovascular events as well as its use as a marker for other disease states. Secondly, the Mediterranean diet, low, and very-low-carbohydrate diets were looked at individually regarding content of the diet and what is known about each diet's effect on plasma levels of CRP and cardiovascular outcomes. Also, the results will address the issue of gender response to dietary intervention and attempt to make recommendations as to which diet is more effective in lowering CRP in males versus females.

Literature Review

Fifty-three articles were chosen to include in the literature review that provided information regarding the Mediterranean diet, low-carbohydrate diet, very-low-carbohydrate diet, or c-reactive protein. A table of all sources sited in this review can be found in Appendix A.

Elevated CRP and risk of CVD and other disease states

Several studies were found that recognized the association of high levels of CRP with cardiovascular disease (CVD)[2, 7, 9-13, 19]. Elevated plasma CRP levels is a risk factor for CVD because foam cells (lipid-laden machrophages) secrete CRP. CRP increases the monocyte recruitment into the intima causing a constant pro-inflammatory environment to be present[9]. Elevated levels of CRP have also been found to be associated with decreased activity of nitric oxide synthase. The lessened activity of this enzyme results in reduced levels of nitric oxide in the intima of the blood vessels. This lack of nitric oxide causes dysfunction of the endothelium of the blood vessels termed "endothelial dysfunction"[9]. Finally, CRP also increases production of tissue factor, which has been found to contribute to thrombosis following arterial plaque rupture[9].

One of the initial studies recognizing the risk of CVD due to elevated levels of CRP was completed in 1997. This study sampled a population of over 1000 healthy male subjects in the Physicians Health Study[7]. In this study, higher baseline concentrations of CRP were associated with both the increased risk of myocardial infarction ($p<0.001$) and increased risk of stroke ($p<0.02$)[7]. In a second study, a random, double blind, placebo trial was performed by Ridker et al on 14,916 healthy male subjects. CRP was found to add to the predictive value in determining first myocardial infarction when used

alongside lipid parameters[19]. In another of Ridker's studies involving 144 healthy men with peripheral artery disease (PAD), baseline CRP levels were found to predict future risk of symptomatic PAD[20]. This information further supported the aforementioned belief that chronic inflammation does play an important role in the pathogenesis of atherosclerosis.

Several articles recognize the association between high CRP levels and insulin resistance that is found in individuals with metabolic syndrome and development of type II diabetes[2, 10, 15, 16]. This is of utmost importance because metabolic syndrome is found to be present in 24% of the United States adult population[15]. Metabolic syndrome is defined as an assemblage of factors that increase an individual's risk for cardiovascular disease and type II diabetes[15]. Recently, studies have been suggesting that a chronic pro-inflammatory state is emerging as a component of Metabolic Syndrome and individuals with this syndrome are presenting with high levels of CRP[10, 15] as well.

Diet and CRP

What one eats does, in fact, influence the amount of inflammation one's body undergoes systemically. Ford, et al performed a cross-sectional study using data from the Third National Health and Nutrition Examination Survey (NHANES), from 1988 to 1994. An inverse relationship was found between the Healthy Eating Index (HEI) and elevated CRP concentrations[21]. To recognize that an individual's eating habits can affect the levels of plasma CRP is an important finding in that it now begs the question as to specifically which types of foods affect the body's state of inflammation.

It is known that the weight loss caused by dietary changes is the primary method of reducing c-reactive protein levels in those individuals who are overweight and at risk

for cardiovascular disease[9]. One study showed that CRP levels do not have a relationship with levels of LDL cholesterol and thus are not significantly affected by fat intake[10]. Therefore, the studies have seemed to shift to investigation of a lower intake of carbohydrates and greater consumption of fruits vegetables, walnuts, and olive oil as an alternate means of lowering CRP levels.

As mentioned before, the Mediterranean diet, recognized by the American Heart Association as having impressive effects on cardiovascular disease progression, has been proven to decrease CRP levels when followed carefully over a two year time period as was done in the study conducted by Esposito, et al[16]. In regards to the low-carbohydrate diet, one study found that very-low-carbohydrate diets and low-calorie diets, less than 1200 calories per day, were successful in lowering CRP[14]. However, the isoenergetic, low-carbohydrate diet was found not to effect the markers of inflammation short-term[14]. However, another study found that very-low-carbohydrate diets, ones in which carbohydrates were reduced to less than 30g/day had a greater reduction in CRP than that of the conventional diet in which calories were decreased by 500 per day and less than 30% of calories were from fat[1]. It is yet to be determined which diet results in the greatest lowering of CRP and is more beneficial to prevention of cardiovascular disease. A systematic review comparing all studies involving the three diets has not yet been performed.

The Mediterranean diet

As explained by Willett, et al the term "Mediterranean Diet" is meant to describe a diet that was typical in Greece, Crete, and Southern Italy in the mid 1900s[22]. It primarily consists of plant foods such as nuts, potatoes, and breads, while olive oil is the

principal source of fat. Fruits are a dessert food and concentrated sweets may only be consumed a few times per week. Dairy products as well as fish and poultry are eaten in moderate amounts while red meats are kept to a minimum. Within the Mediterranean diet, wine is consumed in a moderate amount meaning an average of 1-2 glasses per day[22]. The MD is known to be low in saturated fats as well as total fat due to the minimal amount of animal food intake that is required.

The Mediterranean diet (MD), in particular is recognized for its proven advantageous effects on cardiovascular risk factors. In a study conducted by Lorgeril, et al on 605 post first myocardial infarction men and women, the MD was found to decrease the amount of further coronary artery disease (CAD) related events ($p<0.001$)[23]. Several studies show that adherence to the MD, by individuals of all ages and genders and with varying degrees of cardiac disease, is associated with a reduction in mortality rate[23-27]. Panagiotakos, et al found, in a cross-sectional survey of over 2,200 men and women 18 years of age and older, that the Mediterranean diet has also been found to decrease the risk of hypertension by 26% ($p=0.008$) and the individuals who adhered to the diet with existing hypertension had a 36% odds ratio of better control of blood pressure ($p=0.021$)[28]. Chrysohoou et al also found the Mediterranean diet to reduce blood pressure[29].

A possible explanation for the reduction in mortality with adherence to the MD could be due to its beneficial effects on arteries at the local level. One study of 22 hypercholesterolemic males found an increase in flow-associated vasodilation with adherence to the MD ($p=0.027$) as well as a decrease in cholesterol ($p=0.001$)[30]. Cholesterol is well known to have a large effect on the amount of atherosclerosis and thus

risk of cardiovascular event. The Mediterranean diet does show beneficial effects on HDL cholesterol as well[29]. Any diet that acts favorably on cholesterol levels would have a beneficial effect on risk of future cardiovascular disease.

As mentioned before, a typical Mediterranean diet does include a moderate intake of alcohol. Sierksma, et al, conducted a study on 20 men and women and found that CRP decreased after just three weeks of alcohol, specifically beer, consumption ($p=0.02$) after controlling for BMI[31]. Thus, alcohol and the MD may be atheroprotective.

Omega-3 fatty acid intake is also high in the MD and increased consumption of, or supplementation with, omega-3 fatty acids has been shown to reduce plasma CRP concentration[13, 32]. Fruits and vegetables, another important aspect of the Mediterranean diet, have also been proven to reduce c-reactive protein levels. According to Gao, et al, there is an inverse-dose-response relationship of fruits and vegetable intake to plasma CRP concentration ($p=0.01$)[11].

It is recognizable that there are several aspects of the Mediterranean diet that could be responsible for its effectiveness in lowering cardiovascular mortality. The evidence supporting the use of the Mediterranean diet as a method of decreasing mortality and cardiovascular disease is increasing. It is important to consider the adoption of a Mediterranean-style diet as an effective means of controlling and preventing systemic inflammation as well as cardiovascular disease progression and risk.

The Mediterranean diet and CRP

Due to the fact that knowledge of c-reactive protein's role in atherosclerosis and prediction of cardiovascular disease is relatively new, there are few large studies that examine the effect of the Mediterranean diet on levels of CRP. The ATTICA study was

an epidemiologic study carried out in the province of Attica, Greece that examined over 3,000 healthy men and women ages 18 to 89 years old and graded them on adherence to the Mediterranean diet using a food-frequency questionairre[29]. The higher the diet score, the closer the individual adhered to the MD. Subjects were excluded if they had any prior history of cardiovascular disease or chronic upper respiratory complaints. CRP as well as other inflammation and coagulation markers were measured. Results of the study showed that participants with the most strict adherence to the Mediterranean diet had, on average, 20% lower CRP levels ($p=0.01$)[29]. This was found to hold true after adjusting for differences in BMI. However, although this is an excellent study in that it allows us to recognize the importance of the MD as a lifestyle, it did not involve the MD as an intervention and, thus, does not give us any information as to how effective the MD would be as a treatment for high CRP.

Another study on 732 women ages 43 to 69 showed that a "prudent pattern" characterized by increased intake of fruits and vegetables, legumes, fish, and poultry similar to the Mediterranean diet had an inverse association with CRP ($p=0.02$)[2]. After adjusting for BMI this relationship was still significant for CRP ($p=0.02$). This study also was a cross-sectional study and did not involve the MD as an intervention.

Although the ATTICA study proved that MD as a life-style is beneficial to CRP values, short-term adherence to the Mediterranean diet may not have such beneficial effects on CRP. One study conducted on 21 hypercholesterolemic men and women between the ages of 25 to 75 years old showed no significant change in CRP values when the diet was adhered to for a four week period[33]. In this particular study, however, the MD was the control and individuals had been following a MD diet prior to enrollment in

the study. Nonetheless, similar results were observed in another study of 21 kidney graft patients. No significant changes in CRP as an were found after adhering to the Mediterranean diet for four weeks[34].

Age may also have an effect on the response of CRP levels to the Mediterranean diet. Fourty-two college-age students were examined for the effects of a MD on their CRP levels. There were no significant changes found at any point in the study over a 90 day period[35]. It is likely that the impact of the diet on CRP levels is strongly related to the genetics of the subject, the age and thus disease state of the subject, and the duration of adherence to the diet.

In the studies that did find a significant effect of the MD on CRP levels, it was difficult to distinguish whether these effects were due to the diet itself or to the reduction in BMI and/or weight. Esposito, et al, showed a significant reduction of serum CRP from baseline ($p=0.01$) in 120 pre-menopausal, obese women age 20-46 years with a BMI of >30[36]. Once again, the reduction in CRP was correlated to a decrease in BMI.

When examining the effect of the Mediterranean diet on lowering CRP in individuals with Metabolic Syndrome, the results were much more promising. In one random, single-blind study the effects of two years of adherence to the MD on 180 subjects with known metabolic syndrome were examined. The patients on the Mediterranean diet had a significant decrease in CRP ($p=0.01$) and insulin resistance was also decreased ($p<0.001$)[16]. Weight loss did not prove to be significantly different between treatment groups. Less than half of the patients in the MD intervention group that began the study with the diagnosis of metabolic syndrome still had the diagnosis at the end of the two year treatment.

The low-carbohydrate diet

Low-carbohydrate diets (LCD) are gaining popularity due to the success of achieving weight loss with adherence to a LCD. In a traditional diet, carbohydrates account for roughly 60% of one's total daily calorie intake. For the purpose of this study, a diet will be considered "low-carbohydrate" if the total carbohydrate intake is <46% of the total daily calories (approximately 160 g/day) and "very-low-carbohydrate" if <10% (approximately 35 g/day) of daily caloric intake is from carbohydrates. Proteins and fats make up the majority of the calories in low and very-low-carbohydrate diets while sugars (fruits) are often restricted.

