Effect of Nutritional Status and Dietary Patterns on Human Serum C-Reactive Protein and Interleukin-6 Concentrations\textsuperscript{1,2}

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Abstract
The inflammatory process plays an important role in the pathogenesis of many chronic diseases, such as cardiovascular diseases, diabetes mellitus type 2, and metabolic syndrome. Serum C-reactive protein (CRP) and interleukin-6 (IL-6) are widely tested inflammatory markers involved in the development of these diseases. Several studies indicate a relation between nutritional status and the concentrations of human high-sensitivity CRP and IL-6. Similarly, the role of diet in reducing inflammation and thereby modulating the risk of non-communicable diseases is supported by numerous studies. This review focuses on the effects of the selected nutrition models in humans on the concentrations of CRP and IL-6. It seems that the Mediterranean diet model is most effective in inhibiting inflammation. The Dietary Approaches to Stop Hypertension model and the plant nutrition model also have proven to be beneficial. The data on low-fat and low-carbohydrate diets are inconclusive. Comprehensive studies are necessary, taking into account the cumulative effect of dietary and other factors on the inflammatory process. \textit{Adv Nutr} 2015;6:738–47.

Keywords: inflammation, inflammatory markers, nutrition model, Mediterranean diet, DASH diet

Introduction
In recent years, an increasing incidence of chronic non-communicable diseases (NCDs)\textsuperscript{3} related to diet, obesity, cardiovascular diseases (CVDs), including hypertension and diabetes mellitus type 2 (DM2), are becoming a 21st-century epidemic. A total of 57 million deaths occurred in the world during 2008; 36 million (63\%) were a result of NCDs. The leading causes of NCD deaths in 2008 were CVDs (48\% of NCD deaths). WHO projections show NCDs will be responsible for a substantially increased total number of deaths in the next decade (1). Poland is among the countries in which the high prevalence of chronic NCDs is observed. Similarly, the dominant causes of deaths in Poland are related to CVDs, which in 2010, were responsible for 46\% of the total number of deaths (2). The report from the International Diabetes Federation in 2013 about the incidence of diabetes in different regions of the world and countries showed alarming data. Namely, \textasciitilde 5.1 million people between 20 and 79 y of age died of diabetes in 2013, accounting for 8.4\% of global all-cause mortality among people in this age group. The number of deaths attributable to diabetes in 2013 showed an 11\% increase over estimates for 2011 (3). According to the WHO, obesity is also classified as an epidemic disease (4).

Data in the literature show a relation between inflammation and chronic diseases, such as CVDs, DM2 (5), and metabolic syndrome (6). Inflammation is a necessary response of the immune system to acute infection or trauma; however, a prolonged inflammatory state has detrimental health effects (7).

Subclinical chronic inflammation plays a key role in the development of atherosclerosis, a key factor in the initiation of CVDs (8, 9). The inflammatory process extending into the vascular wall is accompanied by endothelial dysfunction, whereas the activated endothelium taking part in the atherosclerotic plaque destabilization paves the way for future CVD events. Increased expression and activation of C-reactive protein (CRP) and proinflammatory cytokines, such as IL-6, is associated with atherogenesis and CVDs. Biomarkers of inflammation are therefore considered predictors of future CVD events (10, 11). However, high-sensitivity CRP (hsCRP) is a stronger and independent predictor of CVDs than are other inflammatory markers and even serum lipids (9). The data also indicate a significant association...
between elevated concentrations of IL-6 and CRP (12) and the risk of DM2 (7).

CRP is an acute-phase protein and is one of the most sensitive and most recurrent markers of inflammation. CRP is synthesized and excreted primarily by hepatocytes in response to proinflammatory cytokines. CRP is present in the serum of healthy individuals in small quantities, and its concentration increases rapidly over the course of inflammation or necrotic processes (13). However, it was noted that slightly elevated concentrations, measured with the use of hsCRP, indicate that inflammation is under way in the vascular wall (13). Many studies have shown that an increase in the concentration of hsCRP is associated with an increased risk of CVDs in different populations around the world. Mortality from CVDs are 2-fold higher when hsCRP is >3 mg/L. This concentration is considered high risk by the AHA and the CDC, compared with when hsCRP is <1 mg/L (9).

CRP is involved in all stages of the design, remodeling, and rupture of plaque. This increases the influx of inflammatory cells to the walls of the arteries, the expression of adhesion molecules on the surface of endothelial cells, and the synthesis of monocyte chemotactic protein, endothelin-1, plasminogen activator inhibitor-1, while reducing the bioavailability of nitric oxide. It also increases uptake of LDLs by macrophages and is involved in the activation of complement components. In addition, CRP enhances the formation of blood clots, thereby mediating the remodeling and destruction of plaque (13). Elevated concentrations of CRP reflect endothelial dysfunction through the deterioration of its anti-inflammatory activity (14). CRP is correlated with the components of metabolic syndrome: atherogenic dyslipidemia, obesity, and insulin resistance (15).

