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Effect of Dietary Intervention on Inflammatory and Endothelial Dysfunction Markers in Adults with Metabolic Syndrome: A Systematic Review

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Abstract Chronic low-grade inflammation is associated with metabolic syndrome and obesity and is characterized by high serum concentration of inflammatory and endothelial dysfunction markers. Studies have shown that western diets may increase the risk of diabetes mellitus and cardiovascular disease; however, healthy eating interventions have been also shown to improve the inflammatory state and endothelial function. A relationship between mixed diets and markers of inflammation and endothelial dysfunction has been previously suggested, since some foods have antioxidant and anti-inflammatory activity. Therefore, we conducted a systematic review of randomized clinical trials of parallel-group or crossover design studies published in the English language that evaluated the effects of dietary interventions on inflammatory and endothelial dysfunction markers in adults with metabolic syndrome. The literature search included electronic databases, manual search, and peer-reviewed articles published from 2005 to 2015. Fourteen studies, with a total of 1470 participants, met the inclusion criteria. Dietary interventions ranged from 2 to 52 weeks. Half of the studies reported a positive effect of dietary interventions on inflammatory markers, being C-reactive protein the one most frequently quantified. Compared to control groups, diets rich in polyunsaturated fatty acids reduced serum CRP levels; Mediterranean diets enriched in olive oil and nuts reduced serum IL-6; and a decrease in serum ICAM levels was observed in Mediterranean diet rich in olive oil. Four of the analyzed studies measured serum TNF-alpha levels, which did not exhibit a significant variation among groups.

Keywords: *inflammation, endothelial function, biomarkers, metabolic syndrome, mixed diet ormat, microsoft word template, style, insert, template*

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1. Introduction

Metabolic syndrome (MetS) is defined as a group of metabolic alterations clinically evidenced by central obesity, reduced serum levels of high-density lipoprotein cholesterol (HDL-C), hypertriglyceridemia, hypertension, and hyperglycemia [1]. In the majority of cases, MetSis associated with obesity [2] and atherosclerosis [3,4], and is a contributing factor generating non-communicable diseases. Chronic non-communicable diseases (NCD) –such as cardiovascular disease, obesity, and type-2 diabetes mellitus (T2DM)- represent a significant cause of mortality worldwide. Over the past decades, chronic NCD have been associated with chronic low-grade inflammation [4,5,6]. This inflammatory response is mediated by the activation of the transcription factor NF-kB [7], leading to increased expression of proinflammatory and endothelial dysfunction genes; which in turn, increase levels of cytokines derived from adipose tissue and liver [8,9]. As a final result, there is a systemic inflammatory response mediated by C-reactive protein (CRP), inflammatory cytokines (IL-6 andTNF-alpha), vascular cellular adhesion molecules (VCAMs), and intercellular adhesion molecules (ICAM) [10].

C-reactive protein is an acute-phase protein synthesized by hepatocytes stimulated by inflammatory cytokines IL-6 and TNF-alpha [11]. Subtle changes in CRP serum levels are used as a biomarker of subclinical inflammation found in MetS and obesity [12,13,15]. TNF-alpha is associated with insulin resistance [16] by inhibiting translocation of glucose transporters (GLUT-4) to the cellular membrane [17,18]. Adhesion molecules including E-selectin, ICAM-1, and VCAM-1 mediate endothelial cell damage. These molecules are attract macrophages and lymphocytes to the endothelium, produce oxidative stress and increase expression of proinflammatory molecules [19,20]. Inflammatory processes also involve the vascular endothelium [21], which under pathological conditions may lead to atherosclerosis, a critical factor in the development, progression and clinical manifestation of cardiovascular disease and diabetes [22]. These inflammatory proteins –CRP, IL-6, TNF-alpha, VCAM-1, and ICAM-1- have been previously described as biomarkers to assess the effect of dietary intervention on the inflammatory response and endothelial dysfunction in MetS and obese patients.

Because unbalanced diets may support chronic low-grade inflammation and oxidative stress, previous studies have assessed the effect of diet intervention on these inflammatory markers [23,24]. Decreased levels of these molecules would thus suggest a decrease in chronic NCD risk [25,26,27]. A meta-analysis of 17 clinical studies that included 2300 participants showed that an intervention with Mediterranean diet significantly reduced levels of CRP, IL-6, and ICAM [28].Additional studies suggest that the Mediterranean diet may be effective in reducing the prevalence of MetS and the associated risk of cardiovascular disease [29].

