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Integrating diet and inflammation to calculate cardiovascular risk

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Diet; Nutrition; Cardiovascular risk; Dietary inflammatory index; Inflammation

In the last decade, several studies strengthened the idea that a diffuse and systemic inflammation is functionally associated with cardiovascular disease (CVD). The mechanism of atherogenesis, which underlies various acute cardiovascular events, is mainly considered an inflammatory process [1]. Indeed, immunity cells that participate in the inflammatory response, and soluble factors including pro-inflammatory cytokines, play a crucial role in the formation and rupture of atherosclerotic plaques. Moreover, the increase of IL-1, IL-6, and C-reactive protein (CRP) in patients with myocardial infarction or unstable angina, confirms the inflammatory status in the vascular bed of these subjects [2].

Supporting this view, other studies have shown that also a low-grade systemic inflammation leads to an increased risk of cardiovascular events [3]. In particular, high CRP levels have been proposed as an independent risk factor in coronary artery disease [4]. There is a mounting interest towards the molecular mechanisms linking inflammation and cardiovascular events, to find new therapeutic targets for the prevention and treatment of CVD. It is a very complex and multifactorial relation since many elements - from genetic to environmental factors - contribute to the onset of inflammation in the vascular bed. Among these, diet is one of the most important and fascinating factors, and it could actually represent a good and relatively easy point of intervention to reduce the risk of CVD.

1. Inflammatory potential of diet and risk of cardiovascular disease

Numerous studies have demonstrated that diet may have proor anti-inflammatory effects, but the pattern and mechanisms underlining these events are not totally understood. For instance, glucose may produce oxidative stress and consequent inflammatory response: glucose ingestion has been shown to activate the NF-κB pathway, which regulates various pro-inflammatory genes, and to induce an increase of superoxide production in mononuclear cells and leukocytes [5]. Other diet components, such a single high-fat meal, can trigger endothelial activation leading to increased expression of specific adhesion molecules [6],

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whereas the introit of antioxidant vitamins can improve endothelial function, and fiber intake stimulates a characteristic cytokine response [7].

Hence, the specific quality and quantity composition of the diet can be directly related to a pro- or anti-inflammatory dietary pattern; for example the Western diet, mainly characterized by meat consumption, is positively associated with inflammatory biomarkers [8], while the Mediterranean diet has been shown to reduce some inflammatory biomarkers [9].

The relationship between diet and CVD is well recognized: the aforementioned Mediterranean diet is considered a healthy dietary pattern, given its capacity to reduce CVD risk - an increment of approximately 2/9 in the score, that represents the adherence to Mediterranean diet, is associated with 33% reduction in cardiovascular-related mortality [10]. The effect of diet on CVD is also likely linked to the pro- or anti-inflammatory "power" of the diet itself. Indeed, generally, dietary patterns associated with a reduction in the global risk of CVD are also associated with a low pro-inflammatory effect, as seen with the Mediterranean diet [11].

2. The dietary inflammatory index (DII): a mathematical assessment of the potential inflammatory activities of the diet

There is increasing attention towards the possibility to quantify the `inflammatory power' of diet. Indeed, an available index, able to numerically express the inflammatory effect of individual dietary patterns, is useful to study the correlation of diet and inflammation with CVD. Previous studies have analyzed several dietary indexes to express a certain quality of diet, not focusing though on its inflammatory potential; e.g., the score quantifying the level of adherence to French dietary guidelines is associated with the risk of CVD [12]; however, it is not directly correlated with the inflammatory effect of food, and could thereby reflect other mechanisms of action responsible for the observed correlation with CVD.

Obtaining an inflammatory index of diet of a specific individual is not an easy task, because various factors have to be assessed, not only the single type of food, but also possible interactions (neutralization, synergism mechanisms) among different types of food. In 2014, a literature-derived, population-based DII has been developed [13]. To design such index, 45 food parameters have been considered, including micronutrients, macronutrients, and commonly consumed bioactive components such as flavonoids and tea (Table 1). For each food parameter, the inflammatory potential was calculated through an extensive review of the literature published from 1950 to 2010 (a total of 1943 articles were screened).

