Diet, Inflammation And Coronary Heart Disease

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ABSTRACT

In the last few years inflammation has been potentially linked to atherosclerosis. This review gathers information on the effect of diet on coronary heart disease, through an inflammatory pathway. Different methodological approaches to study diet were highlighted: single nutrients and/or foods and dietary patterns, and the relations between them and inflammatory markers were extensively described. Together, findings suggest that inflammation could be a potential pathway by which diet can modulate the coronary risk. However, research is still in progress and many scientific questions have not yet feasible answers. Most of the cohort studies providing dietary evaluations were conducted in the U.S, but the higher food diversity and wide ranges in dietary exposure frequently observed in European populations could provide novel and interesting insights into this filed. The use of different methodological approaches to study diet in a same population, and further providing straight comparisons by sex and obesity status would represent enormous advantages for the clear understanding of the role of diet and obesity in the modulation of coronary risk.

KEY-WORDS: DIET; NUTRIENTS; DIETARY PATTERNS; INFLAMMATION; CYTOKINES; CORONARY HEART DISEASE

ALIMENTAÇÃO, INFLAMAÇÃO E DOENÇA CORONÁRIA

RESUMO

Nos últimos anos tem vindo a ser descrita uma potencial relação entre o processo inflamatório e o aterosclerótico. Esta revisão pretende reunir informação sobre o efeito da alimentação na doença coronária, essencialmente através da via inflamatória. Foram incluídas diferentes abordagens metodológicas para estudar a alimentação: alimentos e/ou nutrientes isolados e padrões alimentares e descritas extensivamente as suas relações com marcadores de inflamação. Globalmente, os estudos sugerem que o processo inflamatório pode ser uma potencial via através da qual a alimentação pode modular o risco coronário. Contudo, a evidência ainda não é totalmente conclusiva e várias questões científicas ainda não têm as devidas respostas. A maioria dos estudos de coorte que avaliam o consumo alimentar foram conduzidos em populações norte-americanas, mas a maior diversidade alimentar e as mais amplas exposições alimentares frequentemente observadas em populações europeias podem providenciar informação interessante e inovadora neste campo do conhecimento. O recurso, numa mesma população, a diferentes abordagens metodológicas para o estudo da alimentação e o estabelecimento de comparações por sexo e níveis de obesidade podem representar vantagens inquestionáveis na clarificação do efeito da alimentação e da obesidade na modulação do risco coronário.

PALAVRAS-CHAVE: ALIMENTAÇÃO; NUTRIENTES; PADRÕES ALIMENTARES; INFLAMAÇÃO; CITOCINAS; DOENÇA CORONÁRIA

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DIFFERENT THEORIES ACROSS TIME ON DIET AND CORONARY HEART DISEASE

In the first part of the twenty century, a diet-heart hypothesis (also named as the lipid hypothesis) was proposed, based on the single principle that there was a direct relation between cholesterol in the diet (i.e. eggs), cholesterol in the blood, cholesterol in the atherosclerotic plaque, and its clinical complications, such as myocardial infarction[13]. This relation has probably risen from the work of Anitschkow on the cholesterol-fed rabbit model[27], years latter supported by Ancel Keys in the Seven Countries Study[50], in which was shown that dietary fat and cholesterol were correlated with the increase of coronary heart disease (CHD) occurred in Western and industrialized countries at that time.

In the second part of the twenty century, it became clear that dietary cholesterol played a minor role in regulating serum cholesterol levels, and that the cholesterol-rich low density lipoprotein (LDL) fraction, and not total cholesterol, was the most strongly related to the development of atherosclerosis and its consequences[36]. Different hypotheses, compatible with each other, have been proposed to explain the launch of the atherosclerotic process (e.g. response-to-injury, response-to-retention)[95], but it was the oxidation hypothesis that became more documented[7,47]. The principle of this hypothesis was based upon the oxidation of native LDL molecules, that once oxidized are preferentially taken up in the arterial wall.

The oxidation hypothesis supports an important role of diet and other lifestyles in atherogenesis, since LDL can be oxidized by smoking, for example, and oxidation can be prevented by dietary antioxidants, such as vitamins and polyphenols. Therefore, it was believed that complex interactions between diet, lifestyles and lipoprotein metabolism were the major determinants of the development of atherosclerosis and its complications. In fact, until recently, major epidemiological investigations of diet and CHD have relied on the classic diet-heart hypothesis.

