Diet and Inflammation: Effects of Macronutrients and Dietary Patterns

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Abstract: Cardiovascular disease (CVD) has already been demonstrated to be related to a chronic and complex inflammatory process, in which the loss of endothelial protective properties - the so-called endothelial dysfunction - plays a central role. A number of different approaches, both pharmacological and non-pharmacological, have been tested with inconclusive results so far. One field of special interest is the impact of the different macronutrients and dietary patterns in the inflammatory response that, ultimately, leads to endothelial dysfunction and increased cardio-metabolic risk. Although apparently simple, interventions regarding dietary habits have complex implications and involve a number of covariates that may interfere in the final results. To date, results about the protective effects of diet - in general - regarding cardio-metabolic risk remain to be fully proven.

Keywords: Inflammation, Endothelial dysfunction, Macronutrients, Diet, Metabolism, Cardiovascular risk.

INTRODUCTION

"Low-grade" chronic inflammation is associated to an altered metabolic state - as in hyperglycemia and hyperlipidemia - which leads to full-blown diseases as type-2 diabetes mellitus (T2DM) and coronary artery disease (CAD). Noteworthy is the fact that all these conditions are related to each other by a common pathway: endothelial dysfunction, a well known pro-inflammatory state.

The accumulation of body fat (especially on the abdomen) secondary to an excessive caloric intake negatively modulates the whole inflammatory state. However, increased inflammatory markers levels are seen acutely after an episode of high energetic intake in a single meal; the same happens after a chronic imbalance on specific nutrients ingestion, even in non-overweight persons. This suggests that diet patterns play an independent role in inflammatory modulation [1].

Hypercaloric and highly processed diets, poor in antioxidant foods leads to a supraphysiological postprandial state characterized by plasmatic peaks of glucose and lipids. This leads to a mitochondrial metabolic overload in the muscular and adipose tissues, resulting in the formation of free radicals - like the superoxide anion - and, consequently, to pro-inflammatory alterations and endothelial dysfunction [2].

Therefore, the aim of this article is to discuss the role of macronutrients and of specific dietary patterns in inflammatory modulation.

1. ENERGY BALANCE

The "meal-related inflammatory induction" can be evidenced by the immediate rise in C-reactive protein (CRP), cytokines and endothelin-1 levels after a hypercaloric meal. Monier *et al.* demonstrated, in persons with T2DM that urinary excretion of 8-isoprostaglandine F2 (PGF2), a marker of oxidative stress, is more strongly related to acute fluctuations of serum glucose levels that to chronic hyperglycemia [3]. Additionally, Ceriello *et al* showed that ingestion of a beverage with 75g of glucose in fresh cream (75g fat, 5g carbohydrate and 6g proteins/m^2 of body surface - 700kcal/m^2) is related to an elevation of serum glucose and triglycerides after 2 to 4 hours; this, in turn, results in immediate oxidative stress and inflammation, with a rise in nitrotirosine and CRP, respectively [4].

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E-ISSN: 2410-2822/15

In this manner, since the magnitude of the postprandial metabolic derangement - and its inflammatory potential - is strongly related to caloric intake, one can expect that fasting may be able to counteract these alterations. However, severe caloric restrictions can also result in inflammatory increase. Experimental studies have shown that a caloric reduction of 30% of the ad libitum intake - since it does lead the subject to a malnutrition state - is capable of decrease inflammatory markers and increase longevity in animal models [5]. In humans, a similar caloric restriction along with a diet that impacts on micronutrients can attenuate both oxidative stress and inflammation [6]. Even diets with a high glycemic load (rich in simple carbohydrates), a 30% caloric restriction can reduce serum levels of CRP in overweight individuals [7].

These findings suggest that energy balance is an important modulator of systemic inflammation (regardless of weight) and that adequate daily caloric intake may play a considerable role in a strategy for preventing and controlling the inflammatory process.

