

More pistachio nuts for improving the blood lipid profile. Systematic review of epidemiological evidence

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Summary. Recent evidence suggests that regular intake of nuts may be associated with reduction of all-cause mortality, especially cardiovascular deaths. Among all types of nuts, pistachio displays the most favorable dietary composition. Therefore, we searched Medline and ISI Web of Science to identify interventional studies which evaluated changes of conventional blood lipids after replacing part of normal caloric intake with pistachio nuts in humans. Overall, 9 studies were finally included in our systematical literature review (4 randomized crossover, 3 randomized controlled and 2 prospective). In 67% interventional studies total cholesterol and low-density lipoprotein cholesterol (LDL-C) decreased, whereas high-density lipoprotein cholesterol (HDL-C) increased. In all studies total cholesterol/HDL-C ratio and LDL-C/HDL-C ratio decreased after replacing caloric intake with pistachio nuts for not less than 3 weeks. A significant reduction of triglycerides could only be observed in 25% studies. Even more importantly, in no interventional study the intake of pistachio nuts was associated with unfavorable changes of the lipid profile. The results of our literature search provide solid evidence that intake of pistachio nuts may exerts favorable effects on the traditional blood profile, provided that their consumption does not increase the habitual or recommended daily caloric intake. It seems also reasonable to suggest that further studies aimed to investigate the favorable effects of nuts on human diseases should distinguish between one type and the others, since the different nuts exhibit unique dietary composition and may hence produce distinctive biological effects in humans. (www.actabiomedica.it)

Key words: lipids, cardiovascular risk, epidemiology, nuts, pistachio, nutrition

Introduction

According to recent statistics of the World Health Organization (WHO), cardiovascular disease represents the leading cause of morbidity and mortality worldwide, causing as many as 17.5 million deaths each year around the globe, i.e., 31% of all global deaths (1). The universally accepted guidelines of the American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA) clearly recommend that risk scoring for cardiovascular disease

should be carried out using multiple traditional risk factors in all asymptomatic adults without a clinical history of cardiovascular disease, in order to establish preventive measures for reducing or delaying the risk of adverse events (2). The traditional cardiovascular risk factors typically include age, sex, cigarette smoking, hypertension, familiar history, obesity, sedentary lifestyle, as well as blood lipids (2). Despite decades of research about the atherogenic role of innovative parameters such as specific apolipoproteins, lipoprotein particle size and density (3,4), their measurement be-

yond the standard fasting lipid profile is not currently advocated for cardiovascular risk assessment in asymptomatic adults (2). Therefore, stratification of cardiovascular risk remains mostly based on conventional lipid parameters, which essentially include total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and triglycerides (5,6).

Since it is now undeniable that cardiovascular disease is a preventable condition, and that most complications can be prevented by targeting a number of behavioral risk factors, the paradigm that dietary interventions may produce equal or even greater benefits than those observed in statin trials, while being also more economically affordable than any other pharmacological therapy, is assuming unquestionable value in a world of limited resources (7). Moreover, dietary interventions are essentially safe, since they are not associated with the side effects potentially occurring during therapy with hypocholesterolemic agents (i.e., pancreatic and hepatic dysfunction, cognitive loss, neuropathy, muscle injury up to rhabdomyolysis in genetically-predisposed individuals) (8-10).

Nuts belong to a generic class of fruits composed of a hard shell and an edible seed, the most popular of which are almond, candlenut, hazelnut, peanut, pistachio and walnut. The health benefits that have been historically attributed to these fruits derive from the remarkable content of antioxidants, vitamins, minerals and omega-3 fatty acids (11). Interestingly, a recent meta-analysis of published epidemiological evidence highlighted that intake of one-serving of nuts per day (i.e., 28 g/day) was associated with a 27% reduction of all-cause mortality (risk ratio [RR], 0.73; 95% confidence interval [CI], 0.60-0.88), which was mostly attributable to decrease of cardiovascular mortality (RR, 0.61; 95% CI, 0.42-0.91) rather than to reduction of cancer deaths (RR, 0.69; 95% CI, 0.33-1.45) (12).