Previous studies have reported an inverse association between fruit and vegetable consumption with serologic levels of inflammatory markers [11]. On one hand, dietary flavonoids, found in fruits and vegetables, have been shown to contribute to the reduction of risk of cardiovascular disease (CVD) [30,31]. Specifically, quercetin –a flavonoid present in fruits and vegetables- has been shown to attenuate TNF-alpha and proinflammatory gene expression, hence reducing the inflammatory response in adipose tissue [32]. Additionally, vegetarian diets have also been found to reduce serum levels of CRP, thus reducing risk of CVD [33]. Interestingly, a study of 3920 participants (≥20 years of age), showed an inverse association of dietary fruit fiber intake with risk of CVD [34].

While several studies focusing on a single type of nutrient or specific diet component [35,36,37], there are few studies that assess the effect of a mixed diet with a variety of component. Therefore, in this review, we analyzed the effect of mixed dietary intervention on inflammatory and endothelial dysfunction makers, as well as its contribution to reducing complications of metabolic syndrome.

2. Materials and Methods

Using the terms “Diet, AND inflammation AND biomarkers”, PubMed, Scopus, and Science Direct databases were searched to identify relevant studies published between 2005 and 2015. Additionally, a manual search was performed for those references found in relevant articles. Language was limited to English, as we did not find studies in other languages.

2.1. Inclusion Criteria

Randomized clinical trials of parallel-group or crossover design, which included adults only (≥18 years old), with a body mass index (BMI) ≥25,00 kg/m², and at least one MetS clinical manifestation as defined by the World Health Organization (WHO) [38]. Studies must have had at least two types of dietary interventions that lasted at least two weeks. Our focus was on studies using dietary interventions in which a mixed diet was included, and its effect on inflammatory and endothelial dysfunction markers was addressed.

2.2. Exclusion Criteria

Studies including children, teenagers, pregnant women, participants with rheumatic disease, hypothyroidism, smokers, medicated patients, or patients participating in a physical exercise program were excluded from this analysis.

2.3. Risk of Bias Assessment

The three authors independently assessed risk of bias by using the Cochrane risk of bias tool (Revman 5.3). This tool assesses risk of bias on the following domains: selection bias, performance bias, detection bias, attrition bias. Studies with high risk of attrition bias were not excluded. We judged risk of bias criteria as ’low risk’, ’high risk’ or ’unclear risk’. Results for assessment of the risk of bias for each domain for each study were compared and disagreements resolved by discussion (Figure 1).

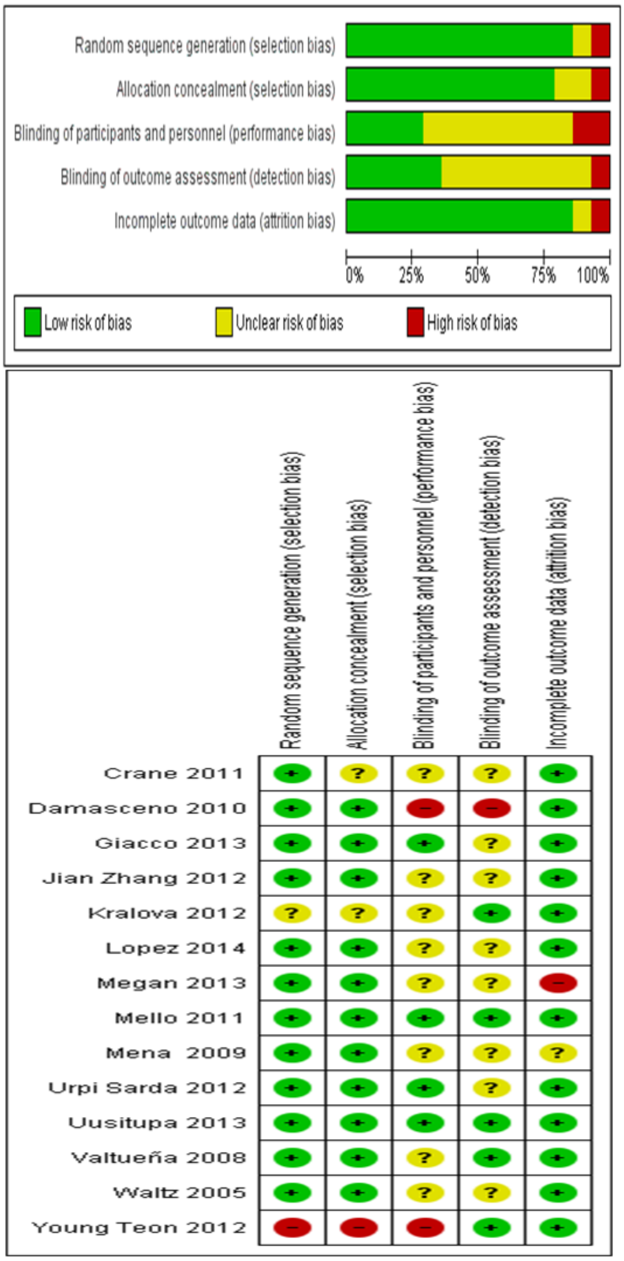

Figure 1. Risk of bias summary: review authors' judgements about each risk of bias item for each included study. Revman 5.3

