Introduction

The diet-heart hypothesis focuses on diet, lipids and the risk of coronary heart disease (CHD). Changes in dietary fat quality influence the levels of low-density lipoprotein (LDL) cholesterol. Meta-analyses indicate an association with reduced coronary heart disease (CHD) risk when saturated fatty acid is replaced with polyunsaturated fatty acid or with low-glycaemic index carbohydrates. A meta-analysis of eight small trials supports this benefit. Secular trends in populations that modified fat intake and quality show a consistent reduction in LDL cholesterol levels and CHD risk. The increase in obesity and diabetes in many developed countries does not track consistently with the implementation of dietary guidelines aimed at lowering fat intake. Obesity is more likely to be due to increases in total energy intake, coupled with an increasingly sedentary lifestyle. However, cohort studies indicate that poor dietary quality is associated with future weight gain. Both cohort studies and secular trends implicate the increased consumption of sugar-sweetened beverages as being associated with obesity, diabetes and cardiovascular disease. Weight reduction can be achieved with a range of energy-restricted diets, including low-fat, high-carbohydrate diets and low-carbohydrate, high-fat diets. Metabolic benefits are proportional to the degree of weight reduction, irrespective of the dietary approach used. The prevention of CHD requires an emphasis on fat quality, rather than fat quantity, while the prevention of obesity and diabetes requires a focus on energy balance and carbohydrate quality.

Abstract

Human feeding studies show that dietary fat quality, but not total fat intake, influences levels of low-density lipoprotein (LDL) cholesterol. Meta-analyses indicate an association with reduced coronary heart disease (CHD) risk when saturated fatty acid is replaced with polyunsaturated fatty acid or with low-glycaemic index carbohydrates. A meta-analysis of eight small trials supports this benefit. Secular trends in populations that modified fat intake and quality show a consistent reduction in LDL cholesterol levels and CHD risk. The increase in obesity and diabetes in many developed countries does not track consistently with the implementation of dietary guidelines aimed at lowering fat intake. Obesity is more likely to be due to increases in total energy intake, coupled with an increasingly sedentary lifestyle. However, cohort studies indicate that poor dietary quality is associated with future weight gain. Both cohort studies and secular trends implicate the increased consumption of sugar-sweetened beverages as being associated with obesity, diabetes and cardiovascular disease. Weight reduction can be achieved with a range of energy-restricted diets, including low-fat, high-carbohydrate diets and low-carbohydrate, high-fat diets. Metabolic benefits are proportional to the degree of weight reduction, irrespective of the dietary approach used. The prevention of CHD requires an emphasis on fat quality, rather than fat quantity, while the prevention of obesity and diabetes requires a focus on energy balance and carbohydrate quality.

The diet-heart hypothesis

The current incarnation of the diet-heart hypothesis is supported by extensive data, plus the ability to synthesise those data by meta-analytic methods (Figure 1). The starting point of the hypothesis is that dietary fat, and more specifically, SAFA and trans fatty acid (TFA), increase serum total cholesterol (TC) and LDL cholesterol, while unsaturated fatty acid decreases the same. The link between the quality of dietary fat and LDL cholesterol has been established by regression equations which summarise the results of controlled feeding studies in humans. As reviewed elsewhere, the relationship of LDL cholesterol with CHD is robustly supported by meta-analyses of cohort studies, genetic studies, meta-analyses of clinical trials and the pathophysiology of atherosclerosis. A direct link between diet and CHD is more difficult to show because of the methodological limitations described herein. Meta-analyses of cohort studies of food intake have given mixed results, and clinical trial evidence is limited to several small older studies. The most robust data derive from population studies on dietary interventions and secular trends, some of which have been described elsewhere.

Human feeding studies

Short-term feeding studies under controlled conditions show that when substituted for carbohydrates, SAFA increases LDL cholesterol, while PUFA, and to a lesser extent, monounsaturated fatty acid (MUFA), decreases LDL cholesterol. Triglycerides are uniformly decreased and high-density lipoprotein (HDL) cholesterol increases when any of these fatty acids are substituted for carbohydrates. A summary measure of lipid effects, the total to HDL cholesterol ratio, is not affected by SAFA, but is decreased by substituting either MUFA or PUFA for carbohydrates. Substituting a mixed fatty acid diet with carbohydrates increases the ratio. Not all SAFA is equal in its effects on LDL cholesterol. The most marked increase occurs...
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Diet-Heart Hypothesis