Several studies have shown a significant degree of weight loss as well as a significant decrease in body mass index (BMI) in individuals following a low or very-low-carbohydrate diet[37-45]. Decreases in weight loss or in BMI will effect CRP levels as c-reactive protein levels have been found to be directly related to BMI and do decrease when BMI decreases or weight loss is achieved[10, 17, 46-48].

A low-carbohydrate diet has been shown to favorably affect one's lipid levels as well as plasma c-reactive protein concentration[39]. Several studies have shown the low-carbohydrate diet to markedly and significantly reduce plasma levels of triglycerides[14, 39-42, 44, 45, 49] while the effect on HDL and LDL cholesterol seems less clear. Some studies support an increase in HDL by following a low-carbohydrate diet[14, 40, 43-45] while others found it to be unaffected[41, 42, 49, 50]. One study even reported an increase in LDL cholesterol after following a low-carbohydrate diet[14]

Safety of low-carbohydrate diet use in those over 50 years old for long periods of time is unknown. Bravata performed a systematic review of the literature regarding this

diet's safety and was unable to make recommendations for individuals over age 50 [51]. In addition, recommendations for long-term use of this diet as well as very-low-carbohydrate diet adherence could not be made[51]. This study did attribute the successful weight loss attained by adherence to the LCD to its lower calorie intake rather than the reduced intake of carbohydrates. Weight loss seemed to be most successful with long-term adherence to the LCD in this particular review[51].

Low-carbohydrate diet and CRP

Low-carbohydrate diets have also been studied for their beneficial effects on plasma levels of CRP. One study, involving a low-carbohydrate (<40% carbohydrates) dietary intervention revealed c-reactive protein to be significantly decreased from baseline levels ($p<0.05$) over a sixty-eight week intervention period[52]. These subjects did lose a significant amount of weight and it is unable to be determined whether weight loss was responsible for the reduction in CRP or if this reduction was due to the diet alone.

As is often the case, there is another study that contradicts the effects of a LCD on CRP. A study performed by Due, et al, sampled 50 overweight subjects (12 male, 38 female) with a BMI of 27 to 34 that were between the ages of 18 to 56 years old. Although Due did find that CRP levels decreased with LCD intervention, the decrease in CRP was not significant[53].

Very-low-carbohydrate diet and CRP

O'Brien, et al, followed 41 females ages 18 and over with a BMI of 30-35 as they followed a very-low-carbohydrate diet (VLCD) of <20 g of carbohydrates per day for three months. The subjects did show a significant 24% reduction in CRP values at the end of the three months from baseline values ($p=0.035$)[38]. The decrease in CRP

concentration from baseline to the end of the three month intervention period was significantly correlated with weight change ($r=0.34$, $p=0.03$)[38]. Weight loss and reduction in BMI was not controlled for in this particular study.

The same association between weight change and CRP that was observed in O'Brien's study was found true in a study performed by Sharman, et al. Sharman's study subjects consisted of 15 overweight men (mean BMI of 34) that ate a very-low-carbohydrate diet with <10% of total calories coming from carbohydrates. The men had a significant decrease in absolute concentration of high-sensitivity CRP ($p=0.0005$) and their reduction in CRP was also due to the decrease in BMI from baseline[46].

There is conflicting data regarding the effects of a very-low-carbohydrate diet and its effects on CRP. Volek, et al also examined the effects of a diet consisting of less than 10% of total daily calories in carbohydrates on c-reactive protein levels. Volek found that over the course of a four-week VLCD no effects on CRP from baseline to the end of the study were found[14]. Sheshadri examined the effects of a VLCD on CRP over a six month period. Those individuals in Sheshadri's study with a baseline CRP that was considered "high risk" exhibited a greater decrease in CRP from baseline to the end of the six months than those whose CRP values at baseline were considered "low risk"[1]. Thus, the results of this study could support the claim of either Volek or O'Brien.

Methods

In this study, a systematic review of the literature available between October 2004 and June 2005 regarding the Mediterranean diet, low-carbohydrate, and very-low-carbohydrate diets and their effects on CRP levels was conducted. The review included the use of the databases Medline, PubMed, and FirstSearch which were searched using the terms c-reactive protein, diet, low-carbohydrate diet, Mediterranean diet, ketogenic diet, and inflammatory markers.

Articles were chosen for inclusion in the review if CRP plasma levels were used as an endpoint with either the Mediterranean diet, low, or very-low-carbohydrate diet as the independent variable. A low-carbohydrate diet is defined in this study as <46% of total caloric intake coming from carbohydrates or approximately <160 grams of carbohydrate daily. A third category, very-low-carbohydrate diet (VLCD), was formed meaning <10% total daily calories coming from carbohydrates or <35 grams of carbohydrates daily. Thus, low-carbohydrate are those diets with >10% but <46% total calories from carbohydrates or >35 grams but <160 grams of carbohydrate daily. The results for the three dietary interventions and their effects on CRP levels were obtained.

The studies were then further separated based on gender of the sample studied into those studies that only sampled women versus those that sampled only men. The results of each diet intervention on CRP levels in females versus males were then obtained. They were categorized as to whether CRP was significantly reduced by dietary intervention or whether no change in CRP was observed.

Results

Twelve studies were found that examined either the MD or LCD and their effects on serum CRP. These studies and their results are summarized in Table 2. Four studies examined the MD while the other eight involved a LCD or VLCD. Two of the articles for the Mediterranean diet showed significant decrease whereas the other two showed no significant change in plasma CRP levels after dietary intevention. Three articles studied very-low-carbohydrate diets. One showed no effect while another showed significant reduction in CRP with dietary adherance. The third revealed no effect on CRP overall, but a significant reduction in those with a high risk CRP levels at baseline. This study is thus classified in Figure 1 as showing a significant reduction in CRP. Two articles examined what would be classified as a VLCD for a few weeks and then increased carbohydrate intake to meet the classifications for a low-carbohydrate. For the purposes of this study these two articles are considered LCD studies. Thus, there are five total studies examining a low-carbohydrate diet. Four articles showed significant reduction in CRP with adherence to the LCD diet while one revealed no evident change (Figure 1).

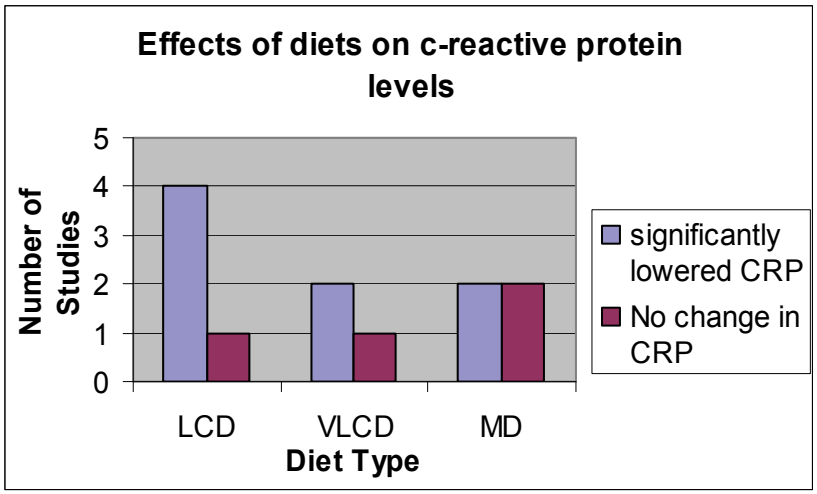

Figure 1

Only two articles examined the effects of diet on c-reactive protein in men alone. In one, a very-low-carbohydrate diet was shown to significantly decrease CRP. The other article involving the Mediterranean diet concluded no significant change in CRP in men (Figure 2).

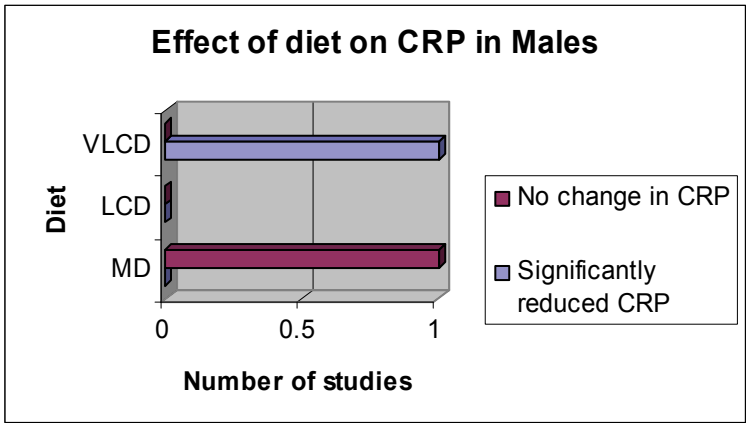

Figure 2

Four articles addressed CRP's response to diet in women. One article showed significant reduction in CRP in females with adherence to the MD. Three articles examined either the LCD or VLCD. LCD was found to significantly decrease CRP in two articles while the lone article examining a VLCD revealed no change in CRP levels in women (Figure 3).

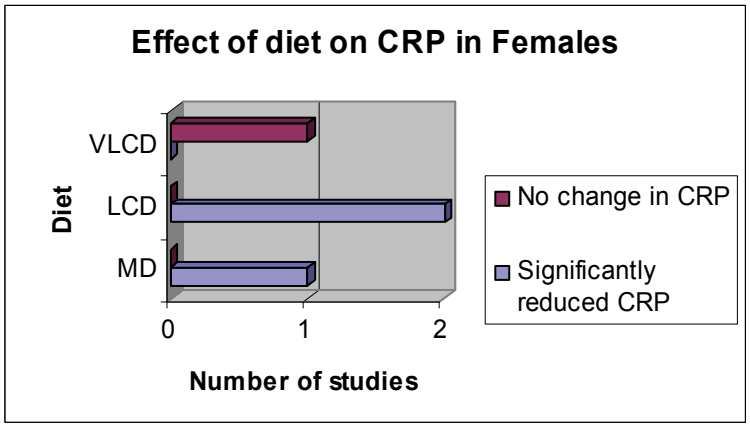

Figure 3

Discussion

Twelve articles were found that investigated the effects of any of the three studied diets on c-reactive protein. A table of the results of these twelve articles may be found in Appendix B. Four articles examined the Mediterranean diet, five researched a low-carbohydrate diet, and three studied a very-low-carbohydrate diet.

In the four diets that looked at the Mediterranean diet, half revealed a significant decrease in CRP, both with p-values of 0.01[16, 36], while the other half showed no significant change in CRP. The studies that revealed a decrease in CRP sampled subjects with either an elevated BMI or the presence of metabolic syndrome which has been linked to abdominal obesity. One of these studies did relate the decrease in CRP to the decrease in BMI[36]. The other, involving the individuals with metabolic syndrome did show a linear increase in plasma level of high-sensitivity c-reactive protein associated the number of components of metabolic syndrome present in the subjects increase[16]. The two that showed no change in CRP sampled subjects that were young (college age) with BMI average of 25 to 26[34, 35]. One must wonder if the variations in results of the MD were due to the diet itself or to the variation in the sample studied. Also, the two studies revealing a change in CRP followed the dietary intervention for two years, whereas the other two diets revealing no change lasted 90 days and six months. More studies, both long-term and short-term need to be performed in order to determine whether the differences in these results are due to length of diet or sample studied.

