Prostaglandins, Leukotrienes and Essential Fatty Acids 133 (2018) 8–15

Contents lists available at ScienceDirect

Prostaglandins, Leukotrienes and Essential Fatty Acids

journal homepage: www.elsevier.com/locate/plefa

Randomized trials of replacing saturated fatty acids with n-6 polyunsaturated fatty acids in coronary heart disease prevention: Not the gold standard?

Jyrki K. Virtanen

University of Eastern Finland, Institute of Public Health and Clinical Nutrition, P.O. Box 1627, Kuopio 70211, Finland

ARTICLE INFO

Keywords:
Polyunsaturated fatty acids
Saturated fatty acids
Coronary heart disease
Prevention
Diet-heart hypothesis
Clinical trials

ABSTRACT

Several trials in the 1950s through 1970s tested the hypothesis that replacing saturated fat in the diet predominantly with n-6 polyunsaturated fat (PUFA) would reduce the incidence of coronary heart disease (CHD), mainly through modifying blood lipid profile. Most of these trials did observe a reduction in serum total cholesterol in the intervention group, but many trials failed to find a significant reduction in the incidence of CHD. However, some meta-analyses have found a reduced incidence of CHD by pooling the results from the trials. Recently, new recovered and reanalyzed data has emerged from two of the old trials. The new findings seemed to counteract the classical diet-heart hypothesis, when they found no cardiovascular benefit and even suggested harm, despite reduction in the serum total cholesterol concentration after replacing saturated fat especially with n-6 PUFA. This has raised criticism regarding the validity of the dietary recommendations that suggest partially replacing saturated fats with n-6 PUFA. This paper introduces the classical diet-heart trials and their main results and how the new findings relate to the overall study data of the cardiovascular effects of the n-6 PUFA. For multiple reasons considered here, it is difficult to draw firm conclusions of the cardiovascular effects of the n-6 PUFA based only on the findings in the old diet-heart trials. A more comprehensive picture emerges when also other lines of evidence is considered. The overall study data, including findings also from prospective cohort studies and from dietary trials with intermediate outcomes, still suggests that replacing saturated fat with n-6 PUFA would rather be beneficial than harmful for the prevention of CHD.

1. Introduction

Partial replacement of dietary saturated fat with polyunsaturated fat (PUFA) is a cornerstone of many dietary recommendations for prevention of coronary heart disease (CHD). This replacement has a beneficial impact on the serum lipid profile, especially on the LDL cholesterol concentrations [1]. This so-called diet-heart hypothesis is also supported by many prospective cohort studies that have shown that replacement of saturated fat with PUFA associates with a lower risk of CHD [2,3].

The diet-heart hypothesis was also tested in several randomized trials, most of which started in the late 1950s and early 1960s (Tables 1 and 2). In these trials, the aim was to replace the sources of saturated fat, such as full-fat dairy, butter and fatty meats, with lean meats, low-fat dairy and especially with vegetable oils and margarines that are rich in n-6 PUFA linoleic acid (LA), while keeping the total fat amount similar in both groups. These dietary changes created a large difference in the intakes of saturated fat and n-6 PUFA between the intervention and control groups and, as expected, many of the trials observed a significant reduction in the serum total cholesterol concentrations (Tables 1 and 2). As a side note, at that time the studies only measured serum total cholesterol, not LDL or HDL cholesterol concentrations. However, in spite of the reduction in the serum total cholesterol, many trials did not find a statistically significant effect on CHD incidence (Table 2). Several meta-analyses have pooled the results from these trials in various combinations in an attempt to increase power, with variable findings [4–12].

In the last few years, new recovered data has emerged from two of the early trials, the Sydney Diet Heart Study [13] and the Minnesota Coronary Survey [14] (Tables 1–3). In addition to presenting the results from the recovered data, both publications presented results from meta-analyses that included the new data. These studies seemed to indicate that replacing saturated fat with only n-6 PUFA might not be such a good idea after all for cardiovascular disease prevention. As expected, these results were received with mixed attitudes among the scientist and understandably may have created confusion and sparked criticism concerning the validity of the dietary recommendations. So what did these two new publications show?

