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VIEWPOINT

The role of nuts in the optimal diet: Time for a critical appraisal?

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Abstract During the last decades, nuts have attracted the attention of researchers for their potential benefits in cardiovascular prevention. We discuss here some aspects of the assumed beneficial effects of nuts, weighing them against potential harm. Epidemiological observations and controlled intervention trials consistently suggest that nuts consumption is associated with improved serum lipid profile, thus helping decrease cardiovascular risk. Being nuts an energy dense food, their impact on energy balance and body weight should be considered. In particular, the claim that adding nuts to the habitual diet, thus increasing calorie intake, does not cause body fat accumulation still needs evidence and biological plausibility. The potential risk associated with the relatively frequent occurrence of allergic reactions following the consumption of nuts is also discussed.

Introduction

The role of diet and, in general, lifestyle choices in relation to many chronic diseases is supported by a huge bulk of evidence. In particular, negative dietary habits affect cardiovascular risk factors and possibly cardiovascular morbidity and mortality. The research about what was referred to as the "optimal" diet(s) for health promotion and prevention of chronic-degenerative diseases adds everyday new evidence to the body of scientific literature.

With particular regard to the prevention of cardiovascular and metabolic diseases, the implications of identifying safer and more effective foods or dietary patterns are enormous and so are the consumers' expectations. Actually, the translation of the scientific data into nutritional claims and guidelines is not an automatic process and is challenged by the high standard of evidence required by the regulatory governmental agencies [1]. On the other hand, the response of the food industry to the researchers' commitment and to consumers' expectations has been the marketing of a rapidly increasing number of products labelled as "functional foods" and/or nutraceuticals, in some cases even before the possible benefits deriving from

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the introduction or the more frequent use of such products in the habitual diet were firmly established.

Presently, steady evidence exists that traditional dietary patterns — like the Mediterranean diet —, or food items — like fruit and vegetables — , may exert a protective role against largely diffused conditions such as cardiovascular and metabolic diseases. Among the foods provided of a favourable potential in terms of cardiovascular risk and other health outcomes, nuts have attracted increasing attention and have been the object of intensive scientific investigation in the last few decades [2,3]. Consistent evidence shows that nuts consumption is associated with improved lipid profile, in both epidemiological and intervention studies, thus suggesting the utility of nuts in the dietary prevention of cardiovascular diseases. On the other hand, less attention has been paid to undesired side effects of increasing nuts consumption — like the possible weight gain due to their energy density — and also to the potentially harmful consequences of nut ingestion in allergic individuals. Here we attempt a critical appraisal of the implications of nuts consumption on human health, aiming to stimulate a debate and, possibly, further research on how to make the great potential of nuts in cardiovascular prevention of practical and safe use.

A brief history of nuts and health

The interest for nuts comes from very far away. In a recent paper, Salas-Salvado et al. accompanied us in a fascinating journey through the cultural and historical aspects of nut consumption, showing that nuts have been part of the human diet since prehistoric times, and that they were consumed not only for their nutritional but also for their therapeutic properties [4].

From the nutritional point of view, the tree nuts family is characterised by a high energy density and a high content in mono- and poly-unsaturated fatty acids, vegetable proteins, fibre, phytosterols, polyphenols, vitamins and minerals. Recently, Bolling et al. [5] carefully reviewed the phytochemicals of tree nuts. This family, too often generically referred as "nuts", includes several species (almonds, Brazil nuts, cashews, hazelnuts, macadamias, pecans, pine nuts, pistachios and walnuts) whose content in nutrients and phytochemicals can vary considerably by nut type, genotype, pre- and post-harvest conditions, as well as storage conditions [5]. Peanuts, which are usually but erroneously included by the consumers in the "nuts family" (while belonging to legume or "bean" family), share a similar nutritional profile with nuts. Of note, chestnuts — which are tree nuts according to the botanical classification — have a largely different macro- and micro-nutrient profile. The pattern of the dietary consumption of nuts also varies in different geographical areas, with some populations eating them as part of the daily diet while in other cases they are consumed as between-meals sweet or salty snacks [6]. Thus, there is still much to learn about the complex composition of nuts (particularly in terms of phytochemicals) and their consumption in different settings and populations.

The nuts hypothesis stemmed from several lines of evidence. In 1992, Fraser et al. firstly reported that subjects who consumed nuts frequently (more than four times per week) experienced substantially fewer definite fatal coronary events and definite nonfatal myocardial infarctions when compared with those who consumed nuts less than once per week [7]. This evidence was corroborated by subsequent large scale epidemiological studies showing that frequent consumption of nuts was associated with a lower risk of coronary events, after adjustment for known coronary risk factors [8—10].

Based on epidemiological data, the Food and Drug Administration released in 2003 a qualified health claim on nuts: "Scientific evidence suggests but does not prove that eating 1.5 ounces (42 g) per day of most nuts as part of a diet low in saturated fat and cholesterol may reduce the risk of heart disease", giving the claimed evidence a relatively low (grade C) level of scientific validity [11].