2.4. Data Extraction

Data extraction was performed by two of the researchers of this study, by using a format that included data on study design, participants, type of intervention, comparisons between intervention diets, and outcomes. A third researcher participated if required to resolve differences between the first two researchers.

2.5. Outcomes

Changes in serum CRP levels were designated as primary outcomes of the effect of diet intervention on inflammatory markers. Changes in serum IL-6 and TNF-alpha levels were defined as secondary outcomes. Additionally, changes in serum VCAM and ICAM levels were designated as an outcome of the effect of diet intervention on endothelial dysfunction.

2.6. Data Analysis

The percent change in serum levels of inflammatory and endothelial dysfunction markers in the intervened and the control groups were calculated and analyzed.

3. Results

3.1. Literature Search and Study

A total of 2052 studies were identified in the searched databases. Of those, 14 studies met the inclusion criteria and accounted for a total of 1470 participants (719 male, 751 female). (Figure 2).

3.2. Characteristics and Selected Studies

As shown in Table 1, 14 studies were included in our analysis. Duration of interventions ranged from 2 to 52 weeks. Sample size varied from 15 and 516 participants, for a total of 1470 (719 male, 751 female). (Table 1)

3.3. Types of Interventions

Of the 14 studies, five compared two interventions to a control group, while the remaining 9 compared one dietary pattern to the control group. Altogether, 33 diets were compared.