Figure 1: Schematic representation of the evidence supporting the diet-heart hypothesis

HDL: high-density lipoprotein, LDL: low-density lipoprotein

It is clear that the nutrients that are substituted for SAFA in the diet matter. The findings for substituting 5% of energy from SAFA with PUFA are rather consistent across the predicted effect on CHD expected from the change in the TC to HDL cholesterol ratio [relative risk (RR) 0.91, 95% confidence interval (CI): 0.87-0.95], to that observed in a meta-analysis of eight randomised controlled trials (RR 0.90, 95% CI: 0.83-0.97), and to a pooled analysis of 11 observational cohorts (RR 0.87, 95% CI: 0.77-0.97). The findings are less consistent on the substitution of SAFA with carbohydrates across these types of studies. Feeding studies predict a neutral effect on CHD risk, since there is a neutral effect on the TC to HDL cholesterol ratio, while the pooled analysis of observational cohorts shows an association with increased CHD risk. However, as noted previously, this increased risk was limited to the substitution of SAFA with high-glycaemic-index carbohydrates. The Women's Health Initiative Dietary Modification trial on the low-fat dietary pattern did not target replacing SAFA with carbohydrates, and will be discussed separately. A reduction in CHD risk was the predicted effect of replacing SAFA with MUFA in feeding studies. However, the pooled analysis of observational studies showed an association with increased CHD risk. However, a recent trial of olive oil supplementation against the background of a Mediterranean diet compared with a lower-fat (higher-carbohydrate) diet showed significant CHD benefit. Increased MUFA and PUFA mainly replaced carbohydrates in this trial.

Population studies and secular trends

Most developed nations have implemented educational programmes and agricultural policies aimed at implementing lower fat and lower SAFA intake, with the substitution of PUFA and carbohydrates with SAFA. These programmes, assisted more recently by the advent of effective treatment to lower cholesterol levels with statins, have been associated with a steep decline in population serum cholesterol levels and CHD mortality rates. These secular trends will be discussed in more detail in relation to obesity trends.

Clinical trials

Unfortunately, no definitive clinical trial has tested the diet-heart hypothesis. Eight small randomised clinical trials performed several decades ago were of varying quality, and focused on increasing PUFA, often to a level beyond that recommended by the dietary guidelines. A meta-analysis of these trials showed a significant decrease in TC level of 0.76 mmol/l (29 mg/dl) and an observed risk reduction of 24% for each 1 mmol reduction in TC; which is remarkably similar to the proportional reduction seen in the meta-analysis of statin trials. Recently recovered data from the small secondary prevention Sydney Diet Heart Study (not included in this meta-analysis), indicated an increased risk of cardiovascular mortality after high-dose supplementation with sunflower oil. However, the margarine used was high in TFA, and this may have accounted for the adverse outcome. The very large Women's Health...
Initiative Dietary Modification trial on a low-fat dietary pattern was not designed to test the diet-heart hypothesis. Rather, it was designed to test whether lowering total fat, without regard to the quality of the fat, would reduce the risk of breast cancer. (Cardiovascular disease was a secondary outcome). A trial of the diet-heart hypothesis would have focused on preferentially decreasing the intake of SAFA and TFA, with some substitution with PUFA. A lowering of total fat intake was accompanied by an increase in carbohydrate intake, mostly of the complex variety, in the Women’s Health Initiative Dietary Modification Trial. As predicted in the dietary feeding studies, the non-differential decrease in total fat in this trial resulted in only a small, albeit significant, lowering of LDL cholesterol, and a small and nonsignificant decrease in CHD risk. There was a significant increase in CHD risk in women with prior cardiovascular disease (CVD), a finding that was probably owing to chance since there is no biological reason to expect an increase in risk specific to this subgroup. It is noteworthy that subgroups of women within the low-fat group who chose to preferentially reduce their SAFA or TFA, or who more markedly increased their fruit and vegetable intake, experienced a significant and proportional reduction in both LDL cholesterol level and CHD risk. Therefore, the Women’s Health Initiative Dietary Modification Trial does not contradict the diet-heart hypothesis, and can be viewed as being supportive, based on the subgroup findings.