Nevertheless, the diet-heart hypothesis seems to be over simplistic, because the effects of diet on CHD seem to be mediated through multiple biological pathways, others than serum total cholesterol or LDL-cholesterol, including blood pressure, insulin sensitivity, oxidative stress, endothelial dysfunction and subclinical inflammation[41].

An inflammatory hypothesis for the development of CHD is currently proposed[40, 55-56, 85] and the understanding if diet could influence CHD, through an inflammatory pathway, is still under research.

RELATION BETWEEN DIET AND INFLAMMATORY MARKERS

CHD is a multifactorial disease, thus study each biological system involved in its etiology is a new and

promising approach. Inflammation is believed to be one of the most important mechanisms linking healthy diets to a reduced CHD risk. Under this point of view, Giugliano and colleagues[35] suggested that each dietary strategy associated with a lower risk of chronic diseases, such as obesity, insulin resistance, metabolic syndrome and CHD may be associated with a lower generation of a proinflammatory milieu.

Scientific research in the last several years supported a beneficial cardiovascular effect of nutrients, such as fatty acids (monounsaturated, polyunsaturated n-3), antioxidant vitamins (E, C, ß-carotene), fiber and ethanol involved in inflammatory and antioxidant processes[35, 41, 76]. Dietary patterns have been also related with several proinflammatory cytokines[12, 21, 26, 32-33, 38, 49, 58, 68-70, 75].

Evidence on single nutrients or foods and inflammatory markers

The intake of n-3 fatty acids (EPA and DHA) has been inversely associated with plasma levels of C-reactive protein (CRP)[17, 59, 61], interleukin 6 (IL-6)[59], E-selectin[59] and tumor necrosis factor-α (TNF-α)[78]. Dietary supplementation with α-linolenic acid (n-3 fatty acid) seems also to decrease cytokine levels in dyslipidemic individuals[6,81], more than the linoleic acid (n-6 fatty acid)[98]. N-3 fatty acids decrease the arachidonic acid content of cell membranes, resulting in the synthesis of eicosanoids with fewer inflammatory properties than those derived from n-6 fatty acids. Other in vitro studies provided support for an anti-inflammatory role of n-3 polyunsaturated fatty acids[14-15, 18]. A synergetic effect between n-3 and n-6 fatty acids may also be present; a study among US women and men has found that the n-3 and n-6 fatty acids combination was associated with lower levels of inflammation than either type of fatty acid alone[78].

Saturated and trans-fatty acids have been also positively associated to inflammation[39, 60, 65-66]. In fact, it seems that dietary fatty acids can differently modulate markers of inflammation, e.g. Baer, et al.[4] in a randomized crossover study with 50 men consuming controlled diets for 5 weeks showed that CRP levels were higher after consumption of the "trans-fatty acids diet" than after consumption of the "carbohydrate diet", but were not significantly different after consumption of the "trans-fatty acids" and "trans-fatty acids plus stearic acid diets" than after consumption of the "saturated fatty acids diet" (8% of energy provided by lauric, myristic and palmitic fatty acids). Additionally, IL-6 concentrations were lower after consumption of the "oleic acid diet" than after consumption of the "saturated fatty acids", "trans-fatty acids", and "stearic acid" diets.

Antioxidant vitamins have been related to inflammatory markers, but most studies have focused on plasma levels of antioxidant vitamins[19,28-29, 31, 53, 88, 91], rather than dietary vitamin intake[9, 84] or vitamin supplement use[10,16]. Whereas observational studies held inverse and independent associations, supplementation studies found inconsistent results regarding the ability of antioxidant vitamins to reduce systemic and vascular inflammation in vivo, especially when dietary rather than pharmacological amounts are considered[10, 86].

Fruit and vegetables are major dietary sources of antioxidant vitamins. Several studies have related fruit and vegetable consumption to decreased inflammatory marker levels[20, 30, 34, 48, 72, 86-87, 93-94]. Most studies were randomized trials with very specific exposures such as high-pressurized orange juice[86], carotenoid-rich vegetables and fruit[94], sweet cherries[48], berries and apple[30], vegetable soup "gazpacho"[87], and provide non-conclusive results, since most of them found decreased inflammatory levels with the intake of these food items, but one failed to show a reduction of CRP after several weeks of intervention[30]. From the few observational studies conducted, some have reported an inverse association between fruit and vegetable intake and inflammatory markers[20,72], mainly in the elderly[34, 93], but further research is needed on the separate effects of fruit and vegetables, by sex and in a broader age spectrum. The antioxidant components of fruit and vegetables, including vitamins and flavonoids, are believed to contribute to their anti-inflammatory effects[62].