Adipose tissue plays an important role in the body's inflammatory processes (8). Adipocytes are, in fact, the source of proinflammatory cytokines, including IL-6, which is one of the most important factors that influences the hepatic production of CRP. Obesity, therefore, contributes to the formation of a proinflammatory environment (16).

It has been shown that anthropometric indicators, such as BMI (in kg/m²) and waist circumference (WC), are correlated with CRP (8, 17). There is also a close relation between CRP and body fat (8). However, the main determinant of serum hsCRP concentration is not only the amount of body fat but also its distribution. It was shown that adipocyte abdominal fat may have a higher concentration of CRP of 0.18 mg/L (18) and higher CRP secretion (19) than subcutaneous depots. CRP concentrations are higher in obese patients, especially patients with excess visceral fat, than in patients of normal weight (20).

Despite intensive research, the cause of chronic inflammation is not known (21). Presumably, it is because of the stimulation of the immune system by external factors [high-fat (HF) and high-calorie diets, infections, mental stress, oxidative stress]. However, a special role is attributed to diet (19). Several studies have shown a significant relation between hsCRP and IL-6 and various dietary factors in humans, suggesting that the concentrations of inflammatory biomarkers can be modified by diet (9). Until now, many studies have focused on the relation between individual nutrients and the concentration of inflammatory markers and risk of NCDs, but, recently, it has been demonstrated that the study of dietary patterns can produce more precise results (5).

The article presents the effect of different nutrition models and the health implications of nutritional status on the concentration of inflammatory markers (CRP and IL-6). Systematization of dietary patterns in relation to inflammation allows for the isolation of the optimal model for the prophylaxis and therapeutic strategies necessary to control chronic inflammatory reactions, consequently reducing the risk of diseases associated with it.

Current Status of Knowledge
Relation between nutritional status and the concentration of CRP and IL-6

Park et al. (16) evaluated the relation between obesity, visceral obesity, and serum concentrations of CRP and IL-6. The study was conducted on a group of 100 Korean adults who were free from preexisting inflammatory disease or cancer. It was found that in the whole cohort, CRP and IL-6 concentrations were significantly correlated with body weight, BMI, WC, hip circumference, and the waist-hip ratio (WHR), but CRP was more strongly correlated than IL-6. Median CRP and IL-6 concentrations were significantly higher in obese subjects than in nonobese subjects. The CRP concentration of obese individuals was significantly correlated with all anthropometric variables measured and the mass of fat, total fat area, and visceral adipose tissue, with the exception of subcutaneous adipose tissue. In contrast, the IL-6 concentration was significantly associated with body weight, BMI, hip circumference, WC, body fat mass, and visceral adipose tissue. Multiple regression analyses showed that CRP was significantly correlated with BMI, whereas IL-6 correlated with visceral adipose tissue in obese individuals. The results of this study confirm the discovery that adipose tissue is an endocrine organ that can secrete a dynamic range of factors that influence inflammation.

Lim et al. (8) rated the relation between hsCRP and various indicators of obesity (body weight, BMI, fat mass, percentage of body fat, WC, WHR, and skinfold thickness) in a group of Koreans aged 40–69 y with hsCRP not exceeding 10 mg/L. The investigators showed that the percentage of body fat was highly correlated with log-transformed hsCRP concentrations. The correlation was stronger in women ($r = 0.24, P < 0.01$) than in men ($r = 0.18, P < 0.01$).

In addition, in the multiple regression model, taking into account sex, age, rural or urban community, BMI, WHR, WC, blood pressure, blood glucose, insulin, and lipids, smoking, alcohol consumption, and physical activity, body fat percentage was most strongly associated with hsCRP. In this study, it was found that in addition to the percentage of body fat, all of the evaluated variables of nutritional status [body weight, BMI, body fat (in kg), WC, hip circumference, WHR, and skinfold thickness] correlated with the concentration of hsCRP.
The exception concerned the correlation between hsCRP and lean body mass in men. Moreover, a downward trend was observed in the concentration of hsCRP, from the lowest tertile to the highest body weight changes, taking into account the change in body weight from the maximum lifetime body weight to the current weight during the study. In addition, study participants who reported an increase in body weight (>2 kg) during the month before the study had higher concentrations of hsCRP than did participants who reported weight loss, but this was of borderline statistical significance \( P = 0.073 \). This result suggests that obesity may be a factor in the concentration of hsCRP and that the reduction of body fat may be useful in reducing the CRP concentration, ultimately contributing to reduced CVD-related mortality. These investigators observed the previously stressed fact that the degree of correlation between the rates of obesity and hsCRP in Asian populations is lower than in the Western populations.