There were five studies that looked at a low-carbohydrate, as defined in this study, and its effect on c-reactive protein. Of those studies, four revealed significant decreases in CRP two with a p-value of <0.05, one with the p-value of <0.0001, and one

p=0.035. Only one study showed no significant change in CRP with a low-carbohydrate diet. All five of these studies did actually show a decrease in CRP from baseline[38, 48, 49, 52, 53], however, Due's results, were non-significant[53]. All of the subjects sampled in these five studies were considered clinically overweight or obese with BMI values greater than or equal to 27[38, 48, 49, 52, 53]. In addition, all five of these subjects were able to correlate changes in CRP (or logCRP in O'Brien's study) to changes in, meaning reduction of, body weight[38, 48, 49, 52, 53]. When Noakes, et al, did adjust for weight loss and change in BMI it was found that the diet alone did not have a significant effect on c-reactive protein levels (p=0.447)[49]. It does appear that a low-carbohydrate diet has advantageous effects on CRP in those individuals who are overweight with elevated BMI levels. This was known prior to this particular study. However, when adjustments for weight loss are made, it appears that a low-carbohydrate diet alone does not significantly effect CRP levels.

Three studies were found that addressed the effects of a very-low-carbohydrate diet. Two revealed significant decrease in CRP with dietary intervention (p=0.00005 and p=0.005)[1, 46]. The third did not reveal significant change in CRP after a very-low-carbohydrate diet was followed[14]. Two studies, by Sharman and Volek, involved a relatively small sample size of only fifteen and ten subjects respectively[14, 46] while the third studied seventy-eight individuals[1]. The same two studies also lasted similar lengths of time at four and six weeks versus the six months that Seshadri's study encompassed. However, the primary difference in the results of these studies appears to be related to the type of subject sampled. Both Seshadri and Sharman sampled overweight and obese individuals and saw a significant decrease in CRP, whereas Volek sampled healthy

individuals with a BMI less than 25 and found no change in CRP values from baseline. The subjects in Volek's study were not only more healthy than the others, but they were also young females ages 20-33[14]. This could account for the lack of change in CRP values with dietary intervention. Thus, there is a high likelihood that a VLCD may have desirable effects on CRP levels when adhered to by overweight individuals. As mentioned before, this is most likely due to weight loss and BMI reductions. However, it also appears that adherence to a very-low-carbohydrate diet does have greater, more significant, reductions in CRP than a low-carbohydrate diet or a Mediterranean-style diet, when comparing levels of significance according to the p-values recorded.

Sheshadri, who examined a VLCD's effect on CRP, further divided the sample's baseline CRP levels into two categories. Baseline levels of 3 mg/dL or greater were considered to be high-risk. Those individuals in this particular study who were classified as "high-risk" with CRP values of greater than 3 mg/dL at baseline did experience a significant reduction in CRP from baseline to end-point of this six month intervention[1]. However, those individuals with a low-risk to moderate-risk baseline CRP level did experience an increase in CRP levels from baseline that was non-significant. There was a significant correlation between high baseline levels of CRP and increasing BMI ($r=0.37$, $p=0.001$)[1] as also was known prior to this study.

In addition, it does not appear that gender has any impact on response of CRP to dietary intervention. Likewise, no statement can be made to recommend one diet over the other for intervention in males or females alone. There were two articles total that looked at men alone and four whose sample subjects consisted of only women.

Of the two articles examining male subjects alone, one looked at a very-low-carbohydrate diet while the other examined the effects of the Mediterranean diet. The first, involving the VLCD was performed by Sharman, et al and revealed a significant decrease in CRP with VLCD intervention[46]. The second, is by Mezzano, et al which involved the Mediterranean Diet and revealed no change in CRP with the change in diet[35]. There were two significant differences between the subjects sampled in these two studies that very well could have influenced their results. The Sharman study evaluated obese males with a high BMI while Mezzano investigated the effects of the diet on University students with healthy BMI values. Thus, these results are non-comparable due to the variances in subjects studied. Also, given the very small number of studies found, no recommendations for a particular diet, in men, can be made at this time.

As mentioned prior, there were four articles who sampled only female subjects. Of these four studies, one included the Mediterranean diet, another used the VLCD, and the final two involved a low-carbohydrate diet. The first, by Esposito et al sampled subjects that were pre-menopausal and obese in the ages of 20 to 46 years old. After two years of MD intervention these subject's CRP levels were significantly reduced ($p=0.01$). These reductions were significantly related to BMI ($p=0.08$)[36]. This is the only article examining the MD and its effect on CRP in women. Thus, no recommendations can be made, at this time, for the MD as an intervention in women with elevated CRP levels.

The second of the studies involving only female subjects is by Volek, et al and used a VLCD as intervention. The subjects involved in this study were 10 healthy 20-33 year old females with a BMI less than 25 mg/dL. No significant effect on CRP was found after four weeks of dietary intervention[14]. Again, with only one article found that

examined a very-low-carbohydrate diet, no recommendations can be made for this diet as an intervention in female subjects to lower CRP.

The final two studies examining women alone involved the LCD and revealed significant decreases in CRP after dietary intervention. O'Brien and Noakes were the authors of these two studies and both studies involved obese female subjects[38, 49]. The studies also both lasted the same period of time of 12 weeks or 3 months. Due to the similarities of subjects studied in these two experiments as well as the similar length of time the subjects were studied, it can be deducted that a low-carbohydrate diet for a short period of time does decrease c-reactive protein levels short-term in obese females. However, long-term CRP results cannot be determined from these two studies.

There are several limitations to this particular study. One such limitation is that the topic of c-reactive protein and its relationship to various disease states is relatively new. There are a limited number of articles in which CRP was a measured variable when one of the two diets studied in this review were used as an intervention. Also, it is difficult to control an individual's diet without monitoring their intake first-hand. Therefore, using diet as intervention allows much room for interpretation by the subjects of each study that would affect the results of the diet. Also, a high body mass index (BMI) has been significantly related to higher levels of c-reactive protein[10, 17]. Many studies fail to control for this relationship.

There also were several differences between the studies regarding length of time adhering to the intervention diet as well as age or disease state of subjects sampled and sample size. A few studies did include subjects with various diseases states including metabolic syndrome, diabetes, hypertension, or dyslipidemia. Lengths of the studies

ranged from four weeks to two years while sample size varied from ten subjects to one-hundred and eight subjects. Also, as previously mentioned, BMI effects CRP levels and subjects with higher BMI values to begin with will, most likely, experience greater reductions in CRP than those with a normal BMI.

Thus, limitations to this study may include access to relevant studies and information necessary to accurately analyze all available information, inability to accurately measure adherence to each diet, failure to control for BMI, variances in sample size, age, and disease state, as well as misinterpretation of the results as portrayed by the authors of studies used.

Conclusions

Twelve articles were found that involved either the Mediterranean diet, a low-carbohydrate diet, or a very-low-carbohydrate diet and measured c-reactive protein as an outcome. All articles that were found were an evidence level of 1B; all randomized, intervention studies.

Thus, an A grade of recommendation can be made that all three diets effectively lower CRP levels in obese or overweight individuals regardless of their gender and regardless of length of dietary intervention when significant weight loss and/or reduction in BMI is observed. Also, it appears that individuals with normal BMI values that are considered to be healthy do not achieve, with adherence to any of the three diets studied, a reduction in CRP.

It does appear as though adherence to a very-low-carbohydrate diet yielded the most significant reduction in CRP levels. It also seems as if adherence to both the Mediterranean diet and a low-carbohydrate diet also yield favorable results in reducing c-reactive protein levels. All of these reductions in CRP appear to be secondary to reductions in weight or BMI. The effects of diet alone on CRP without weight loss or reduction in BMI are difficult to examine. There does not seem to be much benefit on c-reactive protein levels that may be obtained by healthy, individuals with average weight or BMI from adherence to any of the three diets studied. The Mediterranean diet does look as if it is most affective as a treatment when followed for longer periods of time. Thus, it appears to not be as effective short-term as a low-carbohydrate diet or very-low-carbohydrate diet would be for weight reduction, decrease in BMI, and favorable changes in CRP.

However, recommendations as to which diet is the most safe to adhere to cannot be commented on. The majority of the studies included in this review failed to address the issue of diet safety. In addition, due to the aforementioned variances in subjects sampled and small amount of available studies, no recommendations can be made for either gender as far as which diet is more effective at lowering plasma CRP levels. In the articles in which reductions in CRP were observed, almost all attributed these reductions to weight loss or reduction in BMI. Further studies need to be conducted that control for reduction in weight and BMI and examine the effect of the diet and dietary components alone on CRP.

It was well-known prior to this study that weight loss lowers CRP[9] and that those individuals with higher BMI values tend to have elevated levels of CRP[10, 17]. At this point, further testing involving the Mediterranean diet, low-carbohydrate diet, and very-low-carbohydrate diet on c-reactive protein levels should be done and changes in weight and BMI should be controlled for. However, currently, it does appear as though a very-low-carbohydrate diet provides the most immediate and dramatic reduction in plasma levels of CRP in obese individuals with elevated CRP levels due to reduction in weight and BMI.

References

1. Seshadri P, et al. A randomized study comparing the effects of a low-carbohydrate diet and a conventional diet on lipoprotein subfractions and c-reactive protein levels in patients with severe obesity. *American Journal of Medicine.* 15 Sep 2004 2004;117(6):398-405.

2. Lopez-Garcia E, et al. Major dietary patterns are related to plasma concentrations of markers of inflammation and endothelial dysfunction. *American Journal of Clinical Nutrition.* Oct 2004 2004;80(4):1029-1035.

3. King DE. Dietary fiber, inflammation, and cardiovascular disease. *Mol Nutr Food Res.* 2005;49:594-600.

4. Pepys MB, et al. C-reactive protein critical update. *The Journal of Clinical Investigation.* 2003;111(12):1805-1812.

5. Yeh ET. CRP as a mediator of disease. *Circulation.* 2004;109 (suppl II):II11-II14.

6. Koenig W, et al. C-reactive protein, a sensitive marker of inflammation, predicts future risk of coronary artery disease in initially healthy middle-aged men: results from the MONICA (monitoring trends and determinants in cardiovascular disease) Augsburg cohort study, 1984 to 1992. *Circulation.* 1999;99:237-242.

7. Ridker P, Cushman, Mary, Stampfer, Mieir J, Tracy, Russell P, Hennekens, Charles H. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. *The New England Journal of Medicine.* 3 April 1997 1997;336(14):973-979.

8. Kenna GA, et al. Clinical use of c-reactive protein for cardiovascular disease. *Southern Medical Journal.* 2004;97(10):985-988.

9. Labarrere CA, et al. C-reactive protein: from innocent bystander to pivotal mediater of atherosclerosis. *American Journal of Medicine.* 1 Oct 2004 2004;117(7):499-507.

10. Frederikson GN, et al. Association between diet, lifestyle, metabolic cardiovascular risk factors, and plasma c-reactive protein levels. *Metabolism.* Nov 2004 2004;53(11):1436-1442.

11. Gao Xea. Plasma c-reactive protein and homocysteine concentrations are related to frequent fruit and vegetable intake in Hispanic and non-Hispanic white elders1. *Journal of Nutrition.* 2004;134:913-918.