Pistachios are usually marketed with shells partly open and kernels peeking out, thus making the task of separating the kernel from the shell rather simple. They are hence consumed as a snack food, but are also used in baking and cooking. Among all types of nuts, pistachio displays the most favorable dietary composition, containing a considerable amount of proteins

(i.e., 21% compared to 21% in almonds, 15% in hazelnuts, 26% in peanuts and 15% in walnuts) and dietary fibre (i.e., 9% compared to 8% in almonds, 10% in hazelnuts, 8% in peanuts and 6% in walnuts), the lowest amount of total fats (i.e., 44% compared to 51% in almonds, 61% in hazelnuts, 49% in peanuts and 65% in walnuts), as well as a modest quantity of saturated fatty acids (SFAs) (i.e., 5% compared to 4% in almonds, 5% in hazelnuts, 7% in peanuts and 6% in walnuts) and polyunsaturated fatty acids (PUFAs) (i.e., 13% compared to 16% in peanuts and 47% in walnuts) (11). It is hence conceivable that a large part of the beneficial cardiovascular effects associated with consumption of nuts in general, and pistachio in particular, may be mediated by favorable effects on the traditional lipid profile. Therefore, this article was aimed to provide a systematic overview of published evidence about interventional human studies that have explored the association between pistachio nuts consumption and changes in the conventional lipid profile.

Search strategy

We performed an electronic search on Medline (interface PubMed) and ISI Web of Science, using the keywords “pistachio” AND “lipid(s)” OR “lipoprotein(s)” OR “cholesterol” in “Title/Abstract/Keywords”, with no data or language restriction, to identify human prospective or randomized studies which evaluated changes of conventional blood lipids after replacing part of normal caloric intake with pistachio nuts. All documents identified according to the search criteria were independently reviewed by two authors (G.L. and C.M.), and their references were also hand-searched to identify other pertinent studies. Overall, 32 publications were identified, and 23 of them were excluded according to our predefined criteria (Fig. 1). In particular, one study ought to be excluded for presenting duplicate data (13), whereas another did not match our search criteria due to fact that pistachios intake was randomized against a carbohydrate snack (14). Therefore, 9 trials were finally included in our systematical literature review (4 randomized crossover, 3 randomized controlled and 2 prospective studies) (15-23).