Randomized studies (7) that evaluated the impact of the loss of total body fat and region-specific (abdomen and thigh) fat on the concentration of CRP and IL-6 in elderly individuals who are overweight obese with knee osteoarthritis confirmed that loss of body fat is associated with a significant decrease in CRP and IL-6. However, the investigators observed that a loss in the total amount of fat resulted in the best-fit regression model, although the loss of visceral adipose tissue itself also inhibited inflammation (7).

A survey of older people aged 60–90 y confirmed the existence of a correlation between hsCRP and nutritional status. In this study, a significant correlation was found between hsCRP and BMI \( (r = 0.22, P = 0.0082) \) (17). Similar results were found in a group of young people. Namely, it was shown that obese young people had elevated plasma concentrations of CRP compared with nonobese individuals \( (P < 0.001) \). Plasma concentrations of CRP were 3-fold higher in obese \( (3.6 \pm 3.0 \text{ mg/L}) \) than in normal-weight children \( (1.2 \pm 1.7 \text{ mg/L}) \) (22). Research from 2015 also showed that CRP is correlated with body weight, WC, and BMI (12).

Research by Alizadeh Dehnavi et al. (20) suggested, however, that visceral obesity is not a major determinant of inflammation. Indeed, the researchers found no difference in the distribution of body fat in men with hsCRP >2.5 mg/L, compared with the control group \( (\text{hsCRP: } <1.8 \text{ mg/L}) \). At the same time, WC was significantly correlated with CRP \( (r = 0.20, P < 0.001) \), but 18.2% of patients with a WC 94–102 cm had elevated CRP, and 9.6% of patients with WC >118 cm had low concentrations of CRP. Timpson et al. (23) suggested a potential contribution of genetic factors on changes in CRP.

**Effect of diet on CRP and IL-6 concentrations**

Traditionally, nutritional research focuses on the relation between diseases and food groups or certain nutrients. Such studies do not allow for a comprehensive assessment of the complexity of the relation between diet and the risk of diseases. Examination of nutritional models and dietary patterns assessing diet as a whole is a growing field of research, and studying these relations may provide important insights (10, 24).

**Diet high in fruits and vegetables (plant model).** Numerous studies confirm that a high intake of fruit, vegetables, and plant foods are associated with low concentrations of inflammatory markers. It was demonstrated that a vegetarian diet has a beneficial effect on the course of the inflammatory response.

Researchers assessed the concentration of hsCRP among people aged 19–75 y who adhere to different models of diet, including a vegetarian diet (lacto and lacto-ovovegetarian) and a mixed diet. Mean hsCRP was significantly lower in the vegetarian than in the mixed group \( (0.72 \pm 0.07 \text{ compared with } 1.62 \pm 0.12 \text{ mg/L}) \). The study suggested that fruit and vegetables are a source of many anti-inflammatory substances, including salicylates (25). Nettleton et al. (26) showed that a model based on the consumption of whole grains, fruits, nuts, and green leafy vegetables was significantly inversely correlated with concentrations of CRP and IL-6 in a multi-ethnic population. Among the Japanese population, it was demonstrated that a dietary pattern characterized by high consumption of vegetables, fruit, fish, and soy products was significantly inversely associated with serum hsCRP, even after adjustment for age, BMI, smoking, alcohol consumption, and physical activity (27).

The influence of dietary patterns on inflammatory biomarkers in the elderly has also been investigated. In the study by Anderson et al., the following 6 dietary patterns were assessed: healthy food, cereal, meat and alcohol, sweets and desserts, refined grains, and HF dairy products. The health food pattern was characterized by a high intake of low-fat (LF) dairy products, fruits, whole grains, poultry, fish, and vegetables and a low intake of red meat and added fat and high-energy beverages. This model was associated with lower concentrations of IL-6 than diets high in sweets and desserts and HF dairy products, but no difference was found in the CRP concentration with any dietary pattern (28).

Julia et al. (29) confirmed that dietary patterns characterized by consuming high levels of vegetable and vegetable oil, leading to a high supply of antioxidants and essential FAs, are inversely correlated with risk of elevated CRP. In the study by Lee et al. (15), the relation between nutrition patterns and concentrations of CRP were rated in a group of 7574 Koreans.