A score of +1 is assigned to each article showing a positive correlation of the food parameter considered with recognized inflammatory biomarkers (IL-1β, IL-6, TNF-α and CRP) (pro-inflammatory effect), whereas a score of −1 or 0 is assigned to each article showing negative correlation with the above mentioned markers or positive correlation with IL-4 and/or IL-10 (anti-inflammatory effect) or no correlation (no inflammatory effect), respectively. The overall inflammatory effect score (OIES), obtained after further adjustments related to the relevance of each published study, represents the inflammatory potential of a specific type of

food: a high value of OIES indicates high pro-inflammatory effect, while a reduced OIES designates an anti-inflammatory effect of a specific type of food. To calculate the DII for an individual, the specific food-related OIES needs to be multiplied by the amount of each type of food introduced by the subject in a range of time (global daily mean intake). Eventually, to reduce the effect of right skewing and to have a symmetrical distribution (−1, 0, +1), the resultant value is converted to a percentile score.

3. DII and cardiovascular disease: cons and pros

Many investigators focused on the correlation between DII and CVD risk, obtaining contrasting results. Negative evidence is shown in the paper published by Vissers and colleagues in this issue of *Atherosclerosis* [14]. The authors considered 25 (out of 45) food parameters for the calculation of DII in 6972 middle-aged Australian women. The DII was measured only at baseline, as acknowledged in the limitations of the study, and 335 cases of cardiovascular events were registered during an 11-year follow-up. Albeit previous reports in men and general populations had suggested a role for DII in CVD risk prediction, in this cohort of women from the “Australian Longitudinal Study on Women's Health” there was no clear association between DII and multiple cardiovascular and cerebrovascular endpoints. The authors found an 8% increased risk of ischemic heart disease for every 1-standard deviation increase in pro-inflammatory diet, but this finding was not statistically significant when adjusted for common cardiovascular risk factors. Of note, results were not different when examining just postmenopausal women [14]. This study raises some concerns about the validity of expressing the diet-related inflammatory activity - through DII - in different populations.

Some negative evidence is represented by a recent study conducted in Luxemburg on 1352 subjects (18–69 years old). The authors did not find any significant correlation between DII and high-sensitivity CRP in predicting the inflammatory state in relation to cardiovascular-related health outcome [15].

On the other hand, various reports provided evidence of a correlation of DII with CVD risk. In the “Prevención con Dieta Mediterránea” (PREDIMED) study, a prospective (2003–2010) study on a Spanish population (7216 men and women) with high cardiovascular risk but without any manifestation of CVD, the authors randomized the population in three arms: a control group with a classical diet characterized by low fatty acids introit, and the other two groups with diet supplemented by oil or nuts, respectively. The data about the diet of participants were collected using food-frequency questionnaires (FFQ), and, for the calculation of IDD, 32 (out of 45) food parameters were evaluated. Considering DII at baseline as a continuous variable, the authors found that for each increase of 1 DS of DII, the cardiovascular risk in the population increased, in turn, by 22%. The authors also demonstrated that a diet with high inflammatory potential was directly associated with high risk of CVD, showing a linear dose-response trend [16].

In another prospective study, the SUN (“Seguimiento Universidad de Navarra” - University of Navarra follow-up) Cohort study, where 28/45 food parameters were considered, the authors found that the incident rate of CVD (MI, stroke, and CVD death) was 0,58/1000 for

the population with the most anti-inflammatory quartile of DII, while 0,87/1000 in the most pro-inflammatory quartile of DII. Furthermore, the authors observed that when CVD risk was assessed adjusting DII with the Mediterranean diet score, the residual difference between the two results was very low; they interpreted these data as a proof that the Mediterranean diet has an ant-inflammatory effect, and inflammation is the main pathway through which diet has its impact on health [17].

The “Supplémentation en Vitamines et Minéraux AntioXydants” (SU.VI.MAX) study included 7743 participants (middle-aged French adults). The authors studied the association between DII and angina, MI and stroke, on an 11.4-year follow up. For DII computation, 36/45 food parameters were considered, using 24 h dietary records instead of a FFQ. A significant association between DII and MI was detected, but there was no significant association with angina or stroke [18].

The “Geelong Osteoporosis Study” (GOS) study was conducted on 1363 Australian men. For DII calculation, the intake of 22/45 food parameters was assessed via validated FFQ. The authors demonstrated that men with positive DII (high pro-inflammatory diet) had 2 times the probability of CVD compared with men with a negative DII. A very robust result was found when the authors considered only the first three (out of the total five) years of follow-up [19].

The “Third National Health and Nutrition Examination Survey” (NHANES III) is a nationally representative sample (15.693 participants, both women and men) of the civilian, non-institutionalized US population. In a retrospective cross-sectional study, 27 food parameters and 24-h dietary records for DII calculation were evaluated. Participants with high DII (quartile 4) were 1.3 times more likely to have a previous cardiac disorder than participants in the quartile 1 of DII. Interestingly, these findings seem to be sex-dependent: indeed, after stratifying by sex, the significant association between DII and CVD risk was present only in women [20].