E-mail address: jyrki.virtanen@uef.fi.

https://doi.org/10.1016/j.plefa.2018.04.002
Received 16 March 2018; Received in revised form 18 April 2018; Accepted 20 April 2018

Table 1
Description of the diet-heart trials that are commonly included in meta-analyses.

Study name, country	Study start year	Study duration	Study population	Prevention	Sources of PUFA in the intervention group	Control group diet	Intervention diet also contained additional n-3 PUFA?
Rose Corn Oil Trial, UK [30]	Not reported	2 y	54 free-living subjects, aged <70 y (gender not reported)	Secondary	A total of 80 g of corn oil taken 3 times/d with meals. Additional advice: fried foods, fatty meats, sausages, pastry, ice cream, cheese, cakes, etc. were to be avoided. Milk, butter and eggs were restricted	No dietary advice	No
Oslo Diet-Heart Study, Norway [46,47]	1958	5 y	412 free-living men, aged 30–64 y (mean 56 y)	Secondary	0.5 L/wk soy oil either used in food preparation or "taken as medicine". Additional advice: fish, shellfish, whale meat and poultry instead of beef, mutton and pork (canned sardines in cod liver oil provided); lard, shortenings, margarine, whole milk, cream, butter and fatty cheeses restricted, olive oil use discouraged; a maximum of 1 egg yolk/wk; use of brown bread instead of white bread; multivitamin tablets provided	No dietary advice, but multivitamin tablets provided	Yes (EPA and DHA from fish, alpha-linolenic acid from soy oil)
Finnish Mental Hospital Study, Finland [48,49]	1959	6 + 6 y (cross-over design)	922 men aged 34–64 y and 713 women aged 44–64 y from two mental hospitals	Primary / mixed primary and secondary	Soy oil blended with skim milk, ``soft" margarine high in PUFA instead of ``ordinary" margarine and butter	Typical institutional diet	Yes (alpha-linolenic acid from soy oil)
Los Angeles Veterans Administration Study, USA [31,33,50]	1959	8 y	846 semi-institutionalized men, aged 54–88 y (mean 65 y)	Mixed primary and secondary	Soy oil, corn oil, safflower oil, cottonseed oil provided within institutional diet in place of fats of animal origin. The oils were incorporated in the diet as blended in skim milk, imitation ice cream, "unsaturated" margarine, special sausage products, and filled cheeses and also used liberally in cooking and baking. Meat fat minimized by using trimmed lean cuts of meat. Egg yolks restricted to 7/wk	Typical institutional diet that was modified to resemble the experimental diet	Yes (alpha-linolenic acid from soy oil)
Medical Research Council Soy Oil Study, UK [32]	1960	2–7 y	393 free-living men, aged <60 y	Secondary	85 g/d soy oil, of which at least half to be taken unheated (mainly drunk with fruit juice). In ten men, corn oil was substituted because of nausea and diarrhea. Additional advice: 14 g/d margarine allowed; butter, other oils and cooking fats, fatty meat, whole milk, cheese, egg yolk, and most biscuits and cakes forbidden	No dietary advice	Yes (alpha-linolenic acid from soy oil)
Diet and Reinfarction Trial, UK [51,52]	1983	2 y	2033 free-living men, aged <70 y (mean 56 y)	Secondary	Dietary advice recommending thin spreading of a PUFA margarine on bread; skimmed milk instead of fattier milk; fried or roasted foods limited and cooked only in polyunsaturated oil; fatty cheese intake limited to 3 oz/wk and eggs to 2/wk; lean meats (poultry, white fish, very lean beef) instead of fattier meats; cakes pastries, biscuits pies, crisps, chocolates and toffee limited; fat suggested to be replaced by bread, potatoes, rice and pasta	No specific dietary advice, except for a "sensible eating sheet", which did not include dietary advice on any of the intervention diet components	No foods provided for the subjects. Mean EPA intake 0.25 g/d in the intervention group and 0.21 g/d in the control group
St. Thomas Atherosclerosis Regression Study, UK [20,53]	1987	3.3 y	55 free-living men, aged <66 y (mean age 54 y in the intervention group, 49 y in the control group)	Secondary		No dietary advice	Higher intake of EPA and DHA in the intervention group (0.48 g/d) compared to the control group (0.24 g/d)

(*continued on next page*)