12. Ajani UA, et al. Dietary fiber and c-reactive protein: findings from National Health and Nutrition Examination Survey data. *Journal of Nutrition.* May 2004;134(5):1181-1185.

13. Lopez-Garcia E, et al. Consumption of (n-3) fatty acids is related to plasma biomarkers of inflammation and endothelial activation in women. *Journal of Nutrition.* July 2004 2004;134(7):1806-1811.

14. Volek JS, Sharman, Matthew J, Gomez, Ana L, Scheett, Timpothy P, Kraemer, William J. An isoenergetic very low carbohydrate diet improves serum HDL cholesterol and triacyglycerol concentrations, the total cholesterol to HDL cholesterol ratio and postprandial lipemic responses compared with a low fat diet in normal weight, normolipidemic women. *Journal of Nutrition.* Sep 2003 2003;133:2756-2761.

15. Abbatecola AM, et al. Diverse effect of inflammatory markers on insulin resistance syndrome in the elderly. *Journal of American Geriatric Society.* March 2004;52(3):399-404.

16. Esposito K, et al. Effect of a Mediterranean-style diet on endothelial dysfunction and markers of vascular inflammation in the metabolic syndrome. *JAMA.* 22 Sept 2004 2004;292(12):1440-1446.

17. Bertran N, et al. Diet and lifestyle are associated with serum c-reactive protein concentrations in a population based study. *Journal of Laboratory and Clinical Medicine.* 2005;145:41-46.

18. Liu S, et al. Relation between a diet with a high glycemic load and plasma concentrations of high-sensitivity c-reactive protein in middle aged women. *American Journal of Clinical Nutrition.* 2002;75:492-498.

19. Ridker PM, et al. C-reactive protein adds to the predictive value of total and HDL cholesterol in determining risk of first myocardial infarction. *Circulation.* 1998;97:2007-2011.

20. Ridker PM, et al. Plasma concentration of c-reactive protein and risk of developing peripheral vascular disease. *Circulation.* 1998;97:425-428.

21. Ford E, Mokdad, AH, Liu, S. Healthy eating index and c-reactive protein concentration: findings from the national health and nutrition examination survey III, 1988-1994. *European Journal of Clinical Nutrition.* 2005;59:278-283.

22. Willett WC, et al. Mediterranean diet pyramid: a cultural model for healthy eating. *American Journal of Clinical Nutrition.* June 1995 1995;61(6):1402S-1406S.

23. De Lorgeril M, et al. Mediterranean alpha-linolenic acid-rich diet in secondary prevention of coronary heart disease. *Lancet.* 1994;343:1454-1459.

24. Trichopoulou A, et al. Mediterranean diet and survival among patients with coronary artery disease in Greece. *Archives of Internal Medicine.* 2005;165:929-935.

25. De Lorgeril M, et al. Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction. *Circulation.* 1999;99:779-785.

26. Knoops KT, et al. Mediterranean diet, lifestyle factors, and 10-year mortality in elderly European men and women. *JAMA.* 2004;292(12):1433-1439.

27. Trichopoulou A, et al. Adherance to a Mediterranean diet and survival in a Greek population. *The New England Journal of Medicine.* 26 Jun 2003 2003;348(26):2599-2608.

28. Panagiotakos DB, et al. Status and management of hypertension in Greece: role of the adoption of a Mediterranean diet:: the ATTICA study. *Journal of Hypertension.* 2003;21:1483-1489.

29. Chrysohoou C, et al. Adherance to the Mediterranean diet attenuates inflammation and coagulation process in healthy adults: the attica study. *Journal of American College of Cardiology.* 2004;44(1):152-158.

30. Fuentes F, et al. Mediterranean and low-fat diets improve endothelial function in hypercholesteremic men. *Annals of Internal Medicine.* 2001;134:1115-1119.

31. Sierksma A, Van der Gaag, MS, Kluft, C, Hendriks, HFJ. Moderate alcohol consumption reduces plasma c-reactive protein and fibrinogen levels; a

randomized, diet controlled, intervention study. *European Journal of Clinical Nutrition.* 2002;56:1130-1136.

32. Sundrarjun T, et al. Effects of n-3 fatty acids on serum interleukin-6, tumour necrosis factor α, and soluble tumour necrosis factor receptor p55 in active rheumatoid arthritis. *The Journal of International Medical Research.* 2004;32:443-454.

33. Ros E, et al. A walnut diet improves endothelial function in hypercholesterolemic subjects. *Circulation.* 2004;109:1609-1614.

34. Stachowska E, et al. Elements of Mediterranean diet improve oxidative status in blood of kidney graft recipients. *British Journal of Clinical Nutrition.* 2005;93:345-352.

35. Mezzano D, et al. Original Communication: Complementary effects of Mediterranean diet and moderate red wine intake on haemostatic cardiovascular risk factors. *European Journal of Clinical Nutrition.* 2001;55:444-451.

36. Esposito K, et al. Effect of weight loss and lifestyle changes on vascular inflammatory markers in obese women: a randomized trial. *JAMA.* 9 April 2003 2003;289(14):1799-1804.

37. Meckling KA, O'Sullivan, Caitriona, Saari, Dayna. Comparison of a low-fat diet to a low-carbohydrate diet on weight loss, body composition, and risk factors for diabetes and cardiovascular disease in free-living, overweight men and women. *The Journal of Clinical Endocrinology & Metabolism.* 2004;89(6):2717-2723.

38. O'Brien KD, et al. Diet-induced weight loss is associated with decreases in plasma serum amyloid A and c-reactive protein independent of dietary

macronutrient composition in obese subjects. *The Journal of Clinical Endocrinology & Metabolism.* 2005;90:2244-2249.

39. Aude YW, et al. The national cholesterol education program diet vs a diet lower in carbohydrates and higher in protein and monounsaturated fat: a randomized trial. *Archives of Internal Medicine.* 25 October 2004 2004;164:2141-2146.

40. Sharman MJ, et al. A ketogenic diet favorably effects serum biomarkers for cardiovascular disease in normal-weigth men. *Journal of Nutrition.* 2002;132:1879-1885.

41. Sharman MJ, Gomez, Ana L, Kraemer, William J, Volek, Jeff S. Very-low carbohydrate and low-fat diets affect fasting lipids and postprandial lipidemia differently in overweight men. *Journal of Nutrition.* 2004;134:880-885.

42. Samaha FF, et al. A low-carbohydrate as compared with low-fat diet in severe obesity. *The New England Journal of Medicine.* 22 May 2003 2003;348(21):2074-2081.

43. Foster GD, et al. A randomized trial of low-carbohydrate diet for obesity. *The New England Journal of Medicine.* 22 May 2003 2003;348(21):2082-2090.

44. Yancy Jr WS, et al. A low-carbohydrate, ketogenic diet versus a low-fat diet to treat obesity and hyperlipidemia. *Annals of Internal Medicine.* 18 May 2004 2004;140(10):769-777.

45. Brehm BJ, Seeley, Randy J, Daniels, Stephen R, D'Alessio, David A. A randomized trial comparing a very low carbohydrate diet and calorie-restricted low fat diet on body weight and cardiovascular risk factors in healthy women. *The Journal of Clinical Endocrinology & Metabolism.* 2003;88(4):1617-1623.

46. Sharman MJ, et al. Weight loss leads to reductions in inflammatory biomarkers after a very-low carbohydrate diet and low-fat diet in overweight men. *Clinical Science.* 2004;107:365-369.

47. Nicklas BJ, et al. Diet-induced weight loss, exercise, and chronic inflammation in older, obese adults: a randomized controlled clinical trial. *American Journal of Clinical Nutrition.* 2004;79:544-551.

48. Dansinger ML, et al. Comparison of the Atkins, Ornish, Weight Watcher, and Zone diets for weight loss and heart disease reduction. *JAMA.* 5 Jan 2005 2005;293(1):43-53.

49. Noakes M, et al. Effect of energy-restricted, high-protein, low-fat diet relative to a conventional high-carbohydrate, low-fat diet on weight loss, body composition, nutritional status, and markers of cardiovascular health in obese women. *American Journal of Clinical Nutrition.* 2005;81:1298-1306.

50. Sondike SB, Copperman, Nancy, Jacobson, Marc S. Effects of a low-carbohydrate diet on weight loss and cardiovascular risk factors in overweight adolescents. *Journal of Pediatrics.* 2003;142:253-258.

51. Bravata DM, et al. Efficacy and safety of low-carbohydrate diets: a systemic review. *JAMA.* 9 April 2003 2003;289(14):1837-1850.

52. Brinkworth G, et al. Long-term effects of a high-protein, low-carbohydrate diet on weight control and cardiovascular risk markers in obese hyperinsulinemic subjects. *International Journal of Obesity.* 2004;28:661-670.

53. Due A, et al. The effect of diets high in protein or carbohydrate on inflammatory markers in overweight subjects. *Diabetes, Obesity, and Metabolism.* 2005;7:223-229.

Appendix A

Reference	Subjects	Type of Study	Independent Variable (MD, LCD, Both, Neither)	Dependent Variable	CRP*	Results relating to CRP change or diet
Abbatecola, Angela M, et al. Diverse effect of inflammatory markers on insulin resistance and insulin-resistance syndrome in the elderly. *Journal of the American Geriatric Society.* 2004; 52: 399-404.	1,146 non-diabetics (500 men and 646 women) ages 22-104 years old with BMI of 27 + or - 4	Prospective, population-based, cross-sectional study from the cohort study from Greve in Chianti and Bagno a Ripoli	Serum inflammatory markers including; tumor necrosis factor alpha, interleukin 6 (IL-6), soluble interleukin 6 receptor (sIL-6R), interleukin receptor antagonist (IL-1ra), and c-reactive protein (CRP)	Insulin resistance and insulin resistance syndrome	X	Men had significantly higher CRP levels than women. IR correlated with CRP in all subjects ($r=0.83$, $p<0.001$). Also IR was positively correlated with plasma levels of TNF alpha, IL-1ra, IL-6, and sIL-6R.
Ajani, Umed A, Fordk, Earl S, Mokdad, Ali H. Dietary fiber and c-reactive protein: Findings from a national health and nutrition examination survey data. *Journal of Nutrition.* 2004; 134(5): 1181-1185.	3,920 male and female subjects > or = 20 years old	Data from NHANES 1999-2000 was used and a representative sample of non-institutionalized US civilian population was selected by multistage sampling design	Dietary fiber intake	C-reactive protein	X	Highest CRP concentrations were seen in those with the lowest intake of dietary fiber. Dietary fiber is inversely associated with serum concentration of CRP. Higher fiber intake had lower concentrations of CRP

Reference	Subjects	Type of Study	Independent Variable (MD, LCD, Both, Neither)	Dependent Variable	CRP*	Results relating to CRP change or diet
Aude, Y Wady, et al. The National Cholesterol Education Program Diet vs a diet lower in carbohydrates and higher in protein and monounsaturated fat: a randomized trial. *Archives of Internal Medicine.* 2004; 164: 2141-2146.	60 subjects (29 women, 31 men) ages 28-71 years.	Randomized trial	NCEP diet and Modified Low-carbohydrate diet (MLC)	Primary endpoint is weight loss. Secondary endpoints include blood lipid levels and waist-to-hip ratio.		12 week study, MLC diet caused significantly greater weight loss than NCEP ($p=0.02$). No significant differences between groups for LDL, HDL, total cholesterol, or triglycerides.
Bertran, Nuria, et al. Diet and lifestyle are associated with serum c-reactive protein concentrations in a population-based study. *Journal of Laboratory and Clinical Medicine.* 2005; 145(1): 41-46.	172 females, 187 males age 18-75 years, White-Mediterranean in ethnic origin	Population-based study	Dietary intake with 3-day estimated food record	Serum CRP concentrations	X	Older age, increased BMI, serum triglycerides, and folate intake were significantly associated with CRP levels. Higher folate intake was related to lower CRP concentrations.