The Mediterranean diet was recognised as a healthy eating pattern by Ancel Keys after World War II. It is characterised by being largely plant based, with an emphasis on olive oil, fruit, vegetables, nuts and wholegrain cereals, the moderate consumption of fish and poultry, low intake of dairy products, red meat and sweets, and a moderate intake of red wine. A primary prevention trial on the Spanish version of the Mediterranean diet, supplemented with either extra-virgin olive oil rich in MUFA and in polyphenols; or with nuts, rich in plant omega-3 PUFA, MUFA and antioxidants, showed an impressive 30% reduction in the risk of cardiovascular disease (primarily strokes) compared to the control “low-fat” diet. The “low-fat” diet, with 37% of energy coming from fat, was not really a low-fat diet, when compared to the 41% of energy derived from fat in the other two groups. The percentage of energy from SAFA was equal in all three groups (9%). Most of the changes in the Mediterranean diet groups were owing to the supplements of olive oil or nuts, but there were also smaller changes in the consumption of fish, especially fatty fish, and legumes. The results are consistent with those of the smaller secondary prevention Lyon Diet Heart Study in which the increased consumption of plant-based, omega-3 PUFA reduced reinfarction rates. The blood lipid level did not change in the Lyon Diet Heart Study, while the diet induced small favourable changes in lipids and apoproteins in the Spanish trial, which were insufficient in explaining the clinical benefit. There were no significant lipid changes in this group, consistent with the fact that the “low-fat” diet was not low in saturated fat. These trials indicate that the Mediterranean diet is a viable alternative option for CVD risk reduction, and underline the potential health benefits of food that is rich in MUFA, omega-3 PUFA from both seafood and plants, and antioxidants.

The diet-heart hypothesis has been amply supported by accumulating data, which show that elevated LDL cholesterol levels increases the risk of CHD. Conversely, lowering LDL cholesterol levels reduces risk at both individual and population level. Feeding studies show that SAFA increases LDL cholesterol, and that the type of SAFA matters. The ubiquitous palmitic acid has a pronounced adverse effect on LDL cholesterol. Feeding studies and cohort studies show that the substitution of SAFA with PUFA lowers LDL cholesterol and CHD risk. Substituting SAFA with high-quality carbohydrates does not appear to increase CHD risk, but carbohydrates with a high glycaemic index are associated with increased risk. Given the weight of evidence and the likelihood of benefit, the lack of definitive clinical trials on the classic diet-heart hypothesis should not deter dietary recommendations aimed at lowering SAFA and TFA, with partial substitution with PUFA and complex carbohydrates. The Mediterranean diet, high in MUFA, offers an alternative pathway to cardiovascular health, and is supported by both population studies and clinical trials.

Diet, obesity and diabetes

Most experts agree that the long-term excess intake of calories, coupled with reduced physical activity, gradually increases body weight in many people. Modern lifestyle choices, coupled with a human physiology geared towards energy conservation, is conducive to obesity, and makes it difficult to reverse established obesity. Hence, the non-surgical management of obesity requires a durable decrease in energy intake and an increase in energy expenditure. Such decreases in energy intake can be achieved with a variety of dietary patterns, and current recommendations include the ability to tailor the dietary approach to individual preferences. Controversy has arisen in the last decade or two as to whether a conventional energy-restricted, low-fat, high-carbohydrate dietary approach is appropriate for weight management. Criticism has included the fact that such diets stimulate insulin release and worsen glucose tolerance, raise triglycerides and promote weight gain because of insulin resistance. It is not feasible to conduct experiments in humans to induce obesity for ethical reasons, so cohort studies and secular trends in entire populations have to be relied upon to inform the issue of whether or not particular foods or food groups are associated with the development of obesity. On the other hand, it is possible to conduct experiments in obesity prevention or treatment, and these kinds of studies will be reviewed briefly.

Cohort studies

A recent analysis of data from the Harvard cohorts showed that food associated with future weight gain included potato chips, potatoes or fries, processed meats, unprocessed red meat, butter, sweets and desserts, as well as refined grains. Food associated with future weight loss included vegetables, nuts, wholegrains, fruit and yoghurt. Sugar-sweetened beverages and 100% fruit juices are also associated with weight gain. Overall, this study indicates that people who gain weight, and are likely to be overeating, have poor dietary quality, as exemplified by the increased intake of potato chips, fries, processed meat, refined carbohydrates and sugar-sweetened
drinks. A separate meta-analysis of cohort studies found that the intake of wholegrains was associated with a significant reduction in the risk of CHD and diabetes, while meat, especially processed meat, was associated with an increased risk of CHD and diabetes.23

