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Session 4: CVD, diabetes and cancer

A dietary portfolio for management and prevention of heart disease

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CHD is the leading cause of worldwide mortality. The prevalence of heart disease has been linked to the adoption of a sedentary lifestyle and the increased dietary dependence on saturated fats from animal sources and the intake of refined foods. Elevated blood cholesterol level is one of the major risk factors for CHD. While cholesterol-lowering drug therapy (statins) has been effective in reducing the risk of heart disease, there are those individuals who are unwilling or because of muscle pains or raised levels of liver or muscle enzymes are unable to take cholesterol-lowering medication. Fortunately, there is evidence linking a number of dietary components to CHD risk reduction. The strength of this evidence has prompted various regulatory bodies to advocate diet as the first line of defence for primary prevention of heart disease. It was therefore decided to combine four dietary components that have been shown to lower blood cholesterol concentrations (nuts, plant sterols, viscous fibre and vegetable protein) in a dietary portfolio in order to determine whether the combined effect is additive. In a metabolically-controlled setting this dietary portfolio has proved to be as effective as a starting dose of a first-generation statin cholesterol-lowering medication in reducing the risk of CHD. The dietary portfolio has also been shown to be effective in sustaining a clinically-significant effect in the long term under a 'real-world' scenario. However, success of the diet depends on compliance and despite the accessibility of the foods adherence has been found to vary greatly. Overall, the evidence supports the beneficial role of the dietary portfolio in reducing blood cholesterol levels and CHD risk.

Dietary portfolio: CHD: Cholesterol-lowering therapy

IHD is the leading cause of death worldwide, accounting for 17.3% and 11.8% of total deaths in high-income nations and low- and middle-income nations respectively⁽¹⁾. Furthermore, current projections estimate that by 2030 IHD will still be the leading cause of worldwide mortality (13.4% of total deaths)⁽²⁾. Evidence from various drug-therapy trials show that statins have been effective in reducing the risk of heart disease^(3,4). Diet, on the other hand, although publically recognized as first-line therapy⁽⁵⁾, has been considered by many investigators to be ineffective because of the poor response seen in many studies. Despite this deficiency, cohort studies have shown

that the risk of CHD is predominantly diet and lifestyle dependent^(6,7). Furthermore, it is generally accepted that recent changes in human dietary and exercise patterns, stemming from the industrial revolution and the subsequent Westernization of lifestyle, have made a major contribution to the current prevalence of this disease.

The evolution of the human diet remains controversial and the understanding of it is based largely on circumstantial evidence⁽⁸⁾. Yet, analyses of tooth morphology, C isotopes and trace elements, in addition to current dietary patterns of man's distant ape relatives, strongly support the notion that the diet of early hominins was predominantly

Abbreviations: LDL-C, LDL-cholesterol; NCEP, National Cholesterol Education Program; TC, total cholesterol.

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plant-based and composed of unrefined foods including large amounts of foliage, leafy vegetables, shoots, fruit, seeds and nuts^(8–15). This diet, therefore, would have been very high in fibre and rich in sources of plant sterols, vegetable proteins and nuts. However, the introduction of agriculture and animal husbandry practices approximately 10 000 years ago dramatically changed the human diet⁽¹⁶⁾. Despite this change in the diet, food refinement and processing and the increased use of animal products did not become prevalent until the industrial revolution^(17,18). The increase in food processing and meat intake, coupled with the adoption of a sedentary lifestyle resulting from the technological revolution, are thought to be responsible for the present-day prevalence of chronic diseases such as heart disease^(19,20).

This conclusion is strongly supported by evidence from dietary interventions that have demonstrated the ability of ancestral food components such as viscous fibres, plant sterols, vegetable proteins and nuts to reduce the risk of heart disease by lowering serum cholesterol levels^(21–25). The strength of the evidence has prompted various bodies such as the American Heart Association⁽²⁶⁾, the Adult Treatment Panel III of the National Cholesterol Education Program (NCEP)⁽⁷⁾ and the US Food and Drug Administration^(27–31) to endorse the intake of these food components. The Food and Drug Administration has approved health claims for the intake of soyabean protein (25 g/d)⁽³⁰⁾, nuts (42 g/d)⁽²⁷⁾, plant sterols (1.5 g/d)⁽²⁹⁾ and viscous fibres (β -glucan from oats and barley, 3 g/d; psyllium (*Plantago* spp.), 7 g/d)^(28,31).