Reference	Subjects	Type of Study	Independent Variable (MD, LCD, Both, Neither)	Dependent Variable	CRP*	Results relating to CRP change or diet
Bravata, Dena M, et al. Efficacy and safety of low-carbohydrate diets: a systematic review. *JAMA*.2003; 289(14): 1837-1850.	Articles with LCD > 4 days in duration and 500 kcal per day or more, 107 articles with 3,268 male and female total participants	Systematic Review	Low-carbohydrate diets	Body mass index (BMI), lipids, measures for glycemic control, measures of hypertensive control		Insufficient evidence to make recommendations especially age >50, length >90 days, and diets of 20grams/day of carbohydrates or less. Weight loss seems to be due to length of treatment and decrease in total calories - not decrease in carbohydrates.
Brehm, Bonnie J, Seeley, Randy J, Daniels, Stephen R, and D'Alessio, David A. A randomized trial comparing a very low fat diet on body weight and cardiovascular risk factors in healthy women. *The Journal of Clinical Endocrinology and Metabolism*.2003; 88(4): 1617 - 1623.	53 obese females (BMI 30-35) ages 18+ years old	Randomized trial	Very-low-carbohydrate diet and a low fat, calorie-restricted diet	Body composition, weight, and cardiovascular risk factors including EKG, blood pressure, plasma lipids, and fasting hormones		After 3 and 6 months, amount of weight lost was significantly greater in very-low-carbohydrate group compared with low fat ($p<0.001$). No difference in plasma lipids between groups. All subjects significantly decreased total cholesterol, LDL, triglycerides and increased HDL.

Reference	Subjects	Type of Study	Independent Variable (MD, LCD, Both, Neither)	Dependent Variable	CRP*	Results relating to CRP change or diet
Brinkworth, GD, Noakes, M, Keogh, JB, Luscombe, ND, Wittert, GA, and Clifton, PM. Long-term effects of a high-protein, low-carbohydrate diet on weight control and cardiovascular risk markers in obese hyperinsulinemic subjects. *International Journal of Obesity.*2004; 28: 661-670.	43 obese (BMI 27-43) non-diabetic with hyperinsulinemia, 20-65 years old	Outpatient, parallel, clinical intervention study	High protein diet: 30% of energy from protein, 40% from carbohydrates (~140 g/day) and 30% from fat vs standard diet: 15% protein, 55% carbohydrates, 30% fat.	Body composition, weight, body mass, blood pressure, cardiovascular risk factors including lipids, insulin, CRP, etc.	X	68 week study, significant net weight loss due entirely to loss of fat. Significant increase in HDL concentrations by both diets ($p<0.001$) and decreased fasting insulin, insulin resistance, slCAM-1, and CRP levels by both diets ($p<0.05$).
Chrysohoou, Christina, et al. Adherance to the Mediterranean diet attenuates inflammation and coagulation process in healthy adults: the ATTICA study. *Journal of American College of Cardiology*, 2004; 44(1): 152-158.	1,514 males and 1,528 females from Attica, Greece age 18+ y/o	Epidemiologic study from May 2001 to December 2002	Adherance to the MD via diet score	Plasma levels of CRP, Interleukin-6, homocysteine, WBC count,	X	Participants with the best adherance to the MD revealed lower systolic BP and triglyceride levels and higher HDL levels ($p<0.001$). Most strict MD group had 20% lower CRP than those in the lowest MD adhering group ($p<0.015$).

Reference	Subjects	Type of Study	Independent Variable (MD, LCD, Both, Neither)	Dependent Variable	CRP*	Results relating to CRP change or diet
Dansinger, Michael L, Gleason, Joi Augustin, Griffith, John L, Selker, Harry P, Schaefer, Ernst J. Comparison of the Atkins, Ornish, Weight Watcher, and Zone diets for weight loss and heart disease risk reduction: a randomized trial. *JAMA.* 2005; 293(1): 43-53.	160 subjects (81 female, 80 male), with BMI 27-42, ages 22-72 years old with known HTN, dyslipidemia, or fasting hyperglycemia	Single-center randomized trial	Atkins diet <20g/day of carbohydrates which gradually increased to <50g/day, Zone diet, Weight Watchers, and Ornish diets	Weight loss, CRP, lipid levels, insulin levels	X	After 12 months, Atkins diet significantly decreased CRP from baseline ($p<0.05$). Weight loss was significantly associated with CRP change ($r=-0.37$). CRP was significantly associated with weight loss ($r=0.37$).
de Lorgeril, Michel de, et al. Mediterranean alpha-linolenic acid-rich diet in secondary prevention of coronary heart disease. *The Lancet.* 1994; 343: 1454-1459.	603 male and females <70 yeas old and <6 months status-post first MI	Prospective, random, single-blind, control trial	Mediterranean-type diet high in bread, fruits, vegetables, fish, and less meat and pork with moderate wine with meals allowed	Death from cardiovascular causes and non-fatal acute MI		After 5 years, the Mediterranean diet, with canola oil substituted for olive oil as the only fat, increased the absence of cardiac events $p<0.001$ and decreased mortality

Reference	Subjects	Type of Study	Independent Variable (MD, LCD, Both, Neither)	Dependent Variable	CRP*	Results relating to CRP change or diet
de Lorgeril, Michel, et al. Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction. *Circulation.* 1999; 99: 779-785.	423 male and female subjects age <70 years, clinically stable, who survived first myocardial infarction.	Population-based, prospective study	Mediterannean diet vs. control (no diet advice given, Westernized diet)	Cardiac death, non-fatal MI, ustable angina, stroke, heart failure, pulmonary or peripheral embolism, minor events require hospital admission		Cardiac death and non-fatal MI reduced in MD group than Westernized diet (p=0.0001). Mortality (cardiovascular and all-cause) and recurrent MI, cardiac death reduced in MD group (p=0.01).
Due, A, Toubro, S, Stender, S, Skov, AR, and Astrup, A. The effect of diets high in protein or carbohydrate on inflammatory markers in overweight subjects. *Diabetes, Obesity, and Metabolism.* 2005; 7: 223-229.	50 overweight subjects (12 male, 38 female) BMI 27-34, ages 18 - 56 years old	Randomized, controlled trial	Low fat diets (<30% of energy) either high protein and low-carbohydrate (25% and 45% of total calories) or high carbohydrate and low protein (58% and 12% of total calories).	CRP, Haptoglobin, Transferrin, Cholesterol, HDL, TG, LDL, glucose, and insulin	X	After 6 months, LCD group had non-significant decrease in CRP (p<0.06). Change in CRP was associated with change in body weight (r=0.346, p<0.05). Multiple regression analysis showed no influence of protein, fat, or carb % on CRP

Reference	Subjects	Type of Study	Independent Variable (MD, LCD, Both, Neither)	Dependent Variable	CRP*	Results relating to CRP change or diet
Esposito, Katherine, et al. Effect of a Mediterranean-style diet on endothelial dysfunction and markers of vascular inflammation in the metabolic syndrome: a randomized trial. *JAMA*. 2004; 292(12): 1440-1446.	180 subjects (99 male, 81 female) with metabolic syndrome	Randomized, controlled, single-blind trial	Mediterranean diet	Insulin resistance, CRP, IL-6, IL-7, IL-8, endothelial function, serum lipids, weight, BMI, waist circumference, and BP.	X	After 2 years, MD subj. had significant decreases in weight, BMI, waist circumference, BP, levels of glucose, insulin, total cholesterol, and TG and a significant increase in HDL. Hs-CRP was significantly reduced in MD when compared with control (p=0.01).
Esposito, Katherine, et al. Effect of weight loss and lifestyle changes on vascular inflammatory markers in obese women: a randomized trial. *JAMA*.2003; 289: 1799-1804.	120 premenopausal, obese women (BMI>30). Ages 20-46 years. Type 2 Diabetes, HTN, hyperlipidemia and impaired glucose tolerance were excluded	Randomized, controlled, single-blind trial	Low-energy (~1300 calories/day average), 50-60% carbohydrates, 15-20% protein, <30% fat, Mediterranean-style diet	Blood pressure, insulin sensitivity, plasma IL-6, IL-18, CRP, and adiponectin	X	After 2 years, serum CRP was significantly reduced within the MD group from baseline to end (p=0.01), and this is significantly better than the control (p=0.008). Changes in CRP were related to reduction in BMI (r=0.41, p=0.008).

Reference	Subjects	Type of Study	Independent Variable (MD, LCD, Both, Neither)	Dependent Variable	CRP*	Results relating to CRP change or diet
Ford E, Mokdad, AH, Liu, S. Healthy eating index and c-reactive protein concentration: findings from the national health and nutrition examination survey III, 1988-1994. *European Journal of Clinical Nutrition*. 2005; 59: 278-283	13,811 males and females age >20 y/o from the Third National Health and Nutrition Examination Survey (NHANES III)	Cross-sectional study with 24 hour recall dietary sssessment	Healthy eating index (HEI)	Serum c-reactive protein level	X	Subjects with elevated CRP levels were older, less educated, had higher BMI values, consumed less alcohol and total calories. A lower HEI score was inversely associated with CRP levels.
Foster, Gary D, Wyatt, Holly R, Hill, James O, McGuckin, Brian G, et al. A randomized trial of a low-carbohydrate diet for obesity. *The New England Journal of Medicine.* 2003; 348(21): 2082-90.	63 obese subjects (43 female, 20 male)	Randomized, controlled trial	Low-carbohydrate diet (carbohydrates limited to 20g/day and gradually increased until stable and desired weight achieved) vs conventional diet (60% carb, 25% fat, 15% protein)	Weight loss, blood pressure (BP), insulin sensitivity, and lipid levels		After 1 year, low-carb diet lost significantly more weight at 3 and 6 months, but no difference between groups at 12 months. No significant difference in total cholesterol or LDL concentrations. HDL and TG were higher in low-carbohydrate group. Both diets significantly decreased BP.

Reference	Subjects	Type of Study	Independent Variable (MD, LCD, Both, Neither)	Dependent Variable	CRP*	Results relating to CRP change or diet
Frederikson, Gunilla Nordin, Hedblad, Bo, Nilsson, Jan-Ake, Aim, ragnar, Berglund, Goran, Nilsson, Jan. Association between diet, lifestyle, metabolic cardiovascular risk factors, and plasma c-reactive protein levels. *Metabolism.* 2004; 53(11): 1436-1442.	760 male and females participants in Beta-Blocker Cholesterol Lowering Asymptomatic Plaque Study ages 49 to 70 years old with plaque in the R carotid artery without symptoms of carotid artery disease	Dietary analysis	Diet and lifestyle factors	CRP, BMI, blood pressure, plasma lipids	X	CRP increased with BMI, high total cholesterol/HDL ratio and with increased fasting glucose. No relationship between CRP and total cholesterol or LDL. No association between CRP and alcohol consumption or physical activity. Weak inverse association between total carbohydrate intake and CRP ($r=0.07$, $p<0.05$)
Fuentes, Francisco, et al. Mediterranean and low-fat diets improve endothelial function in hypercholesterolemic men. *Annals of Internal Medicine.* 2001; 134(12): 1115-1119.	22 hypercholesterolemic men	Intervention, randomized, cross-over	Diet high in saturated fat and then cross-over to either the NCEP-1 diet or Mediteranean diet	Plasma P-selectin levels, lipid concentrations, endothelial function		Increased flow-mediated vasodilation with MD ($p=0.027$). MD decreased total cholesterol, LDL, apolipoprotein B, and P-selectin.