2. CARBOHYDRATES AND FIBERS

Carbohydrates can act on systemic inflammation but this so-called “inflammatory potential” is subjected to the effects of a number of factors, including glycemic index (GI; *i.e*. measure of the relative impact of an aliment`s carbohydrate content on serum glycemic levels), glycemic load [GL; *i.e.* measure of quality and quantity of ingested carbohydrates: (available amount of carbohydrates in the aliment) x aliment`s GI / 100] and the content of dietetic fibers. The extent to which carbohydrates acutely increase the glycemic response appears to be directly related to the levels of inflammatory markers, as observed after a high GI meal [8]. As a matter of fact, this response seems to be linked to the relationship between GI and GL. In this manner, ingestion of large amounts of low GI foods or ingestion of small portions of high GI aliments are capable of increasing the levels of inflammatory markers. Nonetheless, despite the recognition of the role played by these nutrients in the postprandial metabolic dearragement, their precise effects on the inflammatory response are yet to be conclusive [9, 10].

Observational studies have demonstrated the relationship between GI, GL and inflammatory cytokines. In the Women´s Health Study, which evaluated more than 13,000 women aged > 45 years, higher quintiles of GI and GL were significantly associated to higher levels of CRP [11]. On the other hand, randomized trials did not succeed in showing such relations. Pittas *et al.* demonstrated a 35% reduction on CRP levels in overweight individuals who went on a hypocaloric diet with low GL for 6 months, but this association was shown to be no significant after adjusting for baseline CRP levels and weigh loss variation [12]. Similarly, Shinkany *et al*. did not observed significant differences in inflammatory markers - as CRP, IL-6 and TNF-α - in overweight and obese men after a 4-week hypocaloric diet regardless of GI or GL [13]. Noteworthy is the fact that such divergences may result from the different caloric contents of each study`s diet used for evaluating GI and GL, because not only different amounts of carbohydrates were compared but also the total caloric intake was restricted; this, in turn, may limit the effect of each isolated intervention.

As the ingestion of refined carbohydrates rises, the same happens to overall diet GL but fiber intake is reduced. Since diet fibers play an important role in food absorption - and, hence, in postprandial glycemic control -, this reduction is related to an increase in glucose, insulin and free fatty acids levels, and in hunger and food intake. In this manner, considering the direct relationship between post-prandial hyperglycemia and CRP elevation, one can understand the non-weight-loss-dependent impact of diet fibers in inflammatory markers [14]. These anti-inflammatory effects seem to occur with both diet and supplemental fibers [15].

Esposito *et al*. compared three diets with different contents of carbohydrates, lipids and fibers in persons with and without T2DM. Sixty subjects (30 T2DM x 30 controls) were randomized to receive 3 types of isocaloric diets - separated by 1 week of each other: (1) high lipid diet (28% carbohydrates, 12% proteins, 60% lipids, 2,8g of fibers); (2) high glucose/low fiber diet (70% carbohydrates, 11% proteins, 19% lipids, 4,5g of fibers); (3) high glucose/high fiber diet (67% carbohydrates, 11% proteins, 22% lipids, 16,8g of fibers). Compared to controls, diabetic subjects had higher baseline levels of IL-8 and IL-18, and lower adiponectin concentrations. In both groups, the high lipid diet increased IL-18 and reduced adiponectin levels. On the other hand, the high glucose/high fiber diet decreased IL-18 levels in both diabetic and non-diabetic persons. None of the tested interventions were related to a decrement in IL-8 [16]. So, even though diets rich in fibers and complex carbohydrates are a

better option than diets based on refined carbohydrates, their role in the inflammatory process still needs further investigation.

3. LIPIDS

3.1. Saturated Fat and Trans-Saturated Fatty Acids

Saturated fatty acids (SFA) are defined as inflammatory agents for their capacity of raising the serum levels of biomarkers as CRP, interleukin-6 (IL-6) and E-selectin [17]. Analyses from the National Health and Nutrition Examination Survey (NHANES 1999-2000) demonstrated that the levels of SFA in serum phospholipids are positively related to serum PCR and fibrinogen levels [18]. However, some studies failed to show such correlation, or even demonstrated an inverse relationship between SFA intake and CRP levels [19-21].