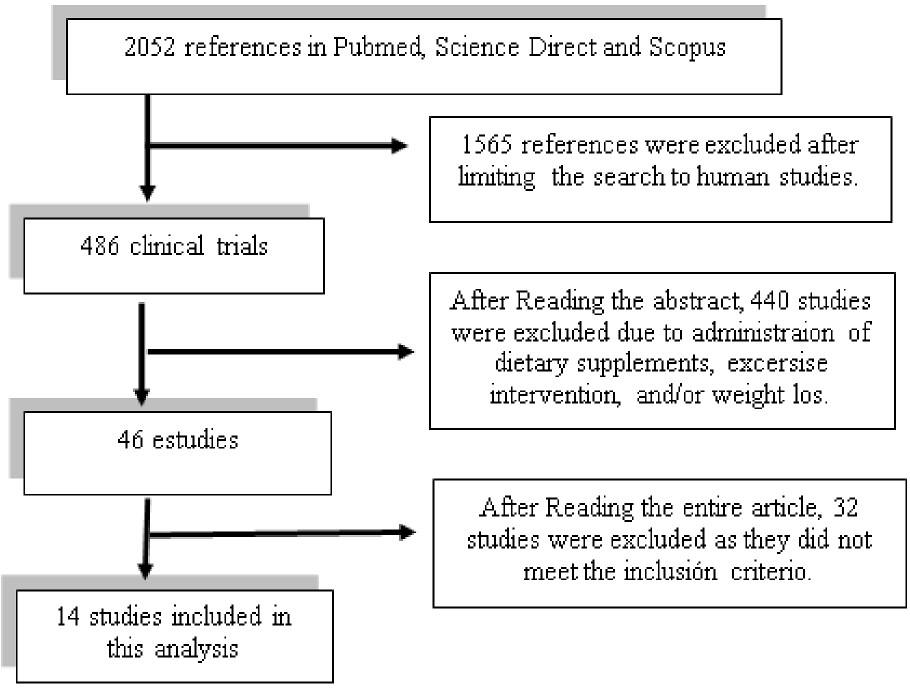

Figure 2. Screening strategy used to identify studies meeting inclusion criteria

Table 1. Summarized effects of diet interventions used in the analyzed studies

Ref	Population	Intervention (s) (n)	Diet	Duration (weeks)	Markers	Baseline	Effect	Conclusion
Mello et al 2011	104 participants Age: 40 - 70 years MetS	HD (36), WGED (34) vs CD (34)	HD: CHO 48.2% protein 21.6%, fat 30.2%, fiber 36.5g	12	CRP mg/L	1.4 vs. 1,5 vs. 1,4	-0,14 vs -0,3 vs -0,11 (p=0,04)	WGED led to significant reduction
			WGED: CHO 47.2% protein 21.7% fat 31.1%, fiber 26.6g		TNFa pg/ml	0.6 vs. 0,7 vs. 0,6	0,03 vs 0,063 vs. 0,018 (p=0,35)	No significant difference
					ICAM ng/ml	601 vs. 602 vs. 596	607 vs 595,9 vs 603,8 p= (0,89)	No significant difference
			CD: CHO 47.2%, fat 31.9%, protein 29.2%, fiber 17.6g		IL-6 pg/ml	1.6 vs. 1,4 vs. 1,3	-0,11 vs 0,04 vs 0,039 (p=0,66)	No significant difference

Ref	Population	Intervention (s) (n)	Diet	Duration (weeks)	Markers	Baseline	Effect	Conclusion
Giaco et al. 2013	24 participants. Ages: 40-65 years. MetS	WG (62) vs CD (62)	WG: CHO 48%, protein 18.7%, Fat 31%, fiber 32.6g CD: CHO 49%, protein 17.8%, fat 30.8%, fiber 19.8g	12	CRP hs mg/L	1.95	-0,59 vs 0,21 (p=0,16)	No significant difference
					TNFa pg/ml	0.73 vs. 0,62	.-0,05 vs 0,1 (p=0,84)	
					IL-6 pg/ml	1.42 vs. 1,41	0,12 vs 0,02 (p=0,52)	
Jian Zhang et al 2012	126 participants. Ages: 35- 70 years. MetS	Sa (32) vs He (29) vs Po (33) vs CD (32)	Salmon: CHO 52.1% protein 15% fat 32.5% Herring: CHO 52.1% protein 15.5% fat 32.4% Pompano: CHO 54.2 protein 14.1% fat 31.7% CD: CHO 54.6% protein 54.2% fat 31.1%	8	IL-6 pg/ml	268.1	-23,1 vs -17,3 vs -17,8 vs -3,5 (p=0,5)	Intake of salmon decreased TNFa and IL-6 levels; intake of herring decreased TNFa and increased adiponectin; and intake of pompano did not. (Highest EPA and DHA content). However, there was no significant statistical difference between groups.
					TNFa pg/ml	13.3	-1,5 vs -1,1 vs 1,0 vs 0,2 (p=0,36)	
					ICAM ng/ml	271	-10,3 vs -18 vs -1,7 vs -11,5 Not reported	
					VCAM ng/ml	319.2	38,6 vs. -32,5 vs 18,6 vs 63,9 Not reported	
					CRP mg/L	2	-0,02 vs -0,13 vs -0,13 vs 0,08 Not reported	
					Adiponectin ug/ml	6.7	0,7 vs 0,9v. 0,6 vs 0,4 (p=0,8)	
Mena et al 2009.	106 participants. Ages: 55 - 80 years. MetS	MD+VO (35) vs MD+N (35) vs LFD (36)	MD+VO: protein 17.8%, CHO 49.9%, fat 35.6%. MD+N: protein 16.3%, CHO: 41.6% fat 37.7%. LFD: protein 19.3%. CHO 42.4%, fat 34.2%	12	PCR mg/L	4,0 vs 2,2 vs 2,8	-1,6 vs 0,35 vs 1,1 (p=0,02)	Both MD showed significant effect
					IL-6 pg/ml	6,8 vs 6,8 v 5,9	-1,09 vs -0,82 vs 1,41 (p=0,001)	Both MD showed significant effect
					ICAM ng/ml	290 vs. 270 vs 239	-58 vs -32,4 vs 76,5 (p=0,003)	Both MD showed significant effect
					VCAM ng/ml	1033 vs 962 vs 1023	-124 vs -20 vs 204,6 (p=0,001)	MD+VO showed significant effect
Valtueña et al 2008	34 participants. Average age: 61 years. Healthy subjects	HT (33) vs LT (33)	HT: protein 14.4%, fat 31.7%, CHO 50.5% vitC 423 mg/day) 2 grp LT: 13.8%protein, fat 33%. CHO 47.5%. vit c 91.7 mg/day)	2 weeks each diet. Cleanse halfway through the study	High sensitivity PCR	3mg/l	-0,72 vs 1,5 (p=0,007)	HT diet showed significant effect
Lopez et al 2014.	96 participants. Average age: 50 years. MetS	RD (48) vs CD (48)	RD: 30% de protein CHO 40%. fat 30% CD: 55%CHO. 30% fat 15% protein	8	IL-6 pg/ml	2.71 vs. 2,61	0,08 vs -0,05 (p=0,71)	No significant changes in inflammatory markers, but LDL cholesterol was significantly reduced. All three diets promoted vegetable intake, and restricted intake of dairy, red meats, and eggs
					TNFa pg/ml	0.76 vs. 0,66	0,02 vs -0,08 (p=0,11)	
					CRP mg/L	3.2 vs. 3,19	0,19 vs -0,84 (p=0,27)	
Megan et al 2013.	33 participants. Ages 21- 62 years. MetS	HFLCD (18) vs LFHCD (15)	**HFLCD:** CHO 10.4% fat 56% Protein 33.5% **LFHCD:** CHO 60%. fat 25%. protein 15%	12	Adiponectin ug/ml	4.01 vs. 4,59	0,4 vs -0,18 (p=0,045)	HFLCD diet decreased CRP and increased adiponectin
					CRP hs mg/L	5.62 vs. 6,94	-1,68 vs -0,19 (p=0,03)	