Reference	Subjects	Type of Study	Independent Variable (MD, LCD, Both, Neither)	Dependent Variable	CRP*	Results relating to CRP change or diet
Gao, Xiang, Bermudez, Odilia, Tucker, Katherine L. Plasma c-reactive protein and homocysteine concentrations are related to frequent fruit and vegetable intake in hispanic and non-hipanic white elders. *Journal of Nutrition.* 2004; 134(4): 913-918.	445 Hispanic elders, 154 Non-hispanic	Cross-sectional study	Fruit and vegetable intake	Plasma CRP and homocysteine levels	X	High CRP was significantly greater in lowest quartile of fruit and vegetable consumption vs highest quartile. Significant inverse dose-response of fruits and vegetables and CRP (p=0.01).
Kenna, George A, Mcgeary, John E, Swift, Robert M. Clinical use of c-reactive protein for cardiovascular disease. *Southern Medical Journal.* 2004; 97(10): 985-988.	No subjects	Review	N/A	N/A		Evidence supports CRP as the marker of choice of inflammatory markers with high-sensitivity CRP methods recommended. AHA levels of low risk (<1.0mg/L), average risk (1.0-3.0mg/L) and high risk (>3.0mg/L).

Reference	Subjects	Type of Study	Independent Variable (MD, LCD, Both, Neither)	Dependent Variable	CRP*	Results relating to CRP change or diet
King, Dana E. Dietary fiber, inflammation, and cardiovascular disease. *Molecular Nutrition Food Research.* 2005; 49: 594-600.	No subjects	Review	N/A	N/A		CRP is an independent risk factor for disease. Elevated levels predict increased risk of recurrent ischemic events, progressio to MI, and revascularization. MD improves survival.
Knoops, Kim, et al. Mediterranean diet, lifestyle factors, and 10-year mortality in elderly European men and women: the HALE project. *JAMA.* 2004; 292(12): 1433-1439.	1507 male 832 female, 70-90 years old. Between the years 1988 and 2000 on subjects from the Healthy Ageing: a Longitudinal study in Europe population (HALE).	Cohort	Mediterranean diet, physical activity level, alcohol use, smoking	Ten-year mortality, coronary artery disease, cardiovascular disease, cancer.		Significant reduction in all-cause mortality with adherance to Mediterranean diet ($p=0.05$)

Reference	Subjects	Type of Study	Independent Variable (MD, LCD, Both, Neither)	Dependent Variable	CRP*	Results relating to CRP change or diet
Koenig, Wolfgang, et al. C-reactive protein, a sensitive marker of inflammation, predicts future risk of coronary heart disease in initially healthy middle-aged men: results from the MONICA (monitoring trends and determinants in cardiovascular disease) Augsburg Cohort Study, 1984 to 1992. *Circulation.* 1999; 99: 237-242.	936 healthy males age 45-64 years old.	Randomized, Cross-sectional , cohort study	C-reactive protein	Incidence of first major coronary heart disease (CHD) event	X	CRP is confirmed to be a sensitive systemic marker for inflammation and is involved in atherosclerosis.
Labarrere, Carlos A, Zaloga, Gary P. C-reactive protein: from innocent bystander to pivotal mediator of atherosclerosis. *American Journal of Medicine.* 2004; 117: 499-507.	No subjects	Review	N/A	N/A		C-reactive protein levels are independently associated with cardiovascular risk in patients with atherosclerosis, patients with other risk factors, and healthy persons.

Reference	Subjects	Type of Study	Independent Variable (MD, LCD, Both, Neither)	Dependent Variable	CRP*	Results relating to CRP change or diet
Liu, Simin, et al. Relation between a diet with a high-glycemic load and plasma concentrations of high-sensitivity c-reactive protein in middle-aged women. *American Journal of Clinical Nutrition.* 2002; 75: 492-498.	244 healthy females	Data from a random, double-blind, placebo study	Diet and measured glycemic load	High-sensitivity CRP	X	Carbohydrate quality and quantity (dietary glycemic load) was associated with increased CRP levels independent of BMI. Stronger association between CRP and BMI when BMI >25.
Lopez-Garcia, Esther et al. Consumption of (n-3) fatty acids is related to plasma biomarkers of inflammation and endothelial activation in women1. *Journal of Nutrition.* 2004; 134: 1806-1811.	727 healthy women from Nurses Health Study 1 cohort. Age 43-69	Cross-sectional study	Dietary intake of omega-3 fatty acids, alpha linolenic acid	Inflammatory markers including; CRP, IL-6, E-selectin, soluble tumor necrosis factor receptor 2 (sTNFR-2), soluble cell adhesion molecules (sICAM-1 and sVCAM-1)	X	CRP levels were 29% lower among those with highest intake of omega-3 fatty acids. Intake of alpha-linolenic acid was inversely related to CRP (p=0.02). Total omega-3 fatty acid had inverse relation with CRP (r=-0.44, p=0.007).

Reference	Subjects	Type of Study	Independent Variable (MD, LCD, Both, Neither)	Dependent Variable	CRP*	Results relating to CRP change or diet
Lopez-Garcia, Esther et al. Major dietary patterns are related to plasma concentrations of markers of inflammation and endothelial dysfunction. *American Journal of Clinical Nutrition.* 2004; 80: 1029-1035.	732 healthy women from Nurses' Health Study 1 cohort. Age 43-69 years and free of cardiovascular disease, cancer and diabetes.	Cross-sectional study	Dietary intake: prudent - similar to MD (intake of fruits, vegetables, legumes, fish, poultry and whole-grains) vs Western (intake of red meat, sweets, desserts, french fries and refined grains)	Inflammatory markers including; CRP, IL-6, E-selectin, soluble cell adhesion molecules (sICAM-1 and sVCAM-1), BMI, physical activity	X	Inverse association between prudent pattern and CRP ($p=0.02$). Western diet had positive correlation to CRP, even after adjustment for BMI ($p=0.02$).
Meckling, Kelly A, O'Sullivan, Caitriona, Saari, Dayna. Comparison of a low-fat diet to a low-carbohydrate diet on weight loss, body composition, and risk factors for diabetes and cardiovascular disease in free-living, overweight men and women. *Journal of Clinical Endocrinology and Metabolism.* 2004; 89: 2717-2723.	31 male and female subjects with a BMI >25	Randomized, controlled trial	Low-carbohydrate diet (LCD): 50-70 grams/day vs low-fat diet (LFD): control	Weight loss, body composition, blood pressure, glucose, insulin and plasma activator inhibitor - 1 (PAI-1), lipids, beta-hydroxybutyrate		After 10 weeks, significant weight loss was achieved in both the LCD and LFD but significant decrease in lean mass seen only in LCD group. LCD did significantly decrease circulating insulin concentrations. LCD also showed significant increase in HDL.

Reference	Subjects	Type of Study	Independent Variable (MD, LCD, Both, Neither)	Dependent Variable	CRP*	Results relating to CRP change or diet
Mezzano, D, et al. Original Communication: Complementary effects of Mediterranean diet and moderate red wine intake on haemostatic cardiovascular risk factors. *European Journal of Clinical Nutrition.* 2001; 55: 444-451.	42 males, mean age under 22 years (college students)	Controlled, prospective intervention study	Mediterranean diet + wine supplementation (days 30-60 only) vs high-fat diet (control)	Plasma concentration of emergent haemostatic cardiovascular risk factors (HCVRF) including: fibrinogen, factor VIIc, factor VIIIc, PAI-1, antithrombin III, protein C, protein S, and CRP	X	After 90 days, no change to CRP at any point in the study either by wine or diet.
Nicklas, Barbara J, et al. Diet-induced weight loss, exercise, and chronic inflammation in older, obese adults: a randomized controlled clinical trial. *American Journal of Clinical Nutrition.* 2004; 79: 544-551.	316 sedentary and obese (BMI > or = 28) males and females >60 years old with radiographic evidence of knee osteoarthritis	Single blind, random, controlled, study	Healthy lifestyle control, diet-induced weight loss, exercise, diet + exercise	IL-6, TNF-alpha, soluble IL-6 receptor (IL-6sR), soluble TNF-alpha receptor 1 (sTNFR1), soluble TNF-alpha receptor 2 (sTNFR2), and CRP	X	After 18 months, diet-induced weight-loss resulted in signifcantly greater reductions in CRP (r=-0.26,p=0.01), IL-6, and sTNFR1 than no weight-loss treatment. Changes in CRP were not correlated with changes in body weight.

Reference	Subjects	Type of Study	Independent Variable (MD, LCD, Both, Neither)	Dependent Variable	CRP*	Results relating to CRP change or diet
Noakes, Manny, Keogh, Jennifer B, Foster, Paul R, and Clifton, Peter M. Effect of an energy-restricted, high-protein, low-fat diet relative to a conventional high-carbohydrate, low-fat diet on weight loss, body composition, nutritional staturs, and markers of cardiovascular health in obese women. *American Journal of Clinical Nutrition.* 2005; 81: 1298-1306.	100 female subjects ages 20 through 65 years with a BMI of 27-40 without metabolic disease, Type 1 or Type 2 Diabetes	Randomized, parallel study design	High-protein, low-saturated-fat diet (46% carbohydrate) vs high-carbohydrate, low-saturated-fat diet	Weight loss, body composition, lipids, plasma insulin, CRP, glucose, nutritional status	X	After 12 weeks, CRP was decreased significantly from baseline to 12 weeks in both diet groups by 19% overall ($p<0.001$) with no significant effect of diet on CRP ($p=0.447$) high-protein vs high-carbohydrate. CRP decrease was related to weight loss.

Reference	Subjects	Type of Study	Independent Variable (MD, LCD, Both, Neither)	Dependent Variable	CRP*	Results relating to CRP change or diet
O'Brien, Kevin D et al. Diet-induced weight loss is associated with decreases in plasma serum amyloid A and c-reactive protein independent of dietary macronutrient composition in obese subjects. *Journal of Clinical Endocrinology and Metabolism.* 2005; 90: 2244-2249.	41 obese female subjects (BMI 30-35), age 18+ years	Randomized trial	Low-fat diet vs very-low-carbohydrate diet (<20 grams of carbohydrate/day for first 2 weeks, <60 grams of carbohydrate/day thereafter)	Body weight, blood pressure, lipids, insulin resistance, and inflammatory markers including CRP and serum amyloid A (SAA)	X	After three months of intervention, there was a significant decrease in CRP values in both diet groups from baseline values (p=0.035). Reduction in SAA was significantly greater for very-low carb group vs low-fat (p=0.04). Weight change was significantly correlated with logCRP (r=0.34, p=0.03). CRP values were log transformed due to highly skewed CRP value distribution.
Panagiotakos, Demosthenes B, et al. Status and management of hypertension in Greece: role of the adoption of the Mediterranean diet: the Attica study. *Journal of Hypertension.* 2003; 21: 1483-1489.	1128 males and 1154 females over 18 years old.	Cross-sectional survey	Mediterranean diet - through questionairre assessment	Blood pressure		26% lower risk of hypertension with Mediterranean diet (p=0.008). 36% odds ratio of better contol of hypertension with Mediterranean diet adherance (p=0.021).