Inspired by the ancestral diets, in 2001 an attempt was made to create a dietary approach based on current dietary recommendations that while being feasible and accessible, maximized the metabolic advantages of plant-based foods. Since the available evidence demonstrates that viscous fibres, plant sterols, vegetable proteins and nuts can each independently lower serum cholesterol by 5–10%^(21–25), it was assumed that the effect of combining these components may be additive and as such lead to clinically-significant reductions in serum cholesterol and consequently lower the risk of developing heart disease. In order to test the efficacy of this approach, a series of trials were conducted that assessed the effect of the dietary portfolio on serum cholesterol levels and other biomarkers of heart disease.

The dietary portfolio

The task was undertaken of creating a vegetable-based diet that was not only accessible and palatable, but also in compliance with the dietary recommendations of the NCEP (Adult Treatment Panel III)⁽⁷⁾. The major recommendations are that <7% energy should come from SFA and that dietary cholesterol intake should be <200 mg/d. The NCEP (Adult Treatment Panel III) also recommends that 50–60% energy should come from carbohydrate, 15% energy from protein and 25–35% energy from fat ($\leq 10\%$ from PUFA and $\leq 20\%$ from MUFA). The recommendation for dietary fibre is 20–30 g/d⁽⁷⁾. The macronutrient profile of the devised dietary portfolio differed between the

Table 1. Nutrient profile and the amount of key foods in the National Cholesterol Education Program (Adult Treatment Panel III)⁽⁷⁾ control diet and the dietary portfolio in metabolically-controlled trials

	Control diet	Dietary portfolio
Total protein (% energy)	21–22.3	20.0–22.4
Vegetable protein (% protein)	19.4–30.1	96.8–99.2
Available carbohydrate (% energy)	52.1–58.8	48.0–56.6
Total fibre (g/4.2 MJ)	22.9–26.6	30.7–37.2
Total fat (% energy)	21.6–25.1	23.2–30.0
SFA (% energy)	4.4–4.7	4.3–6.3
MUFA (% energy)	8.5–10.3	9.5–12.7
PUFA (% energy)	7.5–9.2	7.9–10.1
Dietary cholesterol (mg/4.2 MJ)	11.8–34	10–48
Viscous fibre* (g/4.2 MJ)	0	8.2–9.8
Soyabean protein (g/4.2 MJ)	0	16.2–22.7
Plant sterols† (g/4.2 MJ)	0	1–1.2
Nuts (g/4.2 MJ)	0	14–16.6

*From oats, barley, psyllium (*Plantago* spp.), okra (*Abelmoschus esculentus*) and aubergine (eggplant; *Solanum melongena*).

†From a plant-sterol margarine.

trials but was similar to the NCEP recommendations^(32–34) (Table 1). The ranges of intake for carbohydrates, fats and proteins (% total energy intake) were 48.0–56.6, 23.2–30.0 and 20.0–22.4 respectively. Saturated fats comprised <7.0% total energy and <50 mg dietary cholesterol/4.2 MJ (1000 kcal) was present^(32–34). Furthermore, the diet provided 30.7–37.2 g dietary fibre/4.2 MJ (1000 kcal). As for the main dietary components of the diet, it provided (/4.2 MJ (1000 kcal)) 1–1.2 g plant sterols as a sterol-enriched margarine, 8.2–9.8 g viscous fibres from oats, barley and psyllium, 16.2–22.7 g soyabean protein and 14–16.6 g raw unblanched almonds (*Amygdalus communis* L.; Table 1). In addition to oats, barley and psyllium, okra (*Abelmoschus esculentus*) and aubergine (eggplant; *Solanum melongena*) were also sources of viscous fibre. The sources of soyabean protein were tofu, soya milk, soya yogurt and soya sausages, hot dogs and burgers. Additional vegetable fibre and protein came from legume sources, which included chickpeas (*Cicer arietinum*), beans and lentils (*Lens culinaris*)^(32–34). All the foods were available at local food markets and health stores.

The control diet was a very-low-fat lacto-ovo-vegetarian diet. The control diet lacked the sources of viscous fibres, plant sterols and almonds. Furthermore, skim-milk products replaced soyabean- and vegetable-protein foods. The sources of dietary fibre, the intake of which was 23.3–26.6 g/4.2 MJ (1000 kcal), were generally whole-grain and whole-wheat foods^(33,34).