Four dietary patterns, fruit, vegetables, meat, and coffee, were analyzed. It was shown that the vegetables model was inversely correlated with CRP \( (P\text{-trend } = 0.01) \). In addition, the mean concentration of CRP was 0.04 mg/dL lower in subjects at the highest quartile than in the lowest quartile. Interestingly, this relation was more pronounced in men with hypertension. The anti-inflammatory effect of eating vegetables was confirmed in the study by Ko et al. (9). Women at high CVD risk \( (\text{CRP: } >3 \text{ mg/L}) \) consumed less fruit, vegetables, plant food, potassium, and folic acid than did women of the low-risk group \( (\text{CRP: } <1 \text{ mg/L}) \).
It was also found that a significant inverse correlation was found between hsCRP and the consumption of vegetables and fruits (12). Similarly, a study showed that a vegan diet model has the effect of reducing inflammation. The study included a brief nutritional intervention (3 wk) among 604 people aged 18–90 y. The intervention consisted of a vegan diet rich in fresh fruits and vegetables, whole grains, legumes, nuts, and seeds. This model reduced inflammation measured by CRP. The baseline CRP concentration was an important indicator of the degree of improvement, and higher initial CRP concentrations resulted in a greater reduction after intervention. The interaction between baseline CRP and sex was significant and showed that men with higher baseline CRP concentrations had a stronger decline in CRP during nutritional intervention than did women. It was not shown that the length of nutritional intervention influences the change in CRP. Meanwhile, participants who followed a vegan diet before entering the study had a lower CVD risk, as measured by CRP concentrations (12).

The systematic review by DeFogo et al. (30) confirmed that dietary patterns rich in fruits and vegetables have a beneficial effect on endothelial function, as estimated by the CRP concentration. Presumably, the high supply of vitamins and minerals in the plant model may have anti-inflammatory effects, but the use of supplementation does not bring similar benefits. In a review and meta-analysis of randomized controlled trials conducted by Sun et al. (31), no effect of vitamin–mineral supplementation was found on concentrations of CRP and IL-6. However, Kubota et al. (32) found an inverse correlation between serum concentration of vitamin C and hsCRP concentrations in both men and women, particularly in nonsmokers, non-overweight women, and postmenopausal women.

High-fiber intake in the plant model can also contribute to a reduction in inflammatory markers. It was shown that fiber supplementation is associated with a reduction in CRP (33). The study by Ajani et al. (34) found an inverse correlation between CRP and the consumption of dietary fiber. It was also proven that dietary fiber intake was negatively related to the concentration of IL-6 (P-trend = 0.01 for total dietary fiber, 0.004 for soluble fraction, 0.001 for insoluble fraction). In the same study, however, no significant correlation was found between fiber intake and hsCRP (35).

Mediterranean diet. The Mediterranean diet is the best-studied model of nutrition in the context of many diseases, including all components of the metabolic syndrome. It is a diet typical of the Mediterranean population. Traditionally, the Mediterranean diet is characterized by high consumption of olive oil, vegetables, fruit, vegetable protein, whole grains, legumes, nuts, fish, LF dairy products, low to moderate consumption of poultry, low intake of red meat, and moderate alcohol consumption. Olive oil is the main source of fat in this diet model (11, 24). Many observational, prospective, and randomized studies confirm the inverse relation between the Mediterranean diet and inflammatory markers (24). The Greek ATTICA study (36) found correlations between higher adherence to the Mediterranean diet and the reduction of serum IL-6 and CRP. Participants who were in the highest tertile of consumption had, on average, 20% lower CRP concentrations (P = 0.015) and 17% lower concentrations of IL-6 (P = 0.025) compared with those from the lowest tertile. The results were significant even after correction analysis. The investigators found that adherence to the Mediterranean diet is associated with a decrease in inflammatory markers, which partly explains the beneficial effects of this diet on the cardiovascular system. The Nurses’ Health Study (37) analyzed several diet quality indexes, showing that use of the Mediterranean diet, as measured by the alternative Mediterranean Diet index, was associated with significantly lower concentrations of CRP and IL-6 (24% and 16%, respectively). Interesting results were obtained in the PREDIMED (38) studies. In a group of 772 patients with a high CVD risk, after 3 mo of following the recommendations, patients who consumed the Mediterranean diet supplemented with olive oil had a lower concentration of hsCRP than did patients who consumed the Mediterranean diet supplemented with nuts or a LF diet. Body weight and body fat measurement were decreased in all groups, which supports the view that the change in body weight does not explain the reduction in hsCRP with the Mediterranean diet supplemented with olive oil. The results from the PREDIMED study in 2008 (39) rated the relation between the components of the Mediterranean diet and inflammatory biomarkers in patients with high CVD risk. After adjusting for age, sex, BMI, presence of diabetes, smoking, the use of statins or nonsteroidal anti-inflammatory drugs, and a higher intake of fruits and cereals, the diet was associated with lower concentrations of IL-6 (P = 0.005). Patients with the highest intake of nuts and olive oil showed the lowest concentrations of IL-6 and CRP, but the relation did not reach statistical significance. Ahluwalia et al. (24) evaluated the relation between the different dietary patterns, including the Mediterranean diet, and inflammation, confirming earlier reports about the beneficial effects of this model. The investigators conclude that the protective effect of the Mediterranean diet on inflammatory markers, such as CRP and IL-6, are generally independent of traditional risk factors of CVDs and weight loss. The review used MEDLINE and rated up to 479 articles. In a clinical study on a group of obese patients, adherence to a low-calorie diet that was based on the Mediterranean diet model was associated with a statistically significant improvement in the inflammatory profile (reduction of CRP and IL-6). Reducing the concentration of IL-6 was independent of caloric restriction and weight reduction. Although interesting results were obtained, the study lacked a control group (40). Strong evidence for the anti-inflammatory effects of the Mediterranean diet was provided in randomized trials.