Secular trends
As noted previously, secular trends in several human populations show that a reduced intake of total fat, saturated fat and cholesterol, and an increase in unsaturated fat, is associated with a reduction in serum cholesterol and the risk of CHD.10-16 A decreased intake of total fat necessarily means an increase in carbohydrate intake, yet the obesity rates increased in some, but not all, of these populations. Between 1972 and 2007, Finland experienced a 13% increase in PUFA intake, while serum cholesterol decreased by 21% and CHD mortality by 80%. However, body mass index increased by only 5% in men and did not change in women.10 CHD mortality in men in Poland declined by 38% over a 10-year period, yet the obesity rate did not increase.10,24 Obesity rates are increasing in most developed countries, but the decline in CHD rates has continued nonetheless.10-16 Additionally, lowering fat and increasing carbohydrate intake coincided temporally with increases in overall energy intake, decreased activity levels at work and increased sedentary time.12 The increase in overall energy intake is exemplified by the supersizing of high-fat fast food and restaurant meals, an increase in the size of dinner plates for home cooking, and the increased intake of sugar-sweetened beverages.

The case of Sweden is particularly informative with regard to the potential effect of secular changes in macronutrient intake on serum cholesterol and obesity rates. In the 1970s, northern Sweden had one of the highest CVD rates in the world. In response, a community intervention programme was launched in 1985.26 The central component was an intervention with what was termed a “modified Mediterranean diet”, consisting of a reduction in total fat, a shift from saturated to polyunsaturated fatty acid, fewer eggs and more vegetables, fruit, fish and wholegrain bread. This intervention decreased fat intake and increased carbohydrate intake. The largest contributor to the change in the quality of fat was a shift from a widely used blend of butter and rape seed oil to low-fat margarine. Serum cholesterol levels declined, and by 2002, the CVD rates had declined by 50%. However, owing to media-driven enthusiasm for a low-carbohydrate, high-fat diet to reduce obesity, from 2004 onwards, the pattern was reversed. Carbohydrate intake decreased, fat intake increased, the use of butter and rapeseed oil increased, the use of low-fat margarine plummeted, and serum cholesterol levels rose, despite the increasing use of statins. Strikingly, the rates of obesity continued to increase monotonically during the entire study period, demonstrating that obesity does not relate to the type of macronutrient intake. Under the influence of the low-fat, high-carbohydrate enthusiasts, fat intake in the USA has increased again, and carbohydrate intake has decreased since 2000, yet the obesity rate continued to increase.25

In summary, the studies on secular trends indicate that increasing obesity rates are not uniquely associated with a low-fat, high-carbohydrate diet. Other factors are involved. However, the adoption of the recommended dietary changes is associated with a beneficial reduction in cholesterol levels, CHD risk and total mortality. On the other hand, reversion to a high-fat, low-carbohydrate diet may not reverse the population trend towards obesity, but may reverse the cardiovascular benefits of the dietary recommendations.

Clinical trials
Many clinical trials on weight reduction have been published. For the most part, they illustrate that short-term weight reduction is feasible with a variety of approaches, but with the exception of surgical interventions, they have been less successful in maintaining weight loss. This discussion will focus on trials that inform the question of whether a low-carbohydrate, high-fat diet is superior to a conventional low-fat, high-carbohydrate diet for weight reduction and improved metabolic indices. An early and widely cited study showed that a low-carbohydrate, unrestricted fat diet was more successful than a conventional energy-restricted, low-fat, high-carbohydrate diet for weight loss.24 However, this was a very small study, with a follow-up of only 12 months, by which time differences between the diets had already narrowed. The same group of investigators performed a second, larger trial with a 24-month follow-up, which included behavioural support to both groups.26 Subjects with hypercholesterolemia or diabetes were excluded, so the effects on these conditions could not be assessed. This time, equivalent weight loss was found in the two groups at all time points. Early in the trial, the lipid parameters were more favourable in the low-carbohydrate group, but by 24 months, the only remaining advantage was higher HDL cholesterol. However, the low-carbohydrate group experienced significantly more symptoms, including bad breath, a dry mouth, hair loss and constipation. Foster et al concluded that successful weight loss can be achieved with either a low-carbohydrate or a low-fat diet, coupled with behavioural support.26