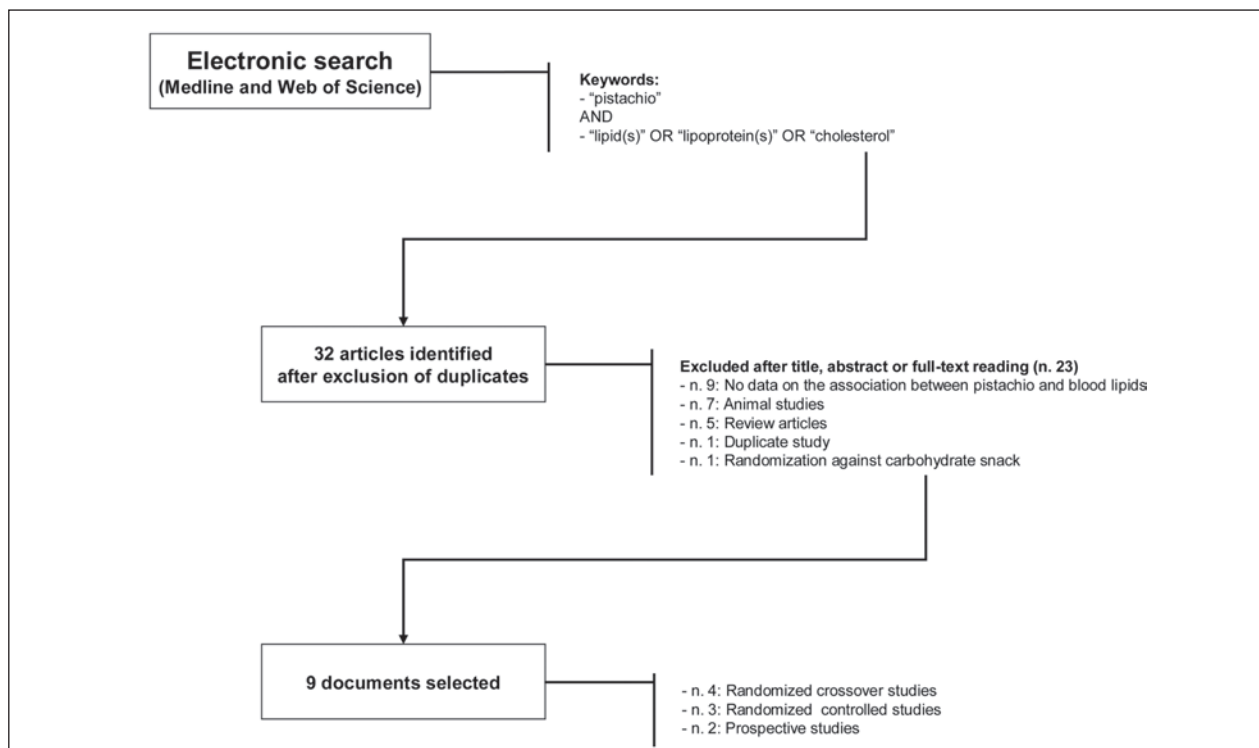


Figure 1. Description of the search methodology

Review of epidemiological evidence

The first study which investigated the effect of nuts intake on the conventional lipid profile was published by Edwards et al, in 1999 (15). The authors performed a controlled, randomized crossover study including ten moderate hypercholesterolemic subjects, who were subjected to 3 weeks of dietary modification with 20% caloric intake from pistachio nuts. A significant improvement of the lipid profile was hence observed after 3 weeks of pistachio diet, with a decrease of total cholesterol, LDL-C, total cholesterol to LDL-C ratio, LDL-C/HDL-C, triglycerides, combined with a significant increase of HDL-C.

Kocyigit et al performed a randomized study including 24 healthy, normocholesterolemic subjects, half of whom were randomized to replace pistachio nuts for 20% of their daily caloric intake for 3 weeks (16). After 3 weeks of pistachio diet, the values of total cholesterol, total cholesterol/HDL-C and LDL-C/HDL-C decreased, whereas the concentration of HDL was

found to be significantly increased. The levels of triglycerides and LDL-C also decreased, but the change did not reach statistical significance.

Sheridan et al performed another randomized crossover study including 15 subjects with moderate hypercholesterolemia, who were randomized to replace pistachio nuts for 15% of their daily caloric intake for 4 weeks (17). The pistachio diet produced statistically significant reductions of total cholesterol/HDL-C, LDL-C/HDL-C, and a statistically significant increase of HDL-C. Conversely, no statistically significant changes were observed for total cholesterol, LDL-C and triglycerides.

Another randomized crossover investigation including 28 hypercholesterolemic subjects was performed by Gebauer et al (18). The study participants were randomized to consume diets including 10% or 20% of energy from pistachios for 4 weeks. Both interventions were effective to produce a dose-dependent decrease of total cholesterol, LDL-C, total cholesterol/HDL-C, LDL-C/HDL-C and triglycerides, whereas

the 20% replacement of energy from pistachios was also associated with a statistically significant increase of HDL-C values.

Sari et al carried out a prospective study including 32 normolipidemic young men (19). A Mediterranean diet was initially administered for 4 weeks. After this period, pistachio was added by replacing the monounsaturated fatty acid content constituting up to 20% of daily caloric intake for additional 4 weeks. After addition of pistachios to the diet, a significant decrease was observed for total cholesterol, LDL-C, total cholesterol/HDL-C, LDL-C/HDL-C and triglycerides, whereas no significant changes were observed for HDL-C.