In the study by Esposito et al. (41), 120 obese premenopausal women aged 20–46 y who consumed a low-energy Mediterranean diet and participated in physical activity showed a statistically significant decrease in the concentration of IL-6 (−1.1 pg/mL; P = 0.009) and CRP (−1.6 mg/L;
that the ratio of n-6/SFA was higher with the Mediterranean diet than with the control group (50–60% carbohydrates, 15–20% protein, <30% fat). The anti-inflammatory effect of the Mediterranean diet model persisted even after adjusting for weight loss. The investigators suggested that the anti-inflammatory effects, in addition to weight loss, involved several mechanisms, including an antioxidant effect of vitamins and n-3 (ω-3) FAs and a reduction in the concentrations of circulating proinflammatory cytokines caused by dietary fiber. However, we cannot assess the impact of the effect of individual nutrients (14).

A systematic review and meta-analysis of intervention studies that evaluated the effect of the Mediterranean diet on endothelial function and inflammation, published in 2014 by Schwingshackl and Hoffmann (11), confirmed the anti-inflammatory effect of this model. Researchers reviewed the literature with the use of MEDLINE, EMBASE, and the Cochrane Library, taking into account the randomized intervention with a minimum period of 12 wk in patients aged ≥19 y. A total of 17 studies, published between 2003 and 2013, including 23,000 people aged 25–77 y, were reviewed. Adherence to the Mediterranean diet resulted in a significant decrease in the concentration of CRP (−0.98 mL/L; 95% CI: −1.48, −0.49; P < 0.0001) and IL-6 (−0.42 pg/mL; 95% CI: −0.73, −0.11; P = 0.008) compared with controls. The results of the meta-analysis provide evidence that this diet could reduce the risk of death and CVDs. It should be noted that reports indicate that the effect of the Mediterranean diet may be stronger in patients with existing CVD risk factors than in healthy individuals with low concentrations of inflammatory markers. These cardioprotective and anti-inflammatory effects of the Mediterranean diet may be less obvious (24, 42).

Ambrin et al. (42) rated the effects of the Mediterranean diet on inflammation and the composition of FAs in blood serum phospholipids of healthy individuals. The women were divided into 2 groups: Mediterranean diet or normal Swedish diet for 4 wk in a crossover trial. It was shown that the ratio of n-6 to n-3 in the serum was significantly lower in the Mediterranean diet group (P < 0.0001). However, no significant reduction was found in hsCRP and IL-6. The study concluded that the Mediterranean diet is associated with a higher concentration of n-3 in blood serum.

**LF compared with LC model.** Studies that evaluated the effect of a LF and low-carbohydrate (LC) diet on weight loss and inflammatory markers produce conflicting results. Sharman et al. (43) compared weight loss with very LC diets (<10% of energy) with low fat (<30% of energy) on inflammatory markers in men with excess body weight. The investigators found that both diets resulted in a significant reduction in body weight, hsCRP, and other determined inflammatory markers. These data suggest that in the short term, weight loss is a major force underlying the reduction of inflammatory markers. Dansinger et al. (44) found similar results when comparing 4 popular weight-loss diets, including the LC Atkins diet and the LF Ornish diet, on the level of CVD risk. In the study, the decrease in CRP was associated with weight loss. However, this decrease was independent of the nutrition models. In addition, in a 3-mo randomized clinical trial that compared nutritional intervention with LC compared with LF diets in obese women, it was found that the decrease in CRP correlated with weight loss. This effect was proportional to the amount of body weight loss (r = 0.35, P = 0.03) but independent of the content of dietary macronutrients (45). In a randomized trial by Sheshardi et al. (46), the effect of LC and conventional diets on the concentration of CRP was compared in patients with obesity (BMI: >35). After 6 mo, greater weight loss was observed with an LC diet (−8.5 ± 9.3 compared with −3.5 ± 4.9 kg), but CRP concentrations decreased slightly in both groups. However, in patients with high baseline CRP (≥3 mg/dL) a higher reduction was found with the LC diet.