Fruit and vegetables are also major sources of fiber. Epidemiologic evidence supports a possible metabolic effect of dietary fiber on markers of systemic inflammation[1, 51-52, 79-80]. A study with individuals who took part in the U.S. National Health and Nutrition Examination Survey (NHANES 99-00) was one of the first to show a specific link between dietary fiber and CRP levels[52]. Although the mechanisms underlying these associations are not fully understood, it is believed that short-term acute hyperglycemia (conducting to uncontrolled production of free radicals which may promote atherogenesis) may increase circulating levels of free radicals and proinflammatory cytokines such as IL-6, IL-18, and TNF-α[24], providing a plausible explanation for the deleterious effects of rapid glycemic waves on vasculature. On the other hand, a high quantity of fiber of a high-carbohydrate meal seems to decrease the inflammatory levels, through the inhibition of IL-18 and stimulation of adiponectin[23].

In the Women's Health Study, a randomized double-blind placebo-controlled trial conducted in healthy middle-aged women, a significant positive association between the dietary glycemic load and plasma CRP levels was also found[57]. Moreover, a dose response gradient between the dietary glycemic load and plasma hs-CRP concentrations was most apparent

in overweight women. Overweight individuals have elevated concentrations of insulin and counterregulatory hormones, which are directly associated with the hepatic production of CRP[71].

Evidence on alcohol and inflammatory markers

Growing evidence supports the hypothesis that the cardiovascular protective effect of moderate alcohol intake could be partly mediated through inflammation[44, 96].

The association between alcohol consumption and inflammation has strong biological plausibility. Ethanol in high quantities and its metabolites may exert direct inflammatory effects on the liver, and acetaldehyde, in particular, may induce free radical production and subsequently increase lipid peroxidation and tissue inflammation[46], and lead to changes in uric acid metabolism[97]. While excessive ethanol has also been associated with increased IL-6 production, lower concentrations, on the other hand, may inhibit IL-6 secretion from adipocytes[63].

Several studies have investigated the association between alcohol consumption and biomarkers of inflammation [2-3, 8, 25, 37, 43, 64, 67, 73-74, 77, 82, 89-90, 92]. The results are mainly dependent of the categories of alcohol intake considered and the exposure range of each specific population. In general, it seems to exist a strong inverse association between alcohol intake, regardless of the type of alcoholic beverage, and biomarkers of inflammation. A U or J-shaped associations, with different nadirs, were found in most populations.

Some authors have also suggested that ingredients of alcoholic beverages other than ethanol might explain the beneficial effects on CHD risk, especially in the case of wine[5, 42]. However, lower levels of inflammatory markers have been reported for moderate consumption of either wine or beer[45, 54, 83], suggesting that ethanol itself might be largely responsible for the potential anti-inflammatory effects of these beverages.

Evidence on dietary patterns and inflammatory markers

The study of diet indexes/scores in relation to markers of inflammation is quite limited. Fung, et al.[32] in the Nurses' Health Study examined the association between several diet-quality scores and plasma concentrations of markers of inflammation. The authors found that the alternate Healthy Eating Index and the alternate Mediterranean Diet Index had the strongest inverse associations with hs-CRP and IL-6 concentrations. The other scores (Healthy Eating Index, Diet Quality Index Revised, Recommended Food Score) had little association with these biomarkers. The authors concluded that diet indexes reflecting current intake guidelines seem to be not predictive of biomarkers of inflammation, while the alternate versions may be useful as guidelines for reducing the risk of diseases involving such biological pathways.

Fargnoli, et al. again in the Nurses' Health Study[26] have evaluated if the adherence to the alternate Healthy Eating Index was associated with lower concentrations of biomarkers of inflammation. Women with the highest adherence to the AHEI had 41% lower hs-CRP, 19% lower E-selectin and 16% lower resistin levels, than did women with the lowest adherence to the AHEI. Associations with TNF-α, IL-6, soluble intercellular adhesion molecule 1, soluble vascular cell adhesion molecule 1 did not remain significant after adjustment for BMI.

A Healthy Dietary Pattern was also a priori defined by the authors of the Multi-Ethnic Study of Atherosclerosis (MESA), reflecting a cardioprotective balance among 36 food groups: 21 food groups rated as positive and 15 food groups rated as negative. The Healthy Dietary Pattern was inversely associated with concentrations of hs-CRP, IL-6, homocysteine and fibrinogen[69].