Aldemir et al studied 17 men with erectile dysfunction, who were subjected to replacement of 20% caloric intake from pistachio nuts for 4 weeks (20). A significant reduction was observed for total cholesterol, LDL-C, total cholesterol/LDL-C, and LDL-C/HDL-C. A concomitant and significant increase was observed for HDL-C, whereas the concentration of triglycerides did not change with pistachio diet. Interestingly, a significant improvement in erectile function parameters was also appreciated.

Baer et al performed a randomized crossover study including 18 normocholesterolemic subjects (21). In brief, 3 different doses of pistachios (0 g/d; 42 g/day, equal to one serving per day; 84 g/day, equal to two servings per day) were administered for 18 days with relative reduction of all foods in the baseline diet in order to maintain isocaloric intake across treatments. Although no effect of the dietary interventions was observed for the concentration of total cholesterol and HDL-C, the levels of LDL-C were found to be significantly decreased.

Gulati et al performed a 3-week randomized controlled trial on 68 subjects with metabolic syndrome, who had 20% of their habitual caloric intake replaced with pistachio nuts (22). The pistachio diet was effective to produce a significant decrease of total cholesterol and LDL-C, whereas the concentration of both HDL-C and triglycerides was not significantly modified. Interestingly, a significant decrease of high-sensitivity C reactive protein (i.e., -19%) was also noticed.

Finally, Kasliwal et al performed a randomized controlled group study including 56 mildly dys-

lipidemic adults, who were randomized to lifestyle modification alone or lifestyle modification and consumption of 80 g/day of pistachios for 3 months (23). Similarly to previous investigations, pistachios supplementation produced a marked and favorable effect on blood lipids, with significant reduction of LDL-C and total cholesterol/HDL-C, and a significant increase of HDL-C levels. However, the concentration of total cholesterol and triglycerides remained unchanged. It is also noteworthy that the changes in blood lipids were accompanied by a substantial improvement of arterial stiffness parameters and brachial artery flow-mediated dilation after the intervention.

Discussion

The results of our systematic literature review provide solid evidence that consumption of pistachio nuts may exerts favorable effects on the traditional blood profile. More specifically, in 67% interventional studies total cholesterol and LDL-C decreased, whereas HDL-C increased. Even more importantly, in all studies total cholesterol to HDL-C ratio and LDL-C/HDL-C ratio were found to be consistently decreased after replacing caloric intake with pistachio nuts for not less than 3 weeks. Less clear information emerged from triglycerides variation, since a significant reduction could only be observed in 25%. Indeed, in no case the intake of pistachio nuts was associated with unfavorable changes of the traditional lipid profile (Table 1).

There are some reasonable biological explanations than can be brought in support of the blood-lipid-lowering mechanisms exerted by pistachio nuts (Fig. 2). Interestingly, Baer et al observed that subjects randomized to receive pistachio nuts displayed a substantially lower digestibility of both fat and energy, while an opposite effect was observed for digestibility of dietary fibre (21). Indeed, the combined evidence that pistachio nuts contain a large amount of dietary fibre and that the fats contained in pistachios are more resistant to absorption supports the hypothesis that the overall intake of dietary fats may be decreased in subjects consuming pistachios, which may be then reflected by favorable changes of total cholesterol, LDL-C and HDL-C. Pistachio nuts are also a rich source of

Table 1.