Rankin et al. (47) obtained different results when studying the impact of diet composition on weight loss and inflammatory markers (CRP, IL-6). The study involved 29 overweight women who were assigned to one of 2 groups: the LC/HF group or the high-carbohydrate (HC)/LF group. The diets were isocaloric but differed in macronutrient supply (LC/HF: 58% of energy from fat, 12% carbohydrates, 30% protein; HC/LF: 24% of energy from fat, 59% carbohydrates, 18% protein). The investigators found that, despite the greater weight loss in the LC/HF group, CRP concentrations increased by 25%. In the HC/LF group, the CRP concentration decreased by 43%. The study suggests that the composition of the diet influences the inflammatory markers, wherein the LC/HF diet increased and the HC/HF diet reduced the concentration of CRP.

The effectiveness of diets low in carbohydrates was also compared with LF diets in patients with hypertriglyceridemia in terms of weight loss and hsCRP concentrations. A LC diet provided 15% of calories from carbohydrates, 20–30% from protein, and the remaining portion (55–65%) from fat and reduced SFAs <10% of the energy value of the diet. The diets were isocaloric but differed in macronutrient supply (LC/HF: 58% of energy from fat, 12% carbohydrates, 30% protein; HC/LF: 24% of energy from fat, 59% carbohydrates, 18% protein). The investigators found that, despite the greater weight loss in the LC/HF group, CRP concentrations increased by 25%. In the HC/LF group, the CRP concentration decreased by 43%. The study suggests that the composition of the diet influences the inflammatory markers, wherein the LC/HF diet increased and the HC/HF diet reduced the concentration of CRP.
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<td>Esposito et al. (41)</td>
<td>120 Obese premenopausal women aged 20–46 y with the use of low-energy MD with physical activity or control diet (followed general recommendation)</td>
<td>IL-6 (P = 0.009) and ↓CRP (P = 0.008) in MD compared with control</td>
</tr>
<tr>
<td>Dietary pattern</td>
<td>Study (reference)</td>
<td>Study design</td>
<td>Results of studies</td>
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<tr>
<td><strong>Esposito et al. (14)</strong></td>
<td>180 Patients with MS, randomized, single-blind trial, MD and control group</td>
<td>Greater $\Delta$hsCRP ($P = 0.01$) and IL-6 ($P = 0.04$) after 2 y of adherence to MD compared with control</td>
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<tr>
<td><strong>Schwingshackl and Hoffmann (11)</strong></td>
<td>Systematic review and meta-analysis of 17 randomized intervention studies, minimum period of 12 wk, patients aged 25–77</td>
<td>$\Delta$CRP ($P &lt; 0.0001$) and $\Delta$IL-6 ($P = 0.01$) in MD group compared with controls</td>
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<tr>
<td><strong>Ambring et al. (42)</strong></td>
<td>22 Individuals, aged 36–51 y, divided to 2 groups: MD and normal Sweden diet for 4 wk each in a crossover</td>
<td>No reduction in hsCRP ($P = 0.39$) and IL-6 ($P = 0.52$)</td>
<td></td>
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<tr>
<td><strong>LF vs. LC model</strong></td>
<td><strong>Sharman and Volek (43)</strong></td>
<td>15 Men in excess body weight, age, 33.2 ± 11.3 y consumed 2 weight-loss diets: VLC or LF (6 wk) in a crossover</td>
<td>$\Delta$hsCRP ($P = 0.00005$) and $\Delta$IL-6 ($P = 0.0001$) in MD group compared with controls</td>
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<tr>
<td><strong>Dansinger et al. (44)</strong></td>
<td>160 Subjects, aged 22–72 y with excess body weight randomly assigned to 4 weight loss diets: LC Atkins diet, Zone diet, Weight Watchers diet, and LF Ornish diet. After 2 mo of maximum effort, participants selected their own levels of dietary adherence for 1 y</td>
<td>No significant difference between diets ($P = 0.48, P = 0.57, P = 0.31$, respectively) for $\Delta$CRP</td>
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<tr>