Reference	Subjects	Type of Study	Independent Variable (MD, LCD, Both, Neither)	Dependent Variable	CRP*	Results relating to CRP change or diet
Pepys, Mark B, and Hirschfield, Gideon M. C-reactive protein: a critical update. *Journal of Clinical Investigation.* 2003; 111: 1805-1812.	No subjects	Review	N/A	N/A		Discussion of c-reactive protein
Ridker, Paul M, Glynn, Robert J, and Hennekens, Charles H. C-reactive protein adds to predictive value of total and HDL cholesterol in determining risk of first myocardial infarction. *Circulation.* 1998; 97: 2007-2011.	14,916 healthy males participating in the Physician's Health Study	Prospective, cohort study	Hypercholesterolemia and CRP	MI present on EKG or cardiac enzymes, death	X	Baseline CRP does add to the predictive value of lipid parameters in determining first MI. Relative risk of MI increased 38% with each increasing quartile of CRP ($p<0.001$).

Reference	Subjects	Type of Study	Independent Variable (MD, LCD, Both, Neither)	Dependent Variable	CRP*	Results relating to CRP change or diet
Ridker P, Cushman, Mary, Stampfer, Mieir J, Tracy, Russell P, Hennekens, Charles H. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. *The New England Journal of Medicine*. April 1997; 336(14): 973-979.	1,086 apparantly healthy men participating in the Physician's Health Study	Prospective, nested, case-control study	C-reactive protein and aspirin use	MiI, stroke, or venous thrombosis	X	Baseline CRP was higher in men who did have MI ($p<0.001$) and ischemic stroke ($p+0.02$) but not in venous thrombosis than those men without any vascular event outcome. ASA was significantly associated with decreased risk of MI. Baseline CRP does predict future risk of stroke and MI.
Ridker, Paul M, et al. Plasma concentration of c-reactive protein and risk of developing peripheral vascular disease. *Circulation.* 1998; 97: 425-428.	144 healthy males from the Physician's Health Study who developed symptomatic peripheral artery disease (PAD)	Prospective, nested, case-control study	Baseline CRP	Development of symptomatic PAD (claudication)	X	Median levels of CRP were significantly higher at baseline in those that developed PAD ($p=0.04$). Relative risk of developing PAD increased significantly with each increasing quartile of CRP baseline concentration ($p=0.03$).

Reference	Subjects	Type of Study	Independent Variable (MD, LCD, Both, Neither)	Dependent Variable	CRP*	Results relating to CRP change or diet
Ros, Emilio, et al. A walnut-diet improves endothelial function in hypercholesterolemic subjects: a randomized crossover trial. *Circulation.* 2004; 109: 1609-1614.	21 male and females ages 25-75 years with hypercholesterolemia	Randomized, cross-over trial	Mediterranean diet (control) vs walnut-enriched, isoenergetic diet	Endothelium-independent vasodilation, intracellular adhesion molecule-1, CRP, homocysteine, and oxidation biomarkers as well as lipids	X	After 4 weeks on Mediterranean diet, no sigificant changes on CRP.
Samaha, Frederick F, et al. A low-carbohydrate as compared with a low-fat diet in severe obesity. *The New England Journal of Medicine.* 2003; 348(21): 2074-2081.	132 male and female subjects ages 18+ years with BMI >35	Randomized trial	Low-carbohydrate diet (< or = 30 grams/day of carbohydrates) vs low-fat diet	Weight loss		After 6 months, LCD lost significantly more weight (p=0.002) and had a significantly greater reduction in triglycerides. No change in LDL, HDL, or total cholesterol within or between groups.

Reference	Subjects	Type of Study	Independent Variable (MD, LCD, Both, Neither)	Dependent Variable	CRP*	Results relating to CRP change or diet
Seshadri, Prakash, et al. A randomized study comparng the effects of a low-carbohydrate diet and a conventional diet on lipoprotein subfractions and c-reactive protein levels in patients with severe obesity. *American Journal of Medicine.* 2004; 117: 398-405.	78 subjects with a BMI >35. 86% had either Diabetes or Metabolic Syndrome	Randomized, controlled trial	Low-carbohydrate diet (<30 grams/day of carbohydrate) vs conventional diet	Weight, blood pressure, CRP, lipids, serum insulin, and glucose.	X	After 6 months, weight loss was greater among the LCD (95% confidence interval). In high-risk individuals at baseline, greater decrease in CRP with LCD were obtained vs conventional diet. Those that were low-risk CRP levels at baseline had an increase in CRP with LCD vs. conventional
Sharman, Matthew J, et al. A ketogenic diet favorably affects serum biomarkers for cardiovascular disease in normal-weight men. *Journal of Nutrition.* 2002; 132: 1879-1885.	20 normal weight, normolipidemic males	Randomized, controlled trial	Very-low-carbohydrate diet (<10% of total calories/day from carbohydrates) vs. habitual diet (control)	Fasting lipids, insulin, LDL particle size, oxidated LDL, and postprandial triacylglycerol (TAG)		After 6 weeks, significant decreases in fasting TAG, post-prandial lipemia, and fasting serum insulin concentrations with ketogenic diet. Significant increase in LDL size and no change in oxidative LDL concentration seen with LCD. LCD did increase HDL (p=0.066).

Reference	Subjects	Type of Study	Independent Variable (MD, LCD, Both, Neither)	Dependent Variable	CRP*	Results relating to CRP change or diet
Sharman, Matthew J, Gomez, Ana L, Kraemer, William J, and Volek, Jeff S. Very-low-carbohydrate and low-fat diets affect fasting lipids and post-prandial lipemia differently in overweight men. *Journal of Nutrition.* 2004; 134: 880-885.	15 males with body fat >25% otherwise healthy	Balanced, randomized, cross-over design	Two experimental diets for 6 week periods: very-low-carbohydrate diet (<10% of total daily calories from carbohydrates) vs low-fat diet	Fasting lipids, insulin, LDL particle size, oxidated LDL, and postprandial triacylglycerol (TAG)		After 6 weeks per diet, total cholesterol and LDL significantly increased at 2nd and 4th week of VLCD ($p<0.05$). Serum HDL significantly increased with VLCD. Serum insulin and insulin resistance were significantly reduced by theVLCD
Sharman, Matthew J, and Volek, Jeff S. Weight loss leads to reductions in inflammatory biomarkers after a very-low-carbohydrate diet and a low-fat diet in overweight men. *Clinical Science.* 2004; 107: 365-369.	15 overweight men (BMI of 34.2 + or - 5.6 kg/m2)	Balanced, randomized, cross-over design	Low-fat diet vs very-low-carbohydrate diet (<10% total daily calories from carbohydrates)	Inflammatory biomarkers including: high-sensitivity IL-6, high-sensitivity TNF-alpha, sICAM-1, sP-selectin, and hsCRP	X	After 6 weeks of VLCD hsCRP was significantly decreased ($p=0.00005$). Both low-fat and VLCD significantly reduced hsTNF-alpha, hsIL-6, hsCRP, and sICAM-1. VLCD significantly decreased body mass ($p<0.01$).

Reference	Subjects	Type of Study	Independent Variable (MD, LCD, Both, Neither)	Dependent Variable	CRP*	Results relating to CRP change or diet
Sierksma, A, et al: *European Journal of Clinical Nutrition*, 2002	10 middle-aged men, 10 post-menopausal women	Randomized, cross-over design	Moderate beer consumption vs moderate non-alcoholic beer consumption	Acute phase CRP and fibrinogen	X	CRP and fibrinogen levels decreased after three weeks of alcohol (beer) consumption p=0.02 and p< or =0.001 respectively
Sondike, Stephen B, Copperman, Nancy, and Jacobson, Marc S. Effects of a low-carbohydrate diet on weight loss and cardiovascular risk factors in overweight adolescents. *Journal of Pediatrics.* 2003; 142: 253-258.	39 subjects with primary obesity with a BMI > 95th percentile for age. Ages 12-18 years old.	Randomized, controlled trial	Low-carbohydrate diet (<20grams/day of carbohydrates for first two weeks, <40grams/day for weeks 3-12) vs low-fat diet (control)	Weight loss and serum lipids		After 12 weeks, LCD lost more weight than low-fat (p<0.05). No significant improvement in LDL levels. Serum triglyceride levels decreased significantly from baseline in LCD group.

Reference	Subjects	Type of Study	Independent Variable (MD, LCD, Both, Neither)	Dependent Variable	CRP*	Results relating to CRP change or diet
Stachowska, Ewa, et al. Elements of Mediterranean diet improve oxidative status in blood of kidney graft recipients. *British Journal of Nutrition.* 2005; 93: 345-352.	21 kidney graft recipients	Randomized, controlled trial	Mediterranean diet vs low-fat diet (control)	Oxidative status involving: alpha-tocopherol, thiobarbituric acid-reactive species (TBARS), activities of superoxide dismutase, catalase, and gluthione peroxidase in erythrocytes. CRP and lipids were also measured.	X	After 6 months, no significant change in CRP induced by diet. Decreased total cholesterol and triglycerides with MD.
Sundrarjun, T, et al. Effects of n-3 fatty acids on serum interleukin-6, tumour necrosis factor-alpha, and soluble tumour necrosis factor receptor p55 in active rheumatoid arthritis. *The Journal of International Medical Research.* 2004; 32: 443-454.	51 females and 9 males with rheumatoid arthritis	Random, double-blind, placebo-controlled trial	Fish oil supplementation	Serum IL-6, TNF-alpha receptor p55, CRP, sed rate, TNF-alpha and linoleic acid	X	Significant reduction in CRP from baseline in fish oil group by 11.1% (p=0.05). Significant reductions in linoleic acid, and sTNEF-r p55 from baseline with fish oil supplementation.

Reference	Subjects	Type of Study	Independent Variable (MD, LCD, Both, Neither)	Dependent Variable	CRP*	Results relating to CRP change or diet
Trichopoulou, Antonia, Costacou, Tina, Bamia, Christina, and Trichopoulos, Dimitrios. Adherance to a Mediterranean diet and survival in a Greek population. *The New England Journal of Medicine.* 2003; 348(26): 2599-2608.	22,043 adults age 20-86 years old.	Population-based, prospective study	Dietary intake and "Mediterranean diet score" figured	Survival		A 2 point increment increase in MD score was associated with a 25% reduction in total mortality ($p<0.001$).
Trichopoulou, Antonia, Bamia, Christina, and Trichopoulos, Dimitrios. Mediterranean diet and survival among patients with coronary heart disease in Greece. *Archives of Internal Medicine.* 2005; 165: 929-935.	28,572 males and females age 20-86 years old	Population-based, prospective study	Dietary intake and "Mediterranean diet score" figured	Survival		Higher adherance to the MD is associated with 27% lower mortality in those with coronary artery disease at enrollment ($p=0.05$).