Authors	Study population	Study design	Intervention	TC	LDL-C	HDL-C	TG	TC/HDL	LDL-C/ HDL-C
Edwards et al, 1999 [15]	10 moderate hypercholesterolemic subjects (6 women and 4 men, age 28–64 years)	Randomized crossover	Replacement of 20% caloric intake with pistachio nuts for 3 weeks	↓ 1.6%	No change	↑ 12.0%	No change	↓ 6.3%	↓ 3.1%
Kocoyigit et al, 2006 [16]	44 nomocholesterolemic subjects (20 women and 24 men)	Randomized controlled	Replacement of 20% caloric intake with pistachio nuts for 3 weeks	↓ 11.5%	No change	↑ 26.7%	No change	↓ 20.3%	↓ 13.2%
Sheridan et al, 2007 [17]	15 subjects with moderate hypercholesterolemia (4 women and 11 men, age 60±3 years)	Randomized crossover	Replacement of 15% caloric intake with pistachio nuts for 4 weeks	No change	No change	↑ 5.6%	No change	↓ 8.3%	↓ 12.5%
Gebauer et al, 2008 [18]	28 hypercholesterolemic subjects (18 women and 10 men, age 48±2 years)	Randomized crossover	Replacement of 10% and 20% caloric intake with pistachio nuts for 4 weeks	↓ 7.2–8.9%	↓ 10.2–13.1%	↑ 3.5%	↓ 8.6–14.3%	↓ 1.8–9.1%	↓ 4.0–13.3%
Sari et al, 2010 [19]	32 normolipidemic young men (21–24 years)	Prospective	Replacement of 20% caloric intake with pistachio nuts for 4 weeks	↓ 21.7%	↓ 23.7%	No change	↓ 18.7%	↓ 14.1%	↓ 20.1%
Aldemir et al, 2011 [20]	17 men with erectile dysfunction (age 48±6 years)	Prospective	Replacement of 20% caloric intake with pistachio nuts for 4 weeks	↓ 17.4%	↓ 20.1%	↑ 47.9%	No change	↓ 44.1%	↓ 46.2%

(continued)

Table 1.

Authors	Study population	Study design	Intervention	TC	LDL-C	HDL-C	TG	TC/HDL	LDL-C/ HDL-C
Baer et al, 2012 [21]	18 normocholesterolemic subjects (9 women and 9 men)	Randomized crossover	Replacement of relative caloric intake with 42 g/day and 84 g/day pistachio nuts for 18 days	No change	↓ 5.6-6.0%	No change	Unavailable	Unavailable	Unavailable
Gulati et al, 2014 [22]	68 subjects with metabolic syndrome (31 women and 37 men, age 42±8 years)	Randomized controlled	Replacement of 20% caloric intake with pistachio nuts for 3 weeks	↓ 5.7%	↓ 8.2%	No change	No change	Unavailable	Unavailable
Kasliwal et al, 2015 [23]	56 mildly dyslipidemic adults (10 women and 46 men, age 39±8 years)	Randomized controlled	Replacement of relative caloric intake with 80 g/day of pistachio nuts for 3 months + lifestyle modification	No change	↓ 7.0%	↑ 5.9%	No change	↓ 8.6%	Unavailable
Summary	-	-	-	↓: 6/9 No change: 3/9	↓: 6/9 No change: 3/9	↑: 6/9 No change: 3/9	↓: 2/8 No change: 6/8	↓: 7/7 No change: 0/7	↓: 6/6 No change: 0/6

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides.