Epidemiological data on the association between nuts consumption and other health outcomes like serum lipids and lipoproteins, diabetes, and obesity were the object of recent accurate reviews (see for instance [2,3,12]). The summary conclusion of these reviews was that a higher consumption of nuts is consistently associated at the population level with a better serum lipid profile, and may reduce the risk of diabetes, without negatively affecting body weight or body weight gain over time. Controversial data have indeed been reported with regard to the association between nut consumption and hypertension [13,14]. However, the cross-sectional design of most of the studies precluded the causality of the associations observed.

In fact, epidemiological studies, even if well-designed and powered, seldom allow for causality. This is particularly true in nutritional epidemiology. Achieving unequivocal evidence of a protective or adverse role of a food or nutrient is indeed difficult for a number of reasons. The most important one is that the large variation in the intake of a given food, both within and between populations, likely contributes to the biological variability, deriving from the interaction between genetic background, food components and multiple pathogenic mechanisms, which makes the same nutrient or food elicit dissimilar responses in different individuals. Furthermore, the accurate estimate of the usual intake of foods and nutrients is hampered by methodological inadequacies that reduce the likelihood to detect true biological associations [15]. The classical investigations over dietary factors and disease risk have included the assessment of food and/or nutrient intake by food histories and food composition tables, only rarely flanked by the measurement of nutrient concentrations, or other biomarkers of exposure in the blood or other tissues. In the absence of validated biomarkers of dietary intakes, the inaccuracy in the estimate of intake in the presence of multiple confounding factors may weaken the associations of specific nutrients or foods with a given risk [16]. In other cases, the results of these studies have led to hypotheses regarding specific nutrients/foods thought to induce protective or negative effects. Actually, it may well be that it is the synergism between the various components of certain foods or food combinations that produces the health benefits observed.

To increase confidence in the association between dietary patterns, foods, nutrients and health outcomes, randomised and possibly long-term, controlled trials are

needed. Unfortunately, randomised controlled trials in the nutritional area are difficult to implement, especially when free-living volunteers are investigated. In particular, controlling and quantifying the subjects' adherence to the intervention and measuring long-term outcomes is a challenging task.

Notwithstanding these limitations, several intervention studies actually suggested that supplementation with different types of nuts may have a beneficial effect on cardiovascular risk factors, including lipids and lipoproteins [17], blood pressure and endothelial function [18—20], and post-prandial glucose response [21—23]. While some studies suggest that nuts supplementation may favourably affect inflammatory markers [24,25], other authors do not confirm this effect [26]. The more solid evidence comes from studies aimed to evaluate the effect of nuts consumption on serum lipids in both normo- and hyper-cholesterolemic individuals. The aggregate results of a recent pooled analysis of 25 nuts consumption trials showed that a mean daily consumption of 67 g (ranging from 23 to 132 g) of nuts was associated with an average 5% reduction of total cholesterol and 5.6% reduction in the ratio of total to HDL cholesterol [17].

From these studies, little doubt remains that nuts may give a small but significant contribution to reduce blood cholesterol under dietary controlled conditions.

Energy intake from nuts: Is it matter of concern?

As already mentioned, nuts are nutrient dense foods. Their calories content ranges from 500 to 600 kcal/100 g, mostly from unsaturated fatty acids. In times of obesity epidemics, much attention should be paid to overconsumption of calories. Before promoting the consumption of whatever energy dense food, we need clear evidence, because the final message for the consumer needs to be as clear as possible.

In the pooled analysis by Sabatè et al. [17], the amount of nuts reported to be associated with improved lipid profile is equivalent to about 400 kcal per day, a not negligible proportion of the daily energy intake. In this pooled analysis, only studies in which there were no body weight changes between diets at the end of the intervention were included, implying that in these studies participants were instructed to isocalorically substitute nuts for other components in the diet. Yet the problem of the caloric load linked to nuts supplementation is still a puzzling one. In the recent 2010 Dietary Guidelines for Americans it is advised that "Because nuts and seeds are high in calories, they should be eaten in small portions and used to replace other protein foods, like some meat or poultry, rather than being added to the diet." [27]. Are 67 g per day of nuts a small portion? How realistic is to imagine that this amount of calories could easily replace an equivalent amount of calories from other foods in everyday life?

Several papers extensively reported about the relationship between increased nuts consumption and body weight [28—30], concluding that the addition of nuts to habitual diets of free-living individuals does not cause weight gain and, in some cases, may even be associated to a weight loss [29]. Another review on the same issue comes indeed to a slightly different conclusion, stating that "when nuts were added to an existing diet without controlling for energy intake, body weight increased, although to a lesser extent than theoretically predicted" [31].