Perhaps the most informative trial randomised more than 800 participants to one of four groups, two of which had a high-fat, and two a low-fat, diet, with varying levels of carbohydrates and proteins.27 All the diets were energy-restricted, with limited saturated fat and cholesterol intake and recommended complex carbohydrates. The diets performed similarly with regard to weight loss, with roughly 6 kg of weight loss at six months, and about half of the lost weight regained by 24 months. The investigators concluded that a reduced energy diet resulted in meaningful weight loss, regardless of which macronutrients were emphasised. All of the diets produced favourable changes in lipids and glucose homeostasis, but with an indication of more LDL cholesterol reduction in the low-fat groups, which macronutrients were emphasised. All of the diets produced favourable changes in lipids and glucose homeostasis, but with an indication of more LDL cholesterol reduction in the low-fat groups, against a greater increase in HDL cholesterol levels in the high-fat groups. As stated by the authors, “In conclusion, diets that are successful in causing weight loss emphasise a range of fat, protein and carbohydrate compositions that have a beneficial effect on risk factors for cardiovascular disease and diabetes. Such diets can also be tailored to individual patients on the basis of their personal and...
cultural preferences, and may therefore have the best chance of long-term success.\textsuperscript{27}

The Women’s Health Initiative Dietary Modification Trial is by far the largest and longest-duration trial on a low-fat, high-carbohydrate diet, compared to the usual diet. The trial enrolled almost 49,000 women and followed them for eight years.\textsuperscript{28} After one year, 24% of energy came from fat and 58% came from carbohydrates in the low-fat group, compared to 35% from fat and 48% from carbohydrates in the usual diet group. Although the women were not advised to restrict their energy intake, the low-fat group lost weight, compared to the usual diet group.\textsuperscript{29} The low-fat group also had a small but significant advantage with respect to LDL cholesterol, diastolic blood pressure and haemostatic factor VIIc.\textsuperscript{8} The low-fat diet had no overall effect on glucose homeostasis, triglycerides or HDL cholesterol, or on the incidence of diabetes, but did modestly increase triglycerides in women with prevalent diabetes.\textsuperscript{30} This trial provided definitive evidence that a low-fat, high-carbohydrate diet does not increase obesity, glucose intolerance or diabetes risk.

On the contrary, the Diabetes Prevention Program trial employed a low-fat diet (coupled with energy restriction if weight-loss goals were not achieved), plus a physical activity intervention to successfully demonstrate that a low-fat diet (< 25% of energy) reduced diabetes risk by 58% in overweight pre-diabetics.\textsuperscript{31} The reduced diabetes risk correlated strongly with the weight loss achieved.\textsuperscript{32} However, in subjects who did not achieve the weight-loss goals, those meeting the physical activity goals experienced independent protection against diabetes.

The LOOK-AHEAD trial employed similar low-fat and exercise interventions in diabetics and demonstrated weight loss, and an improvement in blood lipids and glucose homeostasis, compared to usual care.\textsuperscript{33} However, after 11-years of follow-up, there was improvement in blood lipids and glucose homeostasis, compared to the usual diet group.\textsuperscript{34} The low-fat group also had a small but significant advantage with respect to LDL cholesterol, diastolic blood pressure and haemostatic factor VIIc.\textsuperscript{8} The low-fat diet had no overall effect on glucose homeostasis, triglycerides or HDL cholesterol, or on the incidence of diabetes, but did modestly increase triglycerides in women with prevalent diabetes.\textsuperscript{35} This trial provided definitive evidence that a low-fat, high-carbohydrate diet does not increase obesity, glucose intolerance or diabetes risk.

The findings also underline the importance of preventing the onset of diabetes by lifestyle measures. The ultimate proof of the primacy of energy restriction to reduce weight and improve diabetes control comes from the trials on gastric bypass surgery which demonstrate a durable remission of diabetes for at least up to four years and an improvement in dyslipidaemia, accompanying considerable weight loss.\textsuperscript{36} Approximately one quarter of diabetics do not experience remission, probably because of pancreatic beta cell dysfunction.

Thus, clinical trials on macronutrient composition for weight control and glucose homeostasis show that in the longer term, a diet that is low in fat and high in (good-quality) carbohydrates is not associated with weight gain, an increase in triglycerides or insulin resistance. Any energy-restricted diet that reduces weight improves insulin resistance and blood lipids. In fact, an energy-restricted, low-fat, high-carbohydrate diet can be used to reduce weight and prevent diabetes in patients with impaired glucose tolerance. Severe energy restriction by gastric bypass induces weight loss and the remission of diabetes in most, but not all, diabetics.