The dietary portfolio: metabolic trials

Four 4-week metabolically-controlled randomized clinical trials have tested the effect of the dietary portfolio on markers of heart disease (Fig. 1)^(32–35). The first study was uncontrolled and included thirteen subjects (seven men and six post-menopausal women (BMI 25.6 (SE 0.9) kg/m²), three of whom had blood lipids in the normal range⁽³²⁾. At

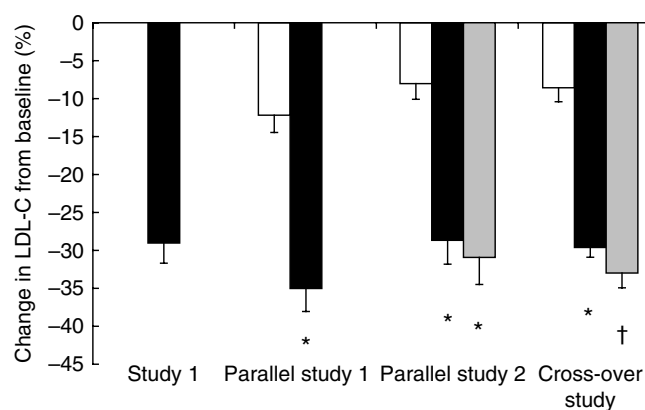


Fig. 1. Effect of the dietary portfolio (■) v. National Cholesterol Education Program (NCEP; □) and NCEP+statin (▒) treatments on baseline LDL-cholesterol (LDL-C) levels in metabolic studies (for details, see text). Mean values were significantly different from those for NCEP control: * $P < 0.05$. Mean value was significantly different from those for dietary portfolio and NCEP control: † $P < 0.05$.

the end of the 4-week intervention total cholesterol (TC; -22.3 (SE 2.0) %), LDL-cholesterol (LDL-C; -29.0 (SE 2.7) %) and apoB (-24.2 (SE 2.0) %) were found to be significantly reduced ($P < 0.001$ for all three markers) when compared with baseline values. TC:HDL-cholesterol, LDL-C:HDL-cholesterol and apoB:apoA-I were also reduced. Overall, there was a 30% reduction in calculated risk of CHD⁽³²⁾.

The promising results from the first trial prompted a second trial⁽³⁴⁾ that compared the effects of the dietary portfolio with that of NCEP-recommended diet⁽⁷⁾. Twenty-five healthy subjects with hyperlipidaemia took part in this parallel-designed 4-week study (sixteen men and nine post-menopausal women; BMI 26.6 (SE 2.9) kg/m²). Similar to the first trial, the portfolio diet (n 13) was found to result in significant reductions in TC (-26.6 (SE 2.8) %), LDL-C (-35 (SE 3.1) %) and apoB (-26.7 (SE 3.3) %) by comparison with the control ($P < 0.001$ for all three measures). TC:HDL-cholesterol, LDL-C:HDL-cholesterol and apoB:apoA-I were also reduced⁽³⁴⁾. However, more importantly, these portfolio-induced reductions in serum TC and LDL-C levels were significantly lower than those caused by the NCEP control diet (-9.9 (SE 2.0) % and -12.1 (SE 2.4) % for serum TC and LDL-C respectively by comparison with baseline values; $P < 0.001$). The dietary portfolio proved to be a more effective approach for lowering the risk of CHD by comparison with the established dietary guidelines for individuals with hyperlipidaemia (calculated reduction in 10-year CHD risk of 31.7% for the dietary portfolio v. 11.2% for the NCEP control; $P < 0.05$)⁽³⁴⁾.