Ref	Population	Intervention (s) (n)	Diet	Duration (weeks)	Markers	Baseline	Effect	Conclusion
Crane et al 2011.	49 participants Ages: 52-65 years, Obese	10 VP (49) vs 5VP (49) vs (49)	**2VP:** 130g **5VP**: 287g **10VP:** 614 g	Each interventio n: 3 weeks. 4 weeks cleanse in between treatments.	CRPhs mg/L	2.5	-0,17 vs -0,08 (p=0,78)	No significant difference between 5 or 10 vegetable servings compared with 2 servings.
Waltz et al 2005	63 participants. Average age: 32 years. Healthy subjects	2FV (21) vs 5FV (21) vs 8FV (21)	**2FV:** CHO 49.8% protein 14.9% fat 35.3% **5FV:** CHO 45.4% protein 15.3% fat 35.3% **8FV:** CHO 47.7% fat 35.3% protein 15%	4	PCR hs mg/L	1.51	1,69 vs 0,84 vs -0,46 (p=0,05)	significant decrease in CRP levels with 8 fruit/vegetable servings per day
Urpisarda et al 2012.	516 participants. Ages 54 -79 years. MetS	MD+VO (178) vsMD+N (175) vs LFD (163)	**MD+VO:** protin 17.8% CHO 49.9% grasa 35.6%. **DM+N:** protein 16.3% CHO: 41.6 fat 37.7% **LFD:** protein 19.3%. CHO 42.4% fat 34.2%	24	IL-6 ng/L	0.9 pg/ml	-0,23 vs -0,33 vs 0,13 (p=<0,001)	Both MD significantly decreased inflammatory markers compared with low fat diet.
					ICAM ng/ml	258	-10 vs -2,0 vs 24 (p=0,001)	
Damasceno et al 2011.	26 participants. Age: 25 - 75 years. Hypercholesterolemia	VOOD (26) vs ND (26) vs AD (269)	**VOOD:** CHO 49% prot 16% fat 32.5% fiber 25g **ND:** CHO 49% protein 16% fat 32.5%. fiber 25g **AD:** CHO 48.5% protein 17% fat 33% fiber 29g	4	ICAM ng/ml	291	-19 vs -53 vs -31 (p=0,182)	No significant changes in inflammatory markers, but LDL was significantly reduced. All three diets promoted vegetable intake, and restricted intake of dairy, red meats, and eggs.
					VCAM ng/ml	670	60 vs 154 vs 90 (p=0,18)	
					PCR hs	2.1	-0,4 vs -0,2 vs -0,4 (p=0,241)	
Uusitupa et al 2013.	166 participants Average age: 55 years.	ND (96) vs HND (70)	**ND:** CHO 46.8% prot 175% fat 31.7% **CD:** CHO 44.6% prot 16.2% fat 35.2%	6 months	PCR mg/L	2,6 vs. 2,4	0,1 vs -0,1 (p=0,18)	Significant changes in other markers including IL-1Ra and non-HDL
					IL-6 ng/L	1,53 vs. 1,51	0,16 vs 0,08 (p=0,44)	
					adiponectin HMW mg/l	5.43 vs. 4,72	0,2 vs -0,04 (p=0,81)	
Kralova et al 2013.	15 participants Age: 45 years and older. Dyslipidemia	PUFA (15) vs SAFA (15)	**PUFA:** CHO 47% fat 40% **SFA:** CHO 46% fat 42%	3	CRP mg/L	6.61 vs. 2,95	-4,05 vs 0,35 (p=<0,01)	PUFA diet significantly reduces CRP levels