In a recent intervention trial aimed to evaluate the long-term cholesterol-lowering effect of almond supplementation, free-living individuals added almonds to their habitual diet (15% of the baseline caloric intake) [32]. Energy intake increased on average by 160 kcal per day. At the end of the 24 weeks intervention, no changes in body weight were observed, against the theoretically predictable 3.5—4 kg weight gain associated to this excess calories. It is thus apparent that some mechanisms should exist to explain the lack of weight gain despite the increased energy intake. In fact, the possible underlying mechanisms of this seemingly paradoxical effect of nuts are presented as working hypotheses in different papers, but no systematic attempt has been made to prove them [12,28,30,31].

Among these mechanisms, dietary compensation seems to be plausible, accounting for about 65—75% of the calorie intake from nuts, that is the excess energy provided by nuts is compensated by the spontaneous reduction of the intake of other foods [33].

Some studies also evaluated the effects of nuts-supplemented diets in the treatment of obesity, suggesting a possible advantage of hypocaloric diets supplemented with nuts over other weight-reducing programs [34—36]. However, the heterogeneity of the design and of the duration of these studies limits the interpretation of their findings.

A recent well-designed long-term intervention trial compared the effects of a hypocaloric, almond-enriched diet with a hypocaloric nut-free diet on body weight and cardiovascular disease risk in obese and overweight individuals [37]. A similar body weight reduction was observed in the two groups. Serum lipids significantly decreased in the almond group as compared to the almond-free group after six months of intervention, but no differences were observed at the final observation at 18 months, neither between the two groups nor as compared to the baseline.

It is evident that mechanistic studies along with more clinical data with greater numbers of subjects and longer study durations are needed, so that more robust conclusions can be drawn before claiming that the *ad libitum* addition of nuts to the habitual diet of free-living individuals does not affect energy balance and finally body weight.

Allergic reactions: A downside of nuts consumption

Another aspect of nut consumption represents a matter of concern, particularly in children and adolescents. Among foods causing allergic reactions, peanuts and tree nuts are responsible for many cases of severe food-induced allergic reactions [38]. Although the exact estimate of the prevalence of this condition is somehow challenged by methodological and sampling heterogeneity [39], data from the United States [40], Canada [41], UK [42], and Australia [43] consistently showed a prevalence of about 2% in children

and adolescents, with concerning indications of an increasing trend over time [44]. The available evidence suggests that a large proportion of peanut and tree nut allergies are permanent, with only 10—20% of patients possibly recovering from this potentially life-threatening condition [45]. While the allergic responses are more frequent and better described for peanuts, there is a documented cross-reactivity also with tree nuts [46]. Since the only current management approach is the strict avoidance of the trigger food, the strategies of prevention are challenged by the presence of nuts in unexpected products and also by the risk of contamination during processing of food products [47]. Furthermore, the consumers' identification of peanuts and tree nuts into a single food category makes the prevention even more difficult.

An in depth analysis of the potential harm associated with nuts consumption because of their allergenic properties is very far beyond the objectives of this viewpoint. However, it seems surprising that in the abundant literature suggesting the beneficial effects of increasing nuts consumption at the population level, small room is given to warn the consumer about this serious side effect. Novel therapeutic strategies are currently developed and appear promising [47]. Until they enter into use, we have the responsibility to inform the public about the need to carefully search and document any potential food allergies, before giving dietary advice to increase nut consumption. At the affected individual's level, the careful inspection of food labels and enquiry about risk of cross-contamination remain the only options to prevent recurrent episodes of allergic reactions [47].

Final remarks

From the evidence discussed here, there are multiple issues that relate to the use of nuts supplements as safe and effective foods for the promotion of cardiovascular health. In particular, there is consistent evidence that nuts may help reduce serum cholesterol when consumed under controlled dietary conditions, isocalorically replacing other food items in the habitual diet. Less evident is how to achieve this replacement, both in terms of amount and type of nuts, given the large heterogeneity of the studies published in this regard. This issue should not be disregarded as a trivial one, since the introduction of higher energy dense foods may result in increased energy intake [48], unless it is accompanied by a continuously reinforced dietary advice. With regard to the claim that adding nuts to the habitual diet — thus increasing calorie intake — does not favour body fat accumulation, we really still need evidence and biological plausibility. Overall, the mechanisms underlying the different aspects of the advocated health effects of nuts need to be elucidated as well. Finally, a clear disclosure that nuts may cause serious reactions in a small, but not negligible, fraction of the population is needed, when an increase in their consumption is proposed at the population level.

In a seminal paper published more than thirty years ago, Sir Geoffrey Rose admonished "In mass prevention each individual has usually only a small expectation of benefit, and this small benefit can easily be outweighed by a small risk." [49]. We think his lesson is still topical, and should be taken into due account by all those involved in the search for healthy foods for healthier people.

Conflict of interest

The authors have no conflicts of interest to disclose.

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