A number of mechanisms have been proposed to explain the inflammatory potential of SFA: (1) accumulation of diacilglycerol e ceramide; (2) activation of nuclear factor kappa beta (NFκB), protein kinase C (PKC) and mitogen-activated protein kinases *(*MAPK) with the subsequent induction of inflammatory genes expression on white adipose tissue (WAT), immune cells and myotubes; (3) reduction of peroxisome proliferator-activated receptor gamma 1a/b (PPARg 1a/b) co-activator and adiponectin production, leading to a diminished oxidation of glucose and fatty acids; and (4) recruitment of immune cells (macrophages, neutrophils and dendritic cells) to WAT and muscle tissue [22].

Evaluating the effects of a diet with reduced cholesterol and saturated fat content (30% total lipids, 5% saturated fat, 200mg/day of cholesterol), Pirro *et al* demonstrated, in 35 subjects with primary hypercholesterolemia, a reduction in arterial stiffness along with reductions of CRP levels [23]. Hypocaloric diets with restricted fat and carbohydrates have been shown to significantly reduce a number of inflammatory markers - like CRP, TNF-α, IL-6 and intercellular adhesion molecule 1 (ICAM-1) - suggesting that, in short term, weight loss would be the one responsible for the modifications on these biomarkers levels [24]. Anyhow, it is expected that each 1% reduction in SFA-derived caloric intake may account for a reduction of 0,14 mg/dL in CRP levels, what makes it reasonable to recommend a SFA intake <7% for overweight and obese subjects [25].

Tans-saturated fatty acids are also associated to increased inflammatory markers. In overweight and obese women, ingestion of this sort of lipid is positively related to higher levels of IL-6 and CRP [26].

3.2. Polyunsaturated Fatty Acids

The polyunsaturated fatty acids (PUFA) families Omega-6 (sunflower oil, soy oil, nuts, grains and integral cereals) and Omega-3 (salmon, sardine, tuna, oil seeds, canola oil) are eicosanoids precursors, which play an important role in inflammatory response. The anti-inflammatory effects of Omega-3 PUFA are associated to the reduction of cell membranes` arachidonic acid content, resulting in the synthesis of eicosanoids with weaker pro-inflammatory properties compared to those derived from Omega-6 PUFA [27].

Observational surveys have demonstrated that natural Omega-3 PUFA or fish ingestion are inversely related to inflammatory markers, as in a sample of 859 healthy men and women, where eicopenthaenoic acid (EPA) and docohexaenoic acid (DHA) - the two Omega-3 PUFA – were related to lower TNF-α levels [28]. However, studies using fish oil in capsules as supplementation failed to demonstrate associations between omega-3 intake, inflammatory markers and outcomes such as heart attack and mortality [29, 30].

Polyunsaturated fatty acids may act differently on inflammatory markers according to their source. Diets rich in alpha-linolenic Omega-3 fatty acid (6.5% of total energy intake) can reduce the levels of CRP, E-selectin and vascular cell adhesion molecule 1 (VCAM-1) strongly then diets rich in linolenic Omega-6 fatty acid (12.6% of total energy intake) [31].

3.3. Monounsaturated Fatty Acids

Few studies have suggested an anti-inflammatory potential for monounsaturated fatty acids (MUFA) consumption, like oleic oil (olive oil and avocado). In healthy men a sole meal with 1000 kcal containing 45% of MUFA reduced in 6% CRP levels after 2 hours [32]. Among overweight individuals, an 8-week diet rich in MUFA rises the expression of anti-inflammatory genes on abdominal fat tissue compared to a diet rich in saturated fat [33]; still, it is seen that the replacement of 8% of overall diet fatty acids for oleic acid can significantly reduce IL-6 concentrations when compared to diets rich in saturated or trans-saturated fatty acids [34]. So, oleic acid can counterbalance the

pro-inflammatory effects of high lipid diets, when in substitution to saturated or trans-saturated fatty acids.

4. PROTEINS

The effects of proteins on inflammation seem to be dependent of its source. Red meat is typically considered a pro-inflammatory factor, possibly for the association between high red meat intake and CAD [35]. However, studies evaluating the ingestion of lean red meat have failed to show a link with an increase in inflammatory markers and mortality from CVD [36, 37]. These data suggest that not only the quality of the meat, but also its fat content, may play a role in its inflammatory potential.