The rise in the prevalence of obesity has been accompanied by a rise in the prevalence of diabetes. However, obesity is far more common than impaired glucose tolerance or diabetes.\textsuperscript{36} These data, together with the improvement in glucose homeostasis after weight reduction, indicate that in most instances obesity drives diabetes, rather than impaired glucose tolerance driving obesity. The pathway is likely to be that excessive energy intake leads to obesity, and subsequent insulin resistance. Over time, the pancreatic reserve fails and frank diabetes develops. It is unclear to what extent, if at all, primary insulin resistance is responsible for obesity and diabetes.

The relationship of glucose homeostasis to CHD risk is complex. A meta-analysis of 102 epidemiological studies showed that diabetes was associated with a twofold increase in CHD risk, and increased risk in subjects with diabetes with suboptimal control of their blood glucose.\textsuperscript{40} However, CHD risk was only modestly associated with fasting blood glucose in non-diabetic subjects, and only at levels above 5.59 mmol/l (100 mg/dl), and the risk of a stroke was not associated with fasting blood glucose. The addition of fasting blood glucose or impaired glucose tolerance to classification models did not improve metrics for vascular disease prediction. This suggests that insulin resistance itself is not directly related to cardiovascular disease, except through its role in diabetes.

Conclusion

Accumulating evidence suggests that some macronutrients are good, others are bad, and some are downright ugly, when it comes to their effects on health. The good nutrients are omega-3 PUFA from seafood and plants, omega-6 PUFAs and MUFA. Bad nutrients include SAFAs, and refined carbohydrates and starches. Industrial TFA is downright ugly. Translated into food choices, this means that people should be encouraged to eat more fish and seafood, wholegrains, fruit, vegetables, nuts, legumes, vegetable oils and low-fat dairy products (Table I).\textsuperscript{23} They should limit the intake of red meat, especially processed meat; starchy vegetables; refined carbohydrates, e.g. pastries, cakes and cookies; and sugar, especially sugar-sweetened beverages; hydrogenated fats and oils, which contain industrial TFA, and salt. Dietary approaches that fit these parameters include those encapsulated in the American Heart Association (AHA) guidelines, the Dietary Approaches to Stop Hypertension diet, vegetarian dietary patterns, Japanese dietary patterns and a Mediterranean diet.\textsuperscript{23}

Table I: Essential dietary habits for health\textsuperscript{23}

<table>
<thead>
<tr>
<th>Eat</th>
<th>Limit</th>
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<tbody>
<tr>
<td>Fish and seafood</td>
<td>Red meat</td>
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<tr>
<td>Wholegrains</td>
<td>Processed meats</td>
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<tr>
<td>Fruit and vegetables</td>
<td>Refined carbohydrates and sugars</td>
</tr>
<tr>
<td>Nuts and legumes</td>
<td>Starchy vegetables</td>
</tr>
<tr>
<td>Vegetable oils</td>
<td>Hydrogenated fats and oils</td>
</tr>
<tr>
<td>Low-fat dairy products</td>
<td>Salt</td>
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It appears that no particular dietary pattern for weight reduction is superior to another. Individual preference determines whether or not to employ a low-fat, high-complex carbohydrate diet; or a low-carbohydrate, high-fat diet; or a diet somewhere in between, provided that the diet also limits energy intake. There is general agreement that refined carbohydrates, starches and sugars need to be limited, or even eliminated, in diets for weight reduction. There is long-term experience of the safety and benefits of the AHA, vegetarian and Mediterranean diets for weight maintenance. There is no similar long-term experience of the safety of the more extreme low-carbohydrate, high-fat diets. In the absence of such evidence, we would do well to heed the advice of Hippocrates: “I will apply dietetic measures for the benefit of the sick, according to my ability and judgement; I will keep them from harm and injustice”, sometimes interpreted as Primum non nocere.41

Declaration

The views expressed in the article do not necessarily represent the views of the National Heart, Lung, and Blood Institute, nor the United States Department of Health and Human Services.

Conflict of interest

The author declares that there were no conflicting interests which may have inappropriately influenced him when writing this article.

References


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