Because it has been suggested that the Mediterranean diet protects against the development and progression of CHD, several authors have hypothesized that the benefits of adherence to the Mediterranean diet could be due to its ability to modulate low-grade systemic inflammation and coagulation mechanisms. Within the ATTICA Study[12, 75], participants who were closer to the Mediterranean diet had lower hs-CRP, IL-6 and fibrinogen levels, as well as white blood cell count, as compared with those who were "away" from this dietary pattern.

A randomized trial conducted by Esposito, et al. also evaluated the Mediterranean dietary pattern in relation to markers of inflammation and endothelial dysfunction, but only among people with the metabolic syndrome[22]. The study randomized 180 patients to receive either the Mediterranean diet (detailed advice about how to increase daily consumption of whole grains, fruit, vegetables, nuts and olive oil) or a "prudent diet" low in fat (50–60% carbohydrates, 15–20% protein, and <30% fat) and followed them for two years. The level of hs-CRP decreased from 2.8 to 1.7 mg/l (p=0.010) in the intervention group (following the Mediterranean diet), while the level did not change in the other group. Because the results were adjusted for body weight changes, these findings suggest that, largely independent of concomitant changes in body weight, a Mediterranean-style diet might play a role in reducing the inflammatory state associated with the metabolic syndrome.

Also, a posteriori dietary patterns have been related to inflammation. "Prudent" dietary patterns, rich in

plant-based foods, have been associated with a more favorable biomarkers´ profile[33, 58], including lower hs-CRP, lower fasting insulin, lower homocysteine and higher folate concentrations. On the other hand, the "Western" pattern, characterized by high intake of red meat, processed meat, refined grains, sweets and dessert, French fries, and high-fat dairy products, has been associated to higher hs-CRP[33, 58], IL-6[21], C-peptide, insulin[33, 49], leptin and homocysteine concentrations[33].

Nettleton et al.[70], also looked at the associations of four dietary patterns, identified by factor analysis, with inflammatory markers in participants of the Multi-Ethnic Study of Atherosclerosis. The fats and processed meats pattern (fats, oils, processed meats, fried potatoes, salty snacks and desserts) was positively and linearly associated with hs-CRP and IL-6. In contrast, the whole grains and fruit pattern (whole grains, fruit, nuts, and green leafy vegetables) was inversely associated with hs-CRP, IL-6 and soluble intercellular adhesion molecule-1, as well as the vegetables and fish pattern (fish and dark yellow, cruciferous and other vegetables), which was inversely related to IL-6. The beans, tomatoes, and refined grains pattern was positively associated with inflammation.

More recently, Hamer and Mishra have also identified four dietary patterns, by factor analysis, similar across genders, named as fast-food, health aware, traditional and sweet[38]. Only the 'health aware' diet pattern (higher loadings for fruit, salad and raw vegetables, wholemeal bread and oil fish) was inversely associated with hs-CRP and homocysteine concentrations, and positively with HDL-cholesterol. Similarly, in a Japanese population, out of four dietary patterns derived from principal component analysis (healthy, high-fat, seafood and Westernized breakfast), only the healthy pattern, characterized by high intakes of vegetables, fruit, soy products and fish, was significantly and inversely related to hs-CRP concentrations[68].

In the Moli-sani project in Italy[11], more three dietary patterns were identified by factor analysis. The "Olive Oil and Vegetables" pattern (high intake of olive oil, vegetables, legumes, soups, fruits and fish) was associated with relatively lower values of glucose, lipids, hs-CRP, blood pressure and a cardiovascular risk score. The "Pasta and Meat" pattern (high intake of pasta, tomato sauce, red meat, animal fats and alcohol) was positively associated with glucose, lipids, hs-CRP and the cardiovascular risk score. The "Eggs and Sweets" pattern (positive loadings of eggs, processed meat, margarines, butter, sugar and sweets) was positively associated with hs-CRP.

Together, all these findings suggest that inflammation could be a potential pathway by which diet can modulate the coronary risk. However, research is still in progress and many scientific questions have not yet feasible answers. Most of the cohort studies providing dietary evaluations were conducted in the U.S, but the higher food diversity and wide ranges in dietary exposure frequently observed in European populations could provide novel and interesting insights into this filed. The use of different methodological approaches to study diet in a same population, and further providing straight comparisons by sex and obesity status would represent enormous advantages for the clear understanding of the role of diet and obesity in the modulation of coronary risk.

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