<td><strong>O’Brien et al. (45)</strong></td>
<td>41 Obese women, mean age 43.7 ± 7.7 y, 3-mo randomized clinical trial that compared LC vs. LF diet</td>
<td>$\log$CRP from baseline to 3-mo ($P = 0.035$), Greater $\Delta$CRP independent of dietary macronutrient ($P = 0.20$)</td>
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<tr>
<td><strong>Seshardi et al. (46)</strong></td>
<td>78 Patients with obesity, mean age 54 y, 6-mo randomized study that compared LC with conventional diet</td>
<td>In patient with high baseline CRP higher $\Delta$CRP on LC ($P = 0.005$)</td>
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<tr>
<td><strong>Rankin et al. (47)</strong></td>
<td>29 Overweight women assigned to isocaloric LC-HF and HC-LF groups for 4 wk</td>
<td>$\uparrow$CRP in LC, $\downarrow$CRP in HC group ($P = 0.002$), No difference in hsCRP between groups after intervention</td>
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<tr>
<td><strong>Stoernell et al. (48)</strong></td>
<td>28 Patients with hypertriglyceridaemia randomly assigned to LC or LF diet intervention (8 wk)</td>
<td>Greater $\Delta$CRP in HC group ($P &lt; 0.05$) than LC</td>
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<tr>
<td><strong>Keogh et al. (49)</strong></td>
<td>99 Patients with abdominal obesity, age 50 ± 8.3 y, randomly assigned to LC, high in SFAs vs. HC, low in SFA isocaloric diets, 8-wk period</td>
<td>Slight $\uparrow$IL-6 after LC meal at 2 wk ($P = 0.08$) after 6 mo $\downarrow$fasting CRP in HF group ($P = 0.001$), no differences in fasting IL-6 concentrations in both groups</td>
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<tr>
<td><strong>Davis et al. (50)</strong></td>
<td>Patients with DM2, age $&gt;18$ y, postprandial (immediate) and chronic (after 6 mo) effects of LC and LF diets on inflammation was rated</td>
<td>No effect of DASH and control diets on hsCRP ($P = 0.87, 0.85$, respectively)</td>
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<tr>
<td><strong>DASH diet</strong></td>
<td>Asemi et al. (51)</td>
<td>32 Women with gestational diabetes, aged 18–40 y, assigned to DASH or control diet (4 wk)</td>
<td>No effect of DASH and control diets on hsCRP ($P = 0.87, 0.85$, respectively)</td>
</tr>
<tr>
<td><strong>Azadbakht et al. (52)</strong></td>
<td>31 Patients with DM2, 8 wk of intervention: DASH or control diet</td>
<td>$\downarrow$hsCRP with the use of DASH diet compared with standard diet ($P = 0.02$)</td>
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<tr>
<td><strong>Esmailzadeh et al. (53)</strong></td>
<td>486 Women, aged 40–60 y, dietary intake obtained with the use of FFQ</td>
<td>High intake of vegetables and fruits inversely correlated with CRP ($P &lt; 0.01$)</td>
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<tr>
<td><strong>Fogarty et al. (54)</strong></td>
<td>2633 Individuals, aged 18–70 y, 24-h urinary sodium excretion and blood samples measurement of CRP were collected</td>
<td>High sodium intake correlated with higher CRP concentration ($P &lt; 0.001$)</td>
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<tr>
<td><strong>Forrester et al. (55)</strong></td>
<td>171 Participants, aged 18–65 y, low-sodium diet period (6 wk)</td>
<td>No effect of low-salt diet on CRP ($P = 0.23$)</td>
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<tr>
<td><strong>Asemi and Esmailzadeh (56)</strong></td>
<td>48 Overweight or obese women with polycystic ovary syndrome, randomly assigned to DASH and control groups (8 wk)</td>
<td>DASH diet correlated with $\downarrow$hsCRP compared with control ($P = 0.009$)</td>
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<tr>
<td><strong>Saneei et al. (57)</strong></td>
<td>60 Girls, mean age 14.2 y with MS, after 4-wk of preparation diet, assigned to DASH or control group (6 wk)</td>
<td>$\downarrow$hsCRP on DASH compared with control diet ($P = 0.002$), no impact on IL-6 of DASH intervention</td>
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</tbody>
</table>

