Original Article

Discrepancies in nutritional recommendations: the need for evidence based nutrition

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The widespread acceptance that 'evidence-based medicine' should determine all aspects of clinical practice leads to a consideration as to whether 'evidence-based nutrition' should be based on similar principles. Randomised controlled trials (RCT) are universally regarded as the gold standard by which to determine whether a drug is appropriate in a particular clinical situation. The evidence for some nutritional recommendations is indeed substantiated by RCT but in the case of some chronic diseases, notably cancers, where nutritional factors may operate as promoters or protectors many years before the onset of clinical disease, RCT may not be particularly appropriate. A range of experimental studies and descriptive epidemiological approaches may be regarded as sufficient to justify nutritional recommendations or dietary guidelines. Recommendations for the prevention and treatment of selected diseases will be considered in the context of their evidence-base.

Key words: Evidence-based medicine, level of evidence, randomised controlled trials, recommendations.

Introduction

Recommendations and guidelines regarding appropriate nutrition are not new. They appear in the Old Testament of the Bible:

> The Lord spoke to Moses and Aaron, saying to them: Speak to the people of Israel saying:
>
> From among all the land animals, these are the creatures you may eat. Any animal that has divided hoofs and is cleft footed and chews the cud – such you may eat. But among those that chew the cud or have divided hoofs, you shall not eat the following: the camel, for even though it chews the cud, it does not have divided hoofs; it is unclean for you …[1]

and more recently Hippocrates offered guidelines that show some remarkable similarities to those of today:

> … to the human body it makes a great difference whether the bread be fine or coarse; with or without the hull, whether mixed with much or little water, baked or raw …
>
> Whoever pays no attention to these things, or, paying attention, does not comprehend them, how can he understand the diseases which befall man?[2]

However, there are innumerable examples where even apparently scientifically well founded recommendations have not been substantiated by later more definitive research. One such example is what might be described as the vitamin E saga. Several well conducted prospective studies suggested an impressive association between vitamin E consumption (as well as some other antioxidant nutrients) and subsequent risk of coronary heart disease in both men and women (Table 1).[3]

When a simple randomised controlled trial confirmed reduced morbidity in patients with coronary heart disease (CHD) given vitamin E supplements many cardiologists and other physicians believed the evidence was sufficiently impressive to routinely recommend vitamin E supplements to patients with this disease.[4] However, several subsequent much larger clinical trials showed no benefit of supplementation to the extent that the aggregated relative risk was 0.97 (95% confidence intervals 0.92–1.02) providing fairly convincing acceptance of the null hypothesis (Table 2).[5]

While the last word on vitamin E has undoubtedly not yet been spoken, perhaps the level of supplementation was inappropriate, perhaps it needs to be used in conjunction with other micronutrients or possibly taken for a longer period of time than has been the case in present trials, there is certainly no justification at present for its use as a cardioprotective agent.

At a time when there is general agreement that drug therapy and other medical practices should be based on evidence-based medicine, there is also acknowledgement that advice regarding nutrition should similarly have an evidence base. Some principles are universally accepted. Recommendations should be based on **all** available evidence and not selected studies and the integrity of 'expert committees'must be beyond reproach. Several systems of grading the level of evidence upon which recommendations are based have been suggested (Tables 3,4).[6] These are firmly

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Table 1. Relative risk of coronary heart disease according to quartile groups for vitamin E and carotene intake among 39 910 male health professionals[3]

	Quintile group					*P*-value for trend
	1	2	3	4	5	
Vitamin E intake						
Median intake 1 U/day	6.4	8.5	11.2	25.2	41.9	
Multivariate RR	1.0	0.90	0.82	0.77	0.64	0.003
(95% CI)		(0.71–1.14)	(0.64–1.07)	(0.60–0.98)	(0.49–0.83)	
Carotene intake						
Median intake 1 U/day	3969	6019	8114	11 653	19 034	0.020
Multivariate RR	1.0	0.93	0.93	0.87	0.71	
(95% CI)		(0.72–1.20)	(0.72–1.20)	(0.67–1.15)	(0.53–0.96)	

RR, relative risk.