Ref	Population	Intervention (s) (n)	Diet	Duration (weeks)	Markers	Baseline	Effect	Conclusion
Jee Young Yeon et al 2012	22 participants, Age: 19-29 years. Overweight	HVFD (26) vs LVFD (26)	**LVF:** CHO 55% fat 25% protein 18% **HVF:** CHO: 61.3%. fat 22.5%. protein 17.2%	26 weeks. 2 weeks each diet. 2 weeks cleanse	CRP mg/L	0.56 vs. 0,54	0,16 vs 0,21 (p=0,064)	No significant changes. However, culture of PBMCs stimulated with LPS showed decreased cytokine (IL-1, IL-6) production in participants in the HVF diet
					IL-6 pg/ml	3.53 vs. 3,65	-0,08 vs - 0,57 (p=0,14)	
					Adiponectin ug/ml	8.56 vs. 8,23	0,66 vs -0,14 (p=0,36)	

HD, healthy diet; CHO, carbohydrates; WGED, whole grain diet; CD, control diet; CRP, C-reactive protein; TNFa, tumor necrosis factor alpha; IL-6, interleukin 6; ICAM, intercellular adhesion molecule; WG, whole grain; VCAM, vascular cell adhesion molecule; Sa, salmon; He, herring; Po, pompano; MD, Mediterranean diet; VO, virgin olive oil; N, nuts; LFD, low-fat diet; HT, high-TAC (Total antioxidant capacity); LT, low-TAC (Total antioxidant capacity); RD, RESMENA diet; ND, Nordic diet; AD; HND; HFLCD, high-fat low-carb diet; LFHCD, low-fat high-carb diet; PUFA, polyunsaturated fatty acids; SFA, saturated fatty acids; 2VP, 2 vegetable portions; 5VP, 5 vegetable portions; 10VP, 10 vegetable portions; HVFD, high vegetable fruit diet; LVFD, low vegetable fruit diet. HMW alto peso molecular.

The dietary interventions included a wide range of mixed diets: Mediterranean diet supplemented with mixed nuts or virgin olive oil; high-fat low-carb diet; low-fat high-carb diet, with whole or refined grains with different types of proteins; different amounts of fruits and vegetables; with different fatty acids; with high and low glycemic index, and with high and low antioxidant power.

3.4. Significant Differences between Dietary Intervention and Control Groups

3.4.1. Primary Outcomes: Variation in Serum CRP Levels

Of the analyzed studies, 13 of 14 measured serum CRP levels. Six studies showed a significant difference between dietary intervention and control groups, being greater in the control group. Particularly, the study by Kralova et al. (2013), detected the greatest changes. Two diets were compared in the intervention group: one diet was rich in polyunsaturated fatty acids, and the second one was rich in saturated fatty acids. The authors reported that the diet rich in polyunsaturated fatty acids reduced serum CRP levels in 4,05 mg/l (6,6 to 2,56mg/l), while the control diet had the opposite effect and instead increased serum CRP levels by 0,35 mg/l (2,95 to 3,3 mg/l).

3.4.2. Secondary Outcomes: Variations in TNF-alpha Serum Levels

Of the analyzed studies, 4 of 14 measured serum TNF-alpha levels. In these four studies, levels of TNF-alpha did not exhibit a significant difference among groups.

3.4.3. Secondary Outcomes: Variations in IL-6 Serum Levels

Of the analyzed studies, 6 of 14 measured serum IL-6 levels. Three studies showed a significant difference between dietary intervention and control groups. Specifically, in the study by Urpisarada et al. (2012), two types of Mediterranean diets were compared: one rich in olive oil and the other one enriched with nuts, which were compared with a low-fat diet. Mediterranean diets enriched in olive oil, and nuts achieved a reduction in serum IL-6 levels of 1,09pg/ml and 0,82 pg/ml respectively compared to the control group, which increased 1,41pg/ml.

3.4.4. Secondary Outcomes: Variations of Serum Levels of the Endothelial Dysfunction Markers VCAM and ICAM

Of the analyzed studies, 4 of 14 assessed markers of endothelial dysfunction. Two of those studies showed a significant difference between dietary intervention and control groups. Specifically, in the study by Urpisarda et al. (2012) two types of Mediterranean diets were compared: one rich in olive oil and the other one enriched with nuts, which were compared with a low-fat diet. A decrease in serum ICAM levels (10ug/l) was observedin the Mediterranean diet rich in olive oil compared with the low-fat diet, which exhibited an increase in ICAM levels of up to 24ug/l. An additional study by Mena et al. (2009) showed that while the control group exhibited increase in serum ICAM (76,5ug/l) and VCAM (204,4ng/l) levels, a Mediterranean diet rich in olive oil led to a decrease in both serum ICAM (58 ug/l) and VCAM (124 ng/l) levels.