On the other hand, ingestion of foods rich in arginine (*i.e*., nuts and fish) had favorable results in terms of diminishing the levels of inflammatory markers. Wells *et al*. evaluated such relation using data from the NHANES III, and demonstrated that a high intake of arginine (>7,5g/day) is associated to lower levels of CRP - even after adjustment for confounding factors [38]. In spite of some studies have tested the use of soy protein as an inflammatory modulator, clinical trials using isoflavones and/or soy protein failed to demonstrate such effects [39]. In this manner, both the kind and amount of protein that would be more effective in reducing systemic inflammation are yet to be established.

5. DIETARY PATTERNS

5.1. Vegetables

An increase in fruits and vegetables intake is strongly recommended because of a number of beneficial effects, including anti-inflammatory properties [40]. Such effects seem reasonable when considering their high concentration of diet fibers, flavonoids, carotenoids and vitamins. A variety of observational studies which included persons with overweight or obesity in their analyses have demonstrated an inverse relationship between high ingestion of fruits and vegetables and levels of inflammatory biomarkers [41, 42]. However, Freese *et al*. did not demonstrated any association between a diet rich in both fruits and vegetables and a number of inflammatory markers, as adiponectin, CRP, IL-6, ICAM-1 and VCAM-1 [43].

Other than the quantity, the variety of ingested fruits and vegetables could have an impact on these biomarkers. Some interventional studies have investigated the global impact of vegetables in general - or even of specific nutrients within them - on serological markers of inflammation. The majority has positive results [41]. Nevertheless, studies regarding only one specific sort of vegetable or fruit - or extracts with high polyphenols concentrations - despite showing some anti-inflammatory potential, rarely demonstrated an extended effect to a number of different biomarkers [44]. So, although consumption of fruits and vegetables are related to a decrease in inflammatory response, there is lack of evidence regarding the use of a single or specific sort of fruit, vegetable or extract.

5.2. Mediterranean Diet

A diversity of studies evaluating diet patterns and inflammation has focused on the Mediterranean diet and its components. The term itself ("Mediterranean Diet") is generally applied to a large specter of diet patterns traditionally found in the olive-growing regions in Southern Europe. Compared to the Western diet, it can be considered relatively rich inα-linolenic acid (approximately 2g/day or 1% of total caloric intake) and with low content of linoleic acid, with a 1: 7 ω-3: ω-6 ratio [45].

The Lyon Heart Diet Study evaluated the impact of different Mediterranean diets in regions of Italy, Spain and Greece. In a large sample of healthy Italian, CRP levels were inversely associated to high consumption of olive oil, vegetable, soup and fish [46]. A little study in Spain, with high cardiovascular risk subjects, did not show any relation between adhesion to the Spanish Mediterranean diet and inflammatory biomarkers reduction, but did show an inverse association between IL-6 levels and the ingestion of fruits and cereals. It also showed that both CRP and IL-6 levels were lower among those with higher intake of olive oil [47].

Esposito *et al*. randomized Italian subjects with metabolic syndrome to Mediterranean diet (increased consumption of fruits, vegetables, olive oil and integral grains) or to a prudent diet as recommended by the American Heart Association (AHA; with high content of carbohydrates and low content of MUFA and MUFA and ω-3 PUFA). After 2 years, individuals on the Mediterranean diet had lower levels of CRP, IL-6, IL-7 and IL-18 than those on the AHA diet [16]. On the other hand, Greek subjects with abdominal obesity who adopted the Mediterranean diet for two months did not have any effects on CRP levels, despite evidence of enhanced endothelial function [48]. A recent meta-analysis concluded that such diet pattern is associated

with reduction of inflammatory markers and of endothelial dysfunction, supporting the findings from observational surveys regarding the Mediterranean diet and an improved inflammatory response [49].

5.3. DASH Diet

It is composed of integral grains, fruits, vegetables and low-fat dairy products associated to reduced levels of total fat and sodium. Its pivotal study was conducted with subjects with hypertension and had marked results on reducing blood pressure (BP) levels [50]. Later it was demonstrated that it was also related to the prevention of CAD, heart failure (HF) and stroke [51].