Most recently, the results of a 10-year follow-up prospective population-based study carried in the greater metropolitan area of Athens in Greece (ATTICA study) were published [21]. The authors demonstrated a protective effect of an anti-inflammatory diet (calculated via DII) towards the 10-year CVD incidence among participants without metabolic syndrome. However, the presence of metabolic syndrome already at baseline blunted the anti-inflammatory diet protective effect [21], underlining the independent importance of the metabolic syndrome on CVD risk.

In most of the studies mentioned above, the study population is characterized by a relatively low number of cases of CVD, so the statistical significance of results may be compromised. Additionally, large confidence intervals for some cardiovascular outcomes strongly suggest a lack of power rather than a lack of effect.

Notably, all of these studies considered a number of food parameters lower than 45 – the parameters evaluated in the seminal study [13] - and the choice of the food parameters included in the calculation of IDD is not always specified. In this sense, some of the foods included might have an active effect (pro or anti-inflammatory) that is not considered in the

final analysis. Among the food parameters selected, the reader can find also cholesterol, which plays a crucial role by itself in the determination of cardiovascular risk [22] and can mask – or alter, at least – the effect of food-related inflammation on cardiovascular outcome. Equally important, some covariates such as hypertension and diabetes are labeled as potential confounders; however, by correcting for these factors, the investigators can partially correct for the effect of DII itself, since these parameters have been independently linked to inflammation [23].

4. Looking for a potential mechanism

Diet is one of the most influential lifestyle factors contributing to the rise of inflammatory disorders. A potential mechanism underlying the association of diet, inflammation and cardiovascular disease can be identified in the gut microbiota. Indeed, diet shapes large-bowel microbial ecology, and changes in the gut microbiota composition are associated with inflammation. Numerous studies have indicated a remarkable role for diet, the gut microbiota, and their metabolites in the pathogenesis of several inflammatory disorders [24].

Interestingly, a recent report demonstrated that adaptive immunity against gut microbiota can enhance immune regulation, reducing atherosclerosis and Western-diet-related inflammation [25]. The gut is in constant contact with food antigens, commensal microbiota and foreign pathogens. To effectively manage these interfaces, the gut has evolved with a highly dynamic anatomy that interacts with the resident microbiota and the mucosal immune system. Therefore, a `leaky gut' in humans and mice, referring to increased gut permeability, disturbed microbial balance and impaired mucosal immunity [26], can be seen as the preceding step to the initiation of diet-related inflammation and subsequent cardiovascular disorders.

5. DII: a standard index with a lot of variability

As described above, DII is the results of two components: 1) statistically inflammatory potential of food parameters, based on literature review, 2) calculation of the intake of the specific food parameter by each subject. Both parts of this index can represent an important source of variability that must be taken into account in the evaluation of DII.

The calculation of the potential inflammatory effect of food parameters (1) is the result of some studies that support an anti-inflammatory effect, and some other studies supporting a pro-inflammatory effect. In certain individuals, food parameters may exert an effect that is just the opposite of that considered for DII calculation, and this can be due to a different genetic pattern of the subject that can respond in a distinctive way or to a diverse genetic-environmental interaction that is not considered in the computation of DII. Besides, in DII computation, the potential interaction between food parameters is not considered, albeit mechanisms of synergism or antagonism between the micro and macronutrients are documentated [15,27].

The calculation of the intake of specific food parameters by each subject (2) is based primarily on dietary self-reports. Indeed, participants have to give information about their personal diet and FFQs may contain a certain degree of measurement error, which might

affect the results derived from such evaluation [28]. Moreover, the different studies did not always use the standard FFQ, further increasing the variability when trying to compare the results from diverse populations. To circumvent these limitations, new dietary indexes assessing inflammation have been developed and validated most recently [29–31], to numerically evaluate dietary patterns in a standardized and reproducible manner across different populations.

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Table 1

Examples of inflammatory score calculated [13] for some food parameters.

	Food parameter	Score
Anti-inflammatory	Fiber	−0.663
	β-Carotene	−0.584
	Vitamin D	−0.446
	Garlic	−0.412
Pro-inflammatory	Saturated fat	+0.373
	Cholesterol	+0.110
	Carbohydrate	+0.097
	Protein	+0.021