Reference	Subjects	Type of Study	Independent Variable (MD, LCD, Both, Neither)	Dependent Variable	CRP*	Results relating to CRP change or diet
Volek, Jeff S, Sharman, Matthew J, Gomez, Ana L, Scheett, Timothy P, and Kraemer, William J. An isoenergetic very-low-carbohydrate diet improves serum HDL cholesterol and triacylglycerol concentrations, the total cholesterol to HDL cholesterol ratio and postprandial lipemic responses compared with a low fat diet in normal weight, normolipidemic women. *Journal of Nutrition.* 2003; 133: 2756-2761.	10 healthy subjects, normal weight (BMI <25), normo-lipidemic females ages 20-33 years old.	Balanced, randomized, two-period, cross-over trial	Very-low-carbohydrate diet <10% carbohydrates vs low-fat diet	Serum lipids, hsCRP, LDL subclasses, and triacylglycerols (oral fat tolerance test)	X	After 4 weeks per diet, total cholesterol and LDL significantly increased at 2 and 4 weeks with the LCD ($p<0.05$). Serum HDL significantly increased with LCD. There was no significant effect of either diet on CRP after 4 weeks.

Reference	Subjects	Type of Study	Independent Variable (MD, LCD, Both, Neither)	Dependent Variable	CRP*	Results relating to CRP change or diet
Willett, Walter C, et al. Mediterranean diet pyramid: a cultural model for healthy eating. *American Journal of Clinical Nutrition*. 1995; 61(6): 1402S-1406S.	No subjects	Review	N/A	N/A		MD consists of an abundance of plant foods with fresh fruit as a typical dessert. Concentrated sugars are only consumed a few times per week and olive oil is the main source of fat. Dairy products are consumed in small amounts and fish and poultry in low to moderate amounts. Red meant in small amounts and wine with meals.

Reference	Subjects	Type of Study	Independent Variable (MD, LCD, Both, Neither)	Dependent Variable	CRP*	Results relating to CRP change or diet
Yancy, William S, Olsen, Maren K, Guyton, John R, Bakst Ronna P, and Westman, Eric C. A low-carbohydrate, ketogenic diet versus a low-fat diet to treat obesity and hyperlipidemia: a randomized, controlled trial. *Annals of Internal Medicine.* 2004; 140: 769-777.	120 male and female subjects ages 18-65 years, with BMI of 30-60 and dyslipidemia	Randomized, controlled trial	Low-carbohydrate diet (initially <20 grams of carbohydrates daily, once half-way to goal weight an additional 5 grams/day were added each week until body weight was maintained) vs low-fat diet	Body weight, BMI, sand serum lipids		After 24 weeks, there was significantly greater weight loss in LCD group (-12.9%, $p<0.001$). LCD had greater change in triglycerides and increased HDL. There was no difference in LDL observed.
Yeh ET. CRP as a mediator of disease. Circulation. 2004; 109 (suppl II): II11-II14	None	Review	N/A	N/A		Discussion of C-reactive protein

***** An X in this column indicates that levels of c-reactive protein were measured and results provided

Appendix B

Reference	Type of Study: Subjects	MD	LCD	VLCD	CRP	Results	LOE*: GOR**
Brinkworth, GD, Noakes, M, Keogh, JB, Luscombe, ND, Wittert, GA, and Clifton, PM. Long-term effects of a high-protein, low-carbohydrate diet on weight control and cardiovascular risk markers in obese hyperinsulinemic subjects. *International Journal of Obesity.*2004; 28: 661-670.	Parallel, randomized, clinical intervention study: 43 obese (BMI between 27 and 43) subjects, 13 male and 45 females, age 20-65 years, non-Diabetic but with hyperinsulinemia	No	Yes, 40% of total calories from carbs (~140 grams/day), 30% fat, 30% protein	No	X	After 68 weeks, CRP decreased significantly from baseline in LCD group ($p<0.05$). Cannot rule out that the reduction in CRP was due to reduction in weight.	1B: A
Dansinger, Michael L, Gleason, Joi Augustin, Griffith, John L, Selker, Harry P, Schaefer, Ernst J. Comparison of the Atkins, Ornish, Weight Watcher, and Zone diets for weight loss and heart disease risk reduction: a randomized trial. *JAMA*. 2005; 293(1): 43-53.	Single-center, randomized trial: 160 subjects (81 female, 80 male) ages 22-72 with known hypertension, dyslipidemia, or fasting hyperglycemia, BMI 27-42	No	Yes, Atkins diet <20 grams/day of carbs gradually increased to <50 grams/day	No	X	After 12 months, the Atkins diet significantly decreased CRP from baseline ($p<0.05$). Weight loss was significantly associated with CRP change ($r=-0.37$).	1B: A

Reference	Type of Study: Subjects	MD	LCD	VLCD	CRP	Results	LOE*: GOR**
Due, A, Toubro, S, Stender, S, Skov, AR, and Astrup, A. The effect of diets high in protein or carbohydrate on inflammatory markers in overweight subjects. *Diabetes, Obesity, and Metabolism.* 2005; 7: 223-229.	Randomized, controlled trial: 50 overweight subjects (12 male, 38 female), BMI 27-34, ages 18-56	No	Yes, <45% of total calories from carbohydrates	No	X	After 6 mohts, LCD group had non-significant decrease in CRP (p=0.06). The change in CRP was associated with change in body weight (r=0.346, p<0.05). Multiple regression analysis showed no influence of protein, fat, or carbohydrate percentage on blood parameters of CRP	1B: A
Esposito, Katherine, et al. Effect of a Mediterranean-style diet on endothelial dysfunction and markers of vascular inflammation in the metabolic syndrome: a randomized trial. *JAMA*. 2004; 292(12): 1440-1446.	Randomized, controollled, single-blind trial: 180 subjects (99 male, 81 female) with metabolic syndrome	Yes, MD	No	No	X	After two years, patients on MD had significant decrease in serum high-sensitivity CRP (p=0.01)	1B: A

Reference	Type of Study: Subjects	MD	LCD	VLCD	CRP	Results	LOE*: GOR**
Esposito, Katherine, et al. Effect of weight loss and lifestyle changes on vascular inflammatory markers in obese women: a randomized trial. *JAMA*.2003; 289: 1799-1804.	Randomized, single-blind: 120 premenopausal obese women (BMI >30) ages 20-46 years, Type 2 diabetes and impaired glucose tolerance were excluded	Yes, diet similar to MD in composition (50-60% carb, 15-20% protein, <30% total fat and <10% saturated fat	No	No	X	After two years, serum CRP was significantly reduced within the MD group from baseline to end p=0.01, but lower CRP levels were correlated with decreased BMI (r=0.41, p=0.008)	1B: A
Mezzano, D, et al. Original Communication: Complementary effects of Mediterranean diet and moderate red wine intake on haemostatic cardiovascular risk factors. *European Journal of Clinical Nutrition*. 2001; 55: 444-451.	Prospective, controlled intervention study: 42 healthy undergraduate or graduate university male students, mean age of 22. BMI at baseline of 23.4+ or - 2.0 in MD diet group and 23.7+ or - 2.5 in high fat diet group.	Yes, MD intervention for 90 days with red wine supplementation on days 30-60	No	No	X	After 90 days of the MD, no significant differences in CRP, nor changes in CRP from baseline induced by diet or wine supplementation	1B: A

Reference	Type of Study: Subjects	MD	LCD	VLCD	CRP	Results	LOE*: GOR**
Noakes, Manny, Keogh, Jennifer B, Foster, Paul R, and Clifton, Peter M. Effect of an energy-restricted, high-protein, low-fat diet relative to a conventional high-carbohydrate, low-fat diet on weight loss, body composition, nutritional staturs, and markers of cardiovascular health in obese women. *American Journal of Clinical Nutrition.* 2005; 81: 1298-1306.	Randomized, parallel: 100 obese females (BMI 27-40), age 20-65 with no history of metabolic disease or Type 1 or 2 Diabetes	No	Yes, 46% carbohydrates, 20% fat, 34% protein of total calories	No	X	After 12 weeks, CRP was decreased significantly from baseline in both diet groups by 19% overall ($p<0.001$) with no significant effect of diet on CRP ($p=0.447$) high-protein vs high-carbohydrate diet. CRP decrease was related to weight loss.	1B: A
O'Brien, Kevin D et al. Diet-induced weight loss is associated with decreases in plasma serum amyloid A and c-reactive protein independent of dietary macronutrient composition in obese subjects. *Journal of Clinical Endocrinology and Metabolism.* 2005; 90: 2244-2249.	Randomized trial: 41 female obese (BMI 30-35) subjects, age 18+, and stable weight over preceding 6 months	No	Yes, <20 grams of carbohydrates week 1 and 2, then <60 grams daily for three months	No	X	After three months of intervention, there was a significant decrease in CRP values in both diet groups from baseline values ($p=0.035$). Weight change was significantly correlated with logCRP ($r=0.34$, $p=0.03$). CRP values were log transformed due to highly skewed CRP value distribution.	1B: A

Reference	Type of Study: Subjects	MD	LCD	VLCD	CRP	Results	LOE*: GOR**
Seshadri, Prakash, et al. A randomized study comparng the effects of a low-carbohydrate diet and a conventional diet on lipoprotein subfractions and c-reactive protein levels in patients with severe obesity. *American Journal of Medicine.* 2004; 117: 398-405.	Randomized trial: 78 severely obese male and female subjects, BMI > or = 35, 86% of subjects had either Metabolic Syndrome or Diabetes	No	No	Yes, < or = 30 grams/day of carbohydrates	X	There was a moderate decrease in CRP levels after six months of intervention. High risk CRP levels at baseline experienced significant reduction in CRP levels p=0.005. Low to moderate baseline risk experienced an increase in CRP levels that was not significant	1B: A
Sharman, Matthew J, and Volek, Jeff S. Weight loss leads to reductions in inflammatory biomarkers after a very-low-carbohydrate diet and a low-fat diet in overweight men. *Clinical Science.* 2004; 107: 365-369.	Randomized, crossover trial: 15 overweight males (mean BMI 34.3 + or - 5.6kg/m2), age 33.2 + or - 11.3 years	No	No	Yes, <10% of total calories from carbohydrates, 30% protein, 60% fat	X	After six weeks of VLCD, high sensitivity CRP was significantly decreased (p=0.00005). Cannot rule out that the reduction in CRP was due to reduction in weight.	1B: A

Reference	Type of Study: Subjects	MD	LCD	VLCD	CRP	Results	LOE*: GOR**
Stachowska, Ewa, et al. Elements of Mediterranean diet improve oxidative status in blood of kidney graft recipients. *British Journal of Nutrition.* 2005; 93: 345-352.	Randomized, controlled trial: 32 kidney graft recipients male and female with average BMI of 25.0 in study group and 26.2 in control group	Yes, MD principles	No	No	X	After six months, there was no significant change in CRP induced by diet	1B: A
Volek, Jeff S, Sharman, Matthew J, Gomez, Ana L, Scheett, Timothy P, and Kraemer, William J. An isoenergetic very-low-carbohydrate diet improves serum HDL cholesterol and triacylglycerol concentrations, the total cholesterol to HDL cholesterol ratio and postprandial lipemic responses compared with a low fat diet in normal weight, normolipidemic women. *Journal of Nutrition.* 2003; 133: 2756-2761.	Randomized, crossover trial: 10 healthy 20-33 year old female subjects, BMI <25, normolipidemic	No	No	Yes, <10% of total calories from carbohydrates	X	After four weeks of the VLCD no significant effect on high-sensitivity CRP was found	1B: A

* Level of Evidence
** Grade of Recommendation

Curriculum Vita

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