After three weeks, both the naturally rich in fibers (30g/day) DASH diet and a diet with supplementary fibers (30g/day of soluble fibers) reduced CRP levels in lean normotensive and in obese hypertensive subjects; however the stratified analysis showed that both diets were effective only in lean individuals, with no significant changes in CRP levels in obese persons with hypertension [52]. In person with diabetes, adopting DASH diet for eight weeks reduced CRP levels in nearly 27% compared to the control diet (5%); the same happened to fibrinogen levels (-11% DASH; -0,5% control) [53]. Teenagers with metabolic syndrome had their CRP levels reduced after six weeks of DAH diet, independently of weight loss or lipid profile; still, there was no significant modification in the levels of TNF-α, IL-2, IL-6 and adiponectin in this population [54].

CONCLUSION

Adopting a diet with adequate caloric intake, rich in fibers, fruits and vegetables associated to a balanced ingestion of macronutrients (Figure **1**) is a valuable non-pharmacologic strategy in reestablishing the balance between pro- and anti-inflammatory factors and processes for managing and preventing obesity, diabetes and cardiovascular disease.

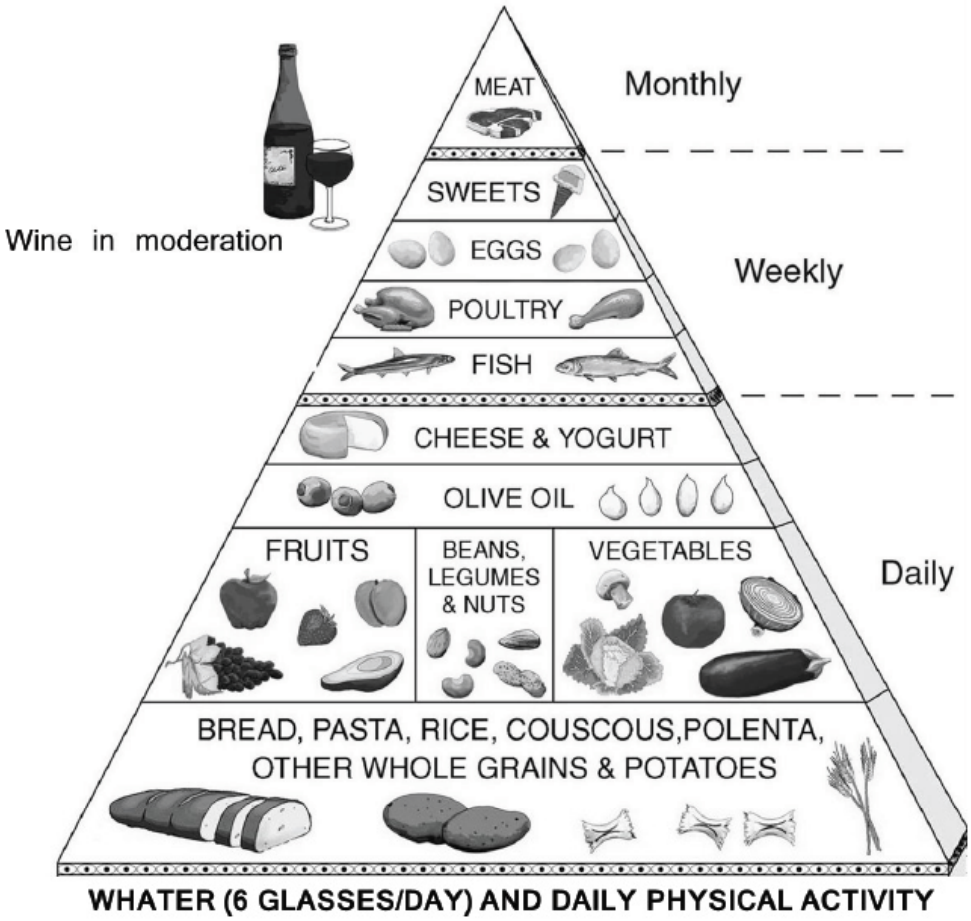

Figure 1: The Mediterranean Diet Pyramid. A simple tool to help in choosing a healthy and anti-inflammatory dietary pattern. Adapted from Willett WC *et al* [55].

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Received on 31-01-2015 Accepted on 29-02-2015 Published on 21-03-2015

http://dx.doi.org/10.15379/2410-2822.2015.02.01.03