Table 2. Meta-analysis the effects of vitamin E on myocardial infarction, stroke or death from cardiovascular causes in large trials (HOPE Investigators)[5]

Study	Dose (mg)	Duration (year)	Relative risk (95% CI)
ATBC	50	5.0	0.96 (0.90–1.03)
CHAOS	≤ 400	1.3	0.60 (0.40–0.89)
GISSI	300	3.5	0.98 (0.87–1.10)
HOPE	400	4.5	1.05 (0.95–1.16)
Total			0.97 (0.92–1.02)

ATBC, Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; CHAOS, Cambridge Heart Antioxidant Study; GISSI, Gruppo Italiano per lo Studio della Sopravvivenza nell"Infarto Miocardico; HOPE, Heart Outcomes Prevention Evaluation Study.

Table 3. Levels of evidence required for guideline development (US Agency for Health Care Policy and Research)[6]

Statements of evidence	Grades of recommendation
Ia: Meta-analysis of randomised controlled trials	A
Ib: At least 1 randomised controlled trial	
IIa: At least 1 controlled study, not a randomised controlled trial	B
IIb At least 1 other well designed 'quasi-experimental' study	
III Well designed, nonexperimental descriptive studies	
IV Expert committee reports	C

Table 4. Proposed levels of evidence for food or health claims (Australia New Zealand Food Authority) 2000[7]

Grade	Type of evidence
A	Systematic review of all relevant randomised controlled trials
B	Properly designed randomised controlled trials or well designed pseudo-randomised controlled trials
C	Cohort (prospective) studies
D	Case control studies or interrupted time series with a control group
E	Comparative studies with historical controls
F	Case series
G	Other relevant information, such as, reports of expert committees

based upon the grading systems that have been suggested for evidence-based medicine in general, and regard the randomised controlled trial (RCT) as the ultimate level of proof. They do not necessarily specify whether the RCT should have conventional endpoints (morbidity and mortality) or whether surrogate endpoints are acceptable. The absence of clear and widely accepted levels of evidence as they apply to nutrition inevitably leads to discrepancies in nutrition recommendations. Some examples are given and suggestions are made for levels of evidence that might apply to nutrition, as distinct from those more relevant to drug treatment.

Nutritional recommendations for people with diabetes

The American Diabetes Association (ADA) has recently reissued its recommendations for the nutritional management of people with diabetes, which are considered to be evidence based.[7] Two recommendations concerning carbohydrate are extracted in Table 5.

Two years previously the Diabetes Nutrition Study Group (DNSG) of the European Association for the Study of Diabetes (EASD) updated the European recommendations for the nutritional management of people with diabetes.[8] Relevant recommendations regarding carbohydrates are summarized in Table 6.

It is clear that there are major discrepancies. The DNSG recommendations do not accept the principle that total carbohydrate is more important than source or type since they offer clear direction regarding preferred sources and support for the use of glycaemic index to guide carbohydrate food choices. Furthermore there is a clear specification regarding the limitation of dietary sucrose. Not surprisingly the two expert groups quote rather different references to support their points of view. It is beyond the scope of this review to consider the evidence in detail. However, the ADA recommendations quote a carefully controlled set of meal experiments in which fructose, sucrose, potato, wheat or glucose provided half the total carbohydrate in a mixed meal.[9] It is hardly surprising that glucose responses after the wheat and potato were similar to those seen after the glucose since they comprise starches readily digested to glucose and efficiently absorbed. Given the difference in absorption and metabolism it is equally unsurprising that a lesser glycaemic response is seen after sucrose or fructose. A totally different response might be expected and indeed is found when low glycaemic index carbohydrate, or foods rich in resistant starch or soluble forms of non-starch polysaccharides are consumed during acute meal experiments and as part of longer term feeding experiments. It was such studies that influenced the DNSG.[10–12] The restriction regarding total quantity of sucrose stems from the fact that the carefully controlled studies suggesting that sucrose was an acceptable component of the diabetic dietary prescription involved modest intakes.[13]