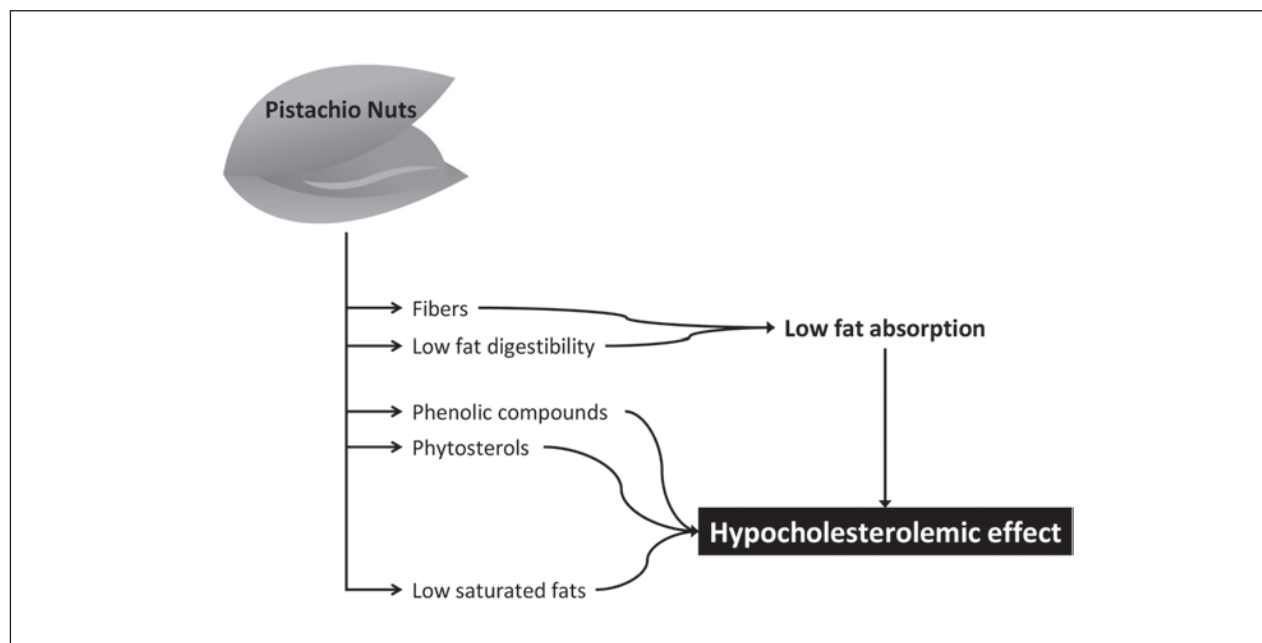


Figure 2. Biological mechanisms supporting the favorable effects of pistachio nuts on blood lipids

phytosterols (up to 289 mg per 100 g of edible fruit), with a content that has been estimated 2- to 3-time higher than that of either almonds or walnuts (24). Phytosterols are effective to reduce both total and LDL cholesterol, also producing some positive effects on the concentration of HDL-C (25). It is hence conceivable that the larger intake of pistachio-derived phytosterols may be associated with a hypocholesterolemic effect. A similar effect has been described for phenolic compounds (26), which are also present in large amount in pistachio nuts (i.e., 1.7 g per 100 g of edible fruit). The low contents of SFAs may also contribute to the putative blood-lipid-lowering effect of pistachio nuts, since it is now clearly established that replacement of polyunsaturated fat for saturated fat is effective to reduce LDL-C and the total cholesterol to HDL-C ratio (27). Interesting information also emerged from a randomized study, which was originally excluded from our literature search due to the fact that the pistachio intake was randomized against a carbohydrate snack rather than against a conventional diet (14). During a 12-week period of 500 calories per day restriction replaced with pistachios and carbohydrate snack, sub-

jects consuming pistachio nuts had their body weight and body mass index decreased by 4.3%, whereas a significantly lower decrease of body weight and body mass index was observed in subjects consuming the carbohydrate snack (-3.2% and -1.9% , respectively). Interestingly, a larger decrease of triglycerides was also observed in the pistachio group compared with the carbohydrate snack group.

In conclusion, the current epidemiological evidence suggests that a balanced consumption of pistachio nuts may be beneficial for lowering the cardiovascular risk, especially that attributable to hypercholesterolemia. Indeed, the total energy provided by pistachio nuts approximates 564 calories per 100 g (24). It is hence obvious that pistachios consumption should not increase the habitual or recommended daily caloric intake, so that the beneficial effects are not abrogated. It seems also reasonable to suggest that further studies aimed to investigate the favorable effects of nuts on human diseases should accurately distinguish between one type and the others, since the different nuts exhibit unique dietary composition and may hence produce distinctive biological effects in humans (11,24).

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