3.5. Study Limitations

Onelimitations of our study is the heterogeneity among the analyzed studies. There was diversity among the analyzed inflammatory and endothelial dysfunction markers, as well as types of diets, duration of intervention, and age of participants. Due to this heterogeneity, we were not able to perform a meta-analysis of the data provided by these studies.

4. Discussion

In this review, we aimed to analyze the effect of mixed dietary intervention on inflammatory and endothelial dysfunction makers, as well as its contribution to reducing complications of metabolic syndrome. We found that 50% of the studies showed positive results of dietary intervention on reducing inflammatory makers, being CRP the one most commonly quantified. The changes in dietary patterns can be grouped into three categories: 1) replacement of refined grains by whole grains, 2) reduction of saturated fatty acids (SFA) and increase of polyunsaturated fatty acids (PUFA), and 3) increase in fruit and vegetable intake.

Regarding the replacement of refined grains by whole grains, an intake of 113 g/d of whole grains and 29g/d of fiber significantly reduced serum CRP [42] levels. This dietary intervention also included berries, vegetables, and fish. Furthermore, the study by Vitaglione et al. 2005 found a decrease in serum TNF-alpha levels with an even lower amount of whole grains (70 g/d). However, a similar study containing comparable intake of whole grain and fiber, 112g/d and 30 g/d respectively, did not show a decrease in either CRP nor IL-6 [44]. In agreement with that study, Giaco et al. (2013) did not observe significant changes in serum CRP, TNF-alpha, or IL-6 levels. Similarly, an additional study comparing an intake of 60 or 120 g/d of whole grains did not report any changes in serum CRP, IL-6, ICAM or VCAM levels.

These discrepancies may be explained, on one hand, by the diversity of grains (oats, rye, or wheat bran), as they contain different amounts of ferulic acid, the phenolic component of whole grains [43,46]. On another hand, the amount and quality of fiber also vary among these grains. Additionally, the duration of the interventions was of different lengths, which may ultimately have an effect on the outcome.

Phenolic components provide anti-inflammatory and antioxidant properties by scavenging free radicals and activating redox enzymes in cells and tissues [47]. However, there are contradictory results regarding the role of whole grains in inflammation. It is possible that in addition to the content of phenolic compounds, the amount of fiber also contributes to the anti-inflammatory effect of whole grains [47]. Fiber may contribute to the changes observed in the inflammatory markers analyzed in studies in which there was an increased intake of whole grains, fruits, and vegetables. The effect may be mediated by the fermentation process in the intestinal microbiota, producing short chain fatty acids, which have anti-inflammatory properties [48].

Regarding changes in dietary patterns in which intake of SFA is reduced and replaced by PUFA, the study by Kralova et al. (2013) reported that a diet rich in PUFA led to a significant decrease in serum CRP (61.3%) levels. In that study, while fat represented 40% to 42% of the total energy, the percentage of SFA and PUFA were significantly different between dietary interventions, being one composed by 29% SFA and 8% PUFA, and the other 6% SFA and 25% PUFA. An additional study by Tee Voon et al. (2011) compared a dietary intervention with a lower amount of total fat (30%) of the total energy (20%) as saturated fats (palmitic, lauric, and myristic acids) to one with 20% PUFA (olive oil) and found no significant differences in serum CRP, IL-6, or TNF-alpha levels.

The study by Ruth et al (2013) showed that, compared to a low-fat high carb-diet (LFHC), a high-fat low-carb diet (HFLC) may be more efficient in reducing serum CRP levels and increasing adiponectin levels. However, that study has significant limitations due to the high desertion rate (48,5%). The Multi-Ethnic Study of Atherosclerosis [51] reported an inverse association between PUFA and serum CRP and IL-6 levels in obese participants compared to normal weight participants. This observation may be partly due to variations in diet and absorption processes. Additional studies in which 5% of the SFA energy was replaced by PUFA showed a risk of coronary heart disease lower than 13% [52,53,54].