1. CRP, C-reactive protein; CVD, cardiovascular disease; DASH, Dietary Approaches to Stop Hypertension; DM2, diabetes mellitus type 2; hsCRP, high-sensitivity C-reactive protein; HC, high-carbohydrate; HF, high-fat; LC, low-carbohydrate; LF, low-fat; MD, Mediterranean diet; MS, metabolic syndrome; VLC, very low-carbohydrate.
SFAs (HC) in patients with abdominal obesity. The planned macronutrient profiles were as follows: 35% energy from protein, 61% fat, 20% SFAs, and 4% carbohydrate with the LC diet; and 24% energy from protein, 30% from fat, <8% SFAs, and 46% carbohydrate with the HC diet. The investigators observed a greater weight loss with the LC diet than with the HC diet but greater decreases in CRP concentrations with the HC diet. The investigators suggested that diets high in SFAs could affect the production of CRP (49).

Davis et al. (50) rated the different effects of LC and LF diets on inflammation and endothelial dysfunction in patients with DM2. The investigators evaluated the postprandial (immediate) and chronic (after 6 mo) effects of these diets. Despite the observed differences in the concentration of glucose and TGs in response to LF and LC diets, no changes in postprandial values on inflammatory markers (CRP, IL-6) were noted. Only a slight increase in the concentration of IL-6 after a LC meal was found over the 2 wk, but the difference was not statistically significant. The mean weight loss did not differ between the groups. Despite similar weight loss observed in both groups after 6 mo of weight reduction, a decrease in fasting CRP was found only in the LF group, from 4.0 ± 0.77 to 3.0 ± 0.77 mg/L (P = 0.01). Significant changes were not observed in the LC group (from 3.1 ± 0.42 to 3.6 ± 0.68 mg/L; P = 0.94). In addition, no significant differences were found in the fasting concentrations of IL-6 in both groups. No correlation was found between the change in body weight and inflammatory markers. However, the investigators observed beneficial effects of the LC diet in decreasing the endothelial dysfunction markers, stressing that both LF and LC diets have a beneficial effect on CVD risk. However, they also consider the likelihood of different mechanisms by which the weight loss from these diets reduces CVD risk.

**DASH diet.** The US National, Heart, Lung, and Blood Institute developed the Dietary Approaches to Stop Hypertension Trial (DASH) diet. This model is characterized by a diet low in cholesterol, saturated fat, and total fat and recommends increased consumption of fruits and vegetables, whole grains, nuts, fat-free or LF milk and milk products, fish, and poultry. The DASH diet also recommends limiting the intake of red meat, sweets, and beverages that contain sugar. This diet is rich in magnesium, potassium, calcium, protein, and fiber and is low in sodium (24).

Currently, little research, to our knowledge, is being conducted on the effects of the DASH diet on the concentration of inflammatory markers. In randomized clinical trials of women with gestational diabetes, no effect of the DASH diet on hsCRP concentrations was observed compared with the control diet. At the same time, however, numerous benefits of this diet were noted on oxidative stress markers and insulin resistance (51). Anti-inflammatory effects of the DASH diet were proven in clinical crossover studies on a group of 31 patients with DM2. The investigators found that hsCRP concentrations declined significantly when the DASH diet model was used compared with a standard (control) diet for the treatment of diabetes. The mean decrease in plasma CRP was $-26.9\% \pm 3.5\%$ for the DASH diet and $-5.1\% \pm 3.8\%$ for the control diet ($P = 0.02$) (52).

Research conducted by King et al. (33) suggested that the high intake of fiber in the DASH diet model may show an anti-inflammatory effect. Studies have shown that high-dietary fiber intake with the DASH diet (30 g/d) or supplementation of dietary fiber (30 g/d) reduces the serum CRP concentration. Similarly, a high intake of vegetables and fruits in this dietary pattern can be inversely correlated with CRP concentration (53).

A limited amount of sodium with the DASH diet may also be associated with an anti-inflammatory effect. In a randomized trial of 2633 people, it was shown that a high-sodium intake was associated with higher CRP concentrations (54). In a randomized, double-blind clinical trial, no confirmation was found that a low-salt diet for 6 wk affected the concentration of inflammatory biomarkers (55). In a randomized study conducted by Asemi and Esmailzadeh (56), a positive impact of the DASH diet on inflammatory markers was confirmed. The study included 48 women who were overweight or obese and were diagnosed with polycystic ovary syndrome. The women were randomly assigned to either the DASH diet or the control diet group for 8 wk. Both diets provided the same percentage of energy from macronutrients. The DASH diet was associated with decreased serum hsCRP concentrations in relation to the control diet ($-763$ and $666 \mu g/L$, respectively; $P = 0.009$). An anti-inflammatory effect of the DASH diet was also evaluated in a group of girls with a mean age of 14.2 y with metabolic syndrome. After 4 wk of preparation diet, patients were assigned to the group who consumed either the DASH diet or the control diet. The control diet group followed general advice about healthy nutrition. Adherence to the DASH diet compared with the control diet resulted in a reduction of serum hsCRP ($P = 0.002$). This effect was significant even after taking into account body weight changes. However, no impact was found on the IL-6 concentration of the DASH diet intervention (57).

The designs and significant results of the studies included in this review of the effects of different dietary patterns on CRP and IL-6 concentration are summarized in Table 1.

**Conclusions**

Reducing the risk of NCDs through the inhibitory effect of diet, altering the course of the chronic inflammatory response is important, even in the face of uncertainty about the causal nature of chronic inflammation. On the basis of our review of the research, it is difficult to determine which diet model is optimal for reducing inflammation in humans. Evidence is strong and consistent of a beneficial effect of the Mediterranean diet on IL-6 and CRP concentrations. Many studies have also demonstrated the anti-inflammatory effect of the plant diet model and the DASH diet. Still, the results of the LF and LC diets on the inflammation process are inconsistent. It is necessary to take into account the testing of complex relations between dietary factors and other factors whose mutual relations can determine the effect of the inflammatory response.
Acknowledgments
Both authors read and approved the final manuscript.

References
40. Hermosdorff HH, Zalet MÁ, Abete I, Martinez JA. Discriminated benefits of a Mediterranean dietary pattern within a hypocaloric diet program on