There is then a need for a set of clearly defined criteria according to which nutritional recommendations might be made. While a meticulously designed and conducted RCT with hard clinical endpoints, or better still a meta-analysis involving a group of such studies, is clearly the ultimate in terms of levels of evidence, such studies are often inappropriate for testing potential nutritional guidelines. A nutrient may be important in the early stages of a disease process and the clinical trial may be started too late to make a difference. The trial may not continue for long enough or may be inappropriately powered. Furthermore dietary compliance may be poor. It is also conceivable that some nutrients or foods may only be protective when consumed together with another nutrient or group of nutrients. Similarly there are difficulties associated with cohort studies that require huge numbers of subjects and meticulous long-term follow up. A one-off dietary assessment may provide a poor reflection of long-term dietary intake, though some recent cohort studies have involved a series of such assessments. There is no universally accepted dietary intake instrument and it may be extremely difficult in cohort studies to cope with confounding variables. For example, individuals who consume a low fat diet, high in non-starch polysaccharides may also be those who are health conscious in other respects and this may not always be easy to measure. Existing statistical techniques may not adequately disentangle separate effects.

Is it possible then to come up with some guidelines for determining the degree of confidence with which nutritional recommendations can be made? Possible criteria for the

Table 5. Carbohydrates and diabetes: American Diabetes Association (ADA) evidence-based nutrition principles and recommendations, 2002[8]

A level evidence
With regard to glycaemic effects of carbohydrates, the total amount of carbohydrate in meals or snacks is more important than source or type.
As sucrose does not increase glycaemia to a greater extent than isocaloric amounts of starch, sucrose and sucrose-containing foods do not need to be restricted to people with diabetes; however, they should be substituted for other carbohydrate sources, or, if added, covered with insulin or other glucose lowering medication.

Table 6. Diabetes Nutrition Study Group (DNSG) of the European Association for the Study of Diabetes (EASD) 1999: Recommendations for the nutritional management of people with diabetes[9]

Concerning carbohydrates
Carbohydrate-containing foods that are rich in dietary fibre or have a low glycaemic index are especially recommended.
Vegetables, legumes, fruits and cereal-derived foods are the preferred sources of carbohydrate since they are rich in fibre, micronutrients and vitamins.
Foods with a low glycaemic index (e.g. legumes, oats, pasta, parboiled rice, certain raw fruits) should be substituted when possible for those with a high glycaemic index.
Concerning sucrose
If desired, moderate intakes of sucrose may be incorporated within the diet for both types of diabetes. As for the general population, intake should not exceed 10% of total energy.

three levels of evidence (convincing, A; probable B; possible C) are suggested in Table 7.

There are some particularly important issues that require emphasis. The criteria apply to evidence that might be applied to both 'prevention' and 'treatment'. Levels A and B, convincing and probable, should be regarded as being sufficiently powerful to extrapolate into recommendations that can be implemented with confidence. Level C, possible, might be regarded as an association that requires further research, that is expected to be beneficial and that is likely to be extrapolated into recommendations when further evidence becomes available. The associations considered in all three levels should be biologically plausible.

Randomised controlled trials are acknowledged as potentially providing the most powerful level of evidence but for the reasons given earlier should not be regarded as the sole source of convincing evidence for nutrition recommendations. Consistent appropriate epidemiological evidence (which will usually but not necessarily be derived from prospective studies) together with consistent experimental studies could also constitute convincing evidence for recommendations. The following definition is suggested for the type of experimental study that would qualify: Meticulously conducted, randomised, controlled human studies in people with or at risk of the condition under consideration, involving dietary manipulation over a period of weeks or months (as relevant) with acknowledged clinically relevant endpoints (unequivocally established risk factors or biomarkers). *In vitro* studies, acute experiments and animal studies may be considered but would not on their own constitute this level of evidence. Level B evidence would be based on similar studies but some inconsistencies and lack of perfection in the nature of the studies would be accepted.