In order to further test the clinical relevance of the dietary portfolio, a third metabolically-controlled trial was conducted that compared the effect of the dietary portfolio with not only the NCEP diet, but also a NCEP diet supplemented with a starting dose of a cholesterol-lowering medication (20 mg lovastatin/d)⁽³³⁾. Forty-six subjects with hyperlipidaemia participated in the study (twenty-five men and twenty-one post-menopausal women; BMI 27.6

(SE 0.5) kg/m²). Similar to the other two trials, subjects on the dietary portfolio arm (n 16) were found to show reductions in all variables measured in previous studies including LDL-C (-28.7 (SE 3.2) % compared with baseline; $P < 0.001$). More importantly, no significant differences were found between the lovastatin (n 14) and the dietary portfolio groups for any of the variables. In fact, both treatments were found to impact similarly on calculated 10-year CHD risk (-24.9 (SE 5.5) % and -25.8 (SE 4.4) % for dietary portfolio and lovastatin groups respectively; $P > 0.05$). These two approaches were shown to be more effective in modifying the risk factors of CHD than the NCEP-derived control⁽³³⁾.

Finally, because there may be inter-individual differences in response to drug or diet therapy, it was decided to test the response of the same individuals to both treatments. A three-phase randomized cross-over study was designed that compared the effects of the NCEP diet, NCEP+statin and the dietary portfolio⁽³⁵⁾. The data for the first phase were taken from the previous study⁽³³⁾ and the subjects were asked to complete the other two treatments⁽³⁵⁾. Thirty-four healthy subjects with hyperlipidaemia completed the study (twenty men and fourteen post-menopausal women; BMI 27.3 (SE 3.3) kg/m²). Similar to previous findings, significant percentage changes from baseline were found for LDL-C (-8.5 (SE 1.9), -33.3 (SE 1.9) and -29.6 (SE 1.3) for the NCEP control, NCEP+lovastatin and portfolio diets respectively; $P < 0.05$ for all treatments). However, in this trial the difference between the statin treatment and the dietary portfolio was found to be significant ($P = 0.013$). Furthermore, 26% (n 9) of the participants were found to show a better response to the portfolio diet compared with the NCEP+statin diet⁽³⁵⁾.

The results of these four metabolically-controlled 4-week trials show that the dietary portfolio of cholesterol-lowering foods is a clinically-relevant approach for reducing the risk of heart disease. Furthermore, the magnitude of its effect is comparable with that of a starting dosage of a first-generation cholesterol-lowering medication^(32–35); thus, reiterating the point that diet is an effective treatment option in primary prevention of heart disease⁽⁷⁾.

The dietary portfolio: long-term sustainability

The metabolic studies indicate that the dietary portfolio is efficacious in reducing serum cholesterol concentrations^(32–35). However, as discussed previously, the aim was to develop a dietary approach that in addition to being effective was also easy to comply with. Thus, with the effectiveness of the dietary portfolio established under well-controlled metabolic studies, the next concern to be addressed was whether the diet was effective in achieving clinically-significant cholesterol reductions under free-living conditions over the long term. Sixty-six healthy subjects with hyperlipidaemia (thirty-one men and thirty-five post-menopausal women; BMI 27.3 (SE 0.4) kg/m²) participated in the 1-year free-living study in which they were provided with advice to follow the dietary portfolio⁽³⁶⁾. Fifty-five subjects (83%) completed the study.

Significant reductions of 12.8 (SE 2.0) % in LDL-C compared with baseline after the 1-year trial were shown by intention-to-treat analysis ($P < 0.001$). Significant reductions in serum TC and TAG and a significant increase in HDL-cholesterol ($P < 0.05$ for all three variables) were also found. For the fifty-five participants who completed the trial the mean reduction in LDL-C was slightly better at 14.6 (SE 2.1) %⁽³⁶⁾. While the reductions achieved under 'real-world' conditions were found to be less than those observed under the tightly-controlled metabolic studies, >30% of the subjects who were recruited into the study managed to achieve >20% reductions in LDL-C (mean 29.7%). In terms of compliance, only two participants followed the vegan recommendations, five remained lacto-ovo-vegetarian and the rest were omnivorous. Compliance with the four dietary components was found to vary (%; 78.8 (SE 3.2), 67.1 (SE 3.2), 55.1 (SE 2.9) and 51.0 (SE 3.0) for almonds, plant sterols, viscous fibres and soyabean protein respectively). Significant correlations were found between compliance and LDL-C reduction for total dietary portfolio compliance ($r = -0.42$, $P < 0.001$), soyabean protein ($r = -0.52$, $P < 0.0001$), fibre ($r = -0.39$, $P = 0.0012$) and almonds ($r = -0.33$, $P = 0.0080$) but not for plant sterols ($r = -0.20$, $P = 0.1232$), possibly because the plant-sterol margarine was easy to comply with, did not displace unhealthy foods and the scatter in the data was not as great⁽³⁶⁾. The study demonstrates that in a 'real-world' setting highly-motivated individuals can achieve cholesterol reductions with the dietary portfolio that are within the clinically-meaningful range based on early statin and prestatin drug criteria^(37,38). Worth noting is that the long-term sustainability of the portfolio diet is still under investigation. Results from the third year of follow-up demonstrate that in both intent-to-treat and completer analyses the reductions in LDL-C are maintained (D. J. A. Jenkins and C. W. C. Kendall, unpublished results).