Fatty acids saturated may act as Toll-like receptor (TLR) 2 and TLR4 ligands, activating inflammatory processes via activation of NF-kB transcription factor, which leads to synthesis of adhesion molecules [54]. In contrast, PUFA, especially omega-3 and omega-9, may inhibit such process by acting as PPAR-gamma ligands [55]. These acids decrease adhesion molecule synthesis, which may diminish migration of leukocytes and smooth muscle cells towards the endothelium, delaying the atherosclerotic process [39,56,57] and thus improving endothelial function [58]. Therefore, increased PUFA (omega-3) intake and decreased SFA intake may play a significant role in the reduction of serum inflammatory markers [40,41]. In agreement with these results, the study by Esposito et al, 2004 showed that increased PUFA intake – as eicosapentaenoic acid (EPA) and docosahexoenoic acid (DHA)- was associated to a reduction in arachidonic acid, a precursor of proinflammatory molecules such as prostaglandins, leukotrienes and thromboxanes [59,60].

Finally, regardingchanges in dietary patterns in which fruit and vegetable intake was increased, a study comparing an intake 800 g (8 portions) with 200 g (2 portions) observed a decrease of 32% in serum CRP levels in the higher fruit and vegetable intake diet [61]. In contrast, a dietary intervention containing 614 g of vegetables did not show an effect on serum inflammatory markers [62].

In the study by Valtueña et al. (2008), including a greater variety of fruits and vegetables (550 g), 200 ml of fruit juice, and additional antioxidant foods in the dietary intervention led to a reduction of 24% in serum CRP levels. In contrast, a dietary intervention with the same total amount of fruit and vegetables but with limited variety, and with less powerful antioxidant foods showed an increase of 62,5% in serum CRP levels.

In this review, we have analyzed the effects of different dietary interventions on the most frequently reported inflammatory (CRP, IL-6, TNF-alpha) and endothelial dysfunction (ICAM and VCAM) markers. The latter were quantified in 4of the 14 identified studies, being reduced by dietary intervention in 2 of the studies [40,41]. However, additional markers not included in this review were also quantified in the analyzed studies. Giacco et al. 2014 used a dietary intervention rich in whole grains and found a decrease in postprandial insulin and triglycerides. Likewise, Damasceno et al. (2011) showed a decrease in low-density lipoprotein (LDL) cholesterol by providing a Mediterranean diet rich in olive oil, almonds or nuts; Urpisarda et al. (2012) observed changes in IL-1 receptor and non-HDL cholesterol. Furthermore, Yeon et al (2012), analyzed the effects of high and low vegetable-fruit (VF) diets in overweight women by isolating and culturing peripheral blood mononuclear cells (PBMCs), and subsequently activating them with lipopolysaccharide (LPS) and quantifying pro-inflammatory molecules. In that study, PBMCs of participants in the high-VF diet produced lower amounts of proinflammatory molecules IL-6 and IL-1 beta. An additional study compared the effect of different kinds of fish intake with chicken and pork intake, and found that 80 gr of salmon reduced to a greater extent serum TNF-alpha, and increased adiponectin levels [67].

Altogether, these studies suggest that a single marker may not be enough to determine the effect of a given dietary intervention on inflammatory and endothelial dysfunction markers. Moreover, it is likely that one or several diet nutrients may selectively improve one, or several, of these markers. Plausibly, the synergistic effect of nutrients and diets in which different food replacements (mixed diets) are simultaneously substituted(refined grains with whole grains, food with greater PUFA than SFA, increased fruit and vegetable intake, greater fish than meat intake) (66), such as the Mediterranean diet, lead to significant decrease on serum levels of CRP (40%), IL-6 (15%), and endothelial dysfunction markers ICAM (20%) and VCAM (25%) [40,41]. Additionally, mixed diets consisting of fruits, vegetables, and whole grains increase polyphenol intake, which contribute to reduce oxidative stress in tissues, thus providing a protective effect on patients with risk of CVD [24,68,69]. Furthermore, Lee et al. 2014 studied the effect of different dietary patterns in a Korean population of 7574 participants and found an inverse relationship between raw vegetable intake (96,3 g/d) and serum CRP levels. This effect was attributed to the association of vitamins, fiber, antioxidants, and polyphenols present in these foods.

In this review we were unable to determine whether one dietary pattern has more beneficial effects on inflammatory and endothelial dysfunction markers than another. This is likely due to the heterogeneity of quantified markers, types and duration of interventions, as well as age of participants. The most striking common feature was that interventions including mixed diets may be the most promising approach to reduce inflammatory and endothelial dysfunction markers. To this end, in order to increase adherence to healthy dietary patterns, it is important to provide a varied diet that is suited to foods available to each region. To this end, in order to increase adherence to healthy dietary patterns, it is important to provide a varied diet that is suited to foods available to each region.

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