Other benefits and future direction

Evidence suggests that the favourable effects of the dietary portfolio of cholesterol-lowering foods on the risk of heart disease are not limited to its role in improving the blood lipid profile. The free-living phase of the study has shown that the dietary portfolio can significantly lower blood pressure (-4.2 (SE 1.3) mmHg ($P = 0.002$) and -2.3 (SE 0.7) mmHg for systolic and diastolic blood pressure respectively; $P = 0.001$)⁽³⁹⁾. This reduction in blood pressure was found to be correlated with consumption of almonds⁽³⁹⁾. Evidence also suggests that the dietary portfolio may have a favourable effect on C-reactive protein^(32,33,40). Inflammation is thought to play a major role in CVD⁽⁴¹⁾ and C-reactive protein, a marker of inflammation, has been proposed as a biomarker of CHD risk^(42,43). Both the dietary portfolio and the statin treatment were found to lead to similar reductions in C-reactive protein, which were shown to be significant in one study (-28.2 (SE 10.8), $P = 0.02$ and -33.3 (SE 8.3) %, $P = 0.002$ respectively)⁽³³⁾ and significant in another when subjects with C-reactive protein levels above the 75th percentile

were excluded (-23.8 (SE 6.9) % ($n = 25$), $P = 0.001$ and -16.3 (SE 6.7) % ($n = 23$), $P = 0.013$ respectively)⁽⁴⁰⁾.

An in-depth look into the effect of the dietary portfolio on LDL-C has demonstrated that this diet is capable of lowering the concentrations of all fractions of LDL-C, including the small dense fraction^(44,45). The dietary portfolio may also reduce oxidative damage to LDL⁽³²⁾. Evidence from one study suggests that adding strawberries to the portfolio diet not only reduces oxidative damage but also increases the palatability of the diet⁽⁴⁶⁾. Another possible beneficial effect of the dietary portfolio may be through its effect on haematological indices⁽⁴⁷⁾. The dietary portfolio has small but favourable effects on packed cell volume and mean platelet volume⁽⁴⁷⁾.

The dietary portfolio has also been effective in reducing blood lipids during weight loss. A recent randomized clinical trial that utilized three components of the dietary portfolio (nuts, viscous fibres and soyabean protein) has shown that an energy-restricted diet containing these components is more effective than an energy-restricted NCEP-derived diet in reducing blood lipids⁽⁴⁸⁾. Furthermore, although not studied, the dietary portfolio may be effective in management of other chronic diseases such as type 2 diabetes, since there is evidence that viscous fibre and nuts (limited evidence) can improve postprandial glycaemic response acutely and glycaemic control in the long term⁽⁴⁹⁻⁵²⁾.

Conclusion

Changes in the dietary pattern of human subjects stemming from increased intake of refined foods and saturated fats, in addition to the adoption of a sedentary lifestyle, may be responsible for the prevalence of chronic diseases such as heart disease. The strength of the evidence from the current body of research suggests that dietary approaches may be an effective first line of defence against heart disease. The key to an effective dietary approach may lie in the ancestral diets. This argument is strengthened by the beneficial effects associated with the dietary portfolio of cholesterol-lowering foods, including nuts, plant sterols, viscous fibres and vegetable proteins, that are thought to have been a major part of the ancestral diets. In the metabolically-controlled setting the dietary portfolio has proved to be as effective as cholesterol-lowering drugs in reducing the risk of heart disease. Furthermore, the reductions are sustainable in the long term in a 'real world' setting; however, compliance is critical for this sustainability. Despite the accessibility to all components of the dietary portfolio compliance varies greatly. The key for the future of dietary approaches is to focus on adherence and to devise diets that are both effective and easy to follow.

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