If these principles are accepted it is of interest to consider the evidence base underpinning dietary recommendations for the prevention and treatment of diabetes and the extent to which modification of the recommendations might be required. In terms of RCT with clinical endpoints there are now two impressive clinical trials in which diets low in saturated fatty acids and high in legumes, pulses, other vegetables, fruit and wholegrain cereals and designed to achieve weight loss in conjunction with exercise programs achieved reductions in progression of impaired glucose tolerance (IGT) to type 2 diabetes.[14,15] Prospective studies have consistently shown that overweight and obesity (especially when centrally distributed) and lack of physical activity increase risk of type 2 diabetes.[16,17] Impressive experimental data confirm that voluntary weight loss, increased physical activity and high intakes of vegetables, fruit and wholegrain cereals as part of a low saturated fat diet reduce insulin resistance, the major underlying abnormality in type 2 diabetes.[18] There is some evidence from prospective studies that cereal derived non-starch polysaccharides (NSP) are protective against type 2 diabetes and a high glycaemic load promotes the development of type 2 diabetes.[19] Experimental studies conforming to the criteria specified in Table 7 confirm, in terms of glucose and insulin levels as well as lipids and lipoproteins, the beneficial effect of low glycaemic index foods[11] and diets high in soluble forms of non-starch polysaccharides.[12] With regard to the latter observation, there is one inconsistency: while it appears to be the soluble forms of NSP that produce improved glycaemic and metabolic control, it is cereal fibre (i.e. insoluble forms of NSP) that have been shown to be protective in prospective studies. Thus, Table 8 summarizes the levels of evidence that would appear to support various dietary recommendations for the prevention and treatment of type 2 diabetes.

Clearly the role of central adiposity and physical inactivity in the development of insulin resistance and diabetes, and the benefit of weight loss, qualify as recommendations underpinned by level A evidence. Given the slight inconsistencies regarding the nature of the most beneficial forms of NSP, the fact that not all glycaemic index studies confirm benefit in terms of glycaemic and risk factor control and that the evidence regarding saturated fat is less extensive than weight loss and enhanced activity, it seems appropriate that recommendations regarding these aspects be accorded a

Table 7. Suggested levels of evidence for nutrition recommendations

Convincing (A)
Several randomised controlled trials, appropriate duration, power and quality, showing consistent effects; and/or
Consistent associations in appropriate epidemiological studies (usually prospective cohort) plus consistent experimental studies demonstrating favourable effect*
Probable (B)
Randomised controlled trials and prospective studies may not be entirely consistent or may have shortcomings (e.g. trials may be of short duration or include insufficient numbers; prospective studies may include cohorts of insufficient size or have incomplete follow-up. Some data may be from non-randomised trials.
Experimental studies confirm favourable effect on risk factors.
Possible (C)
Epidemiological evidence based principally on case control and cross sectional studies. No good randomised controlled trials or prospective studies. Some experimental studies confirm favourable effect on risk factors.

*Suggested definition for experimental studies: Meticulously conducted and controlled studies in relevant groups of individuals (usually those at risk of developing, or with, a particular condition), involving dietary manipulations over a period of weeks or months and with acknowledged clinically relevant endpoints (biological markers or established risk factors).

Table 8. Levels of evidence for various lifestyle factors related to the risk of developing type 2 diabetes.

Evidence	Decreased risk	Increased risk
Convincing	Voluntary weight loss in overweight and obese people Physical activity	Overweight and obesity Abdominal obesity Physical inactivity
Probable	Non-starch polysaccharides	Saturated fats Intrauterine growth retardation
Possible	n-3 fatty acids Low glycaemic index foods Exclusive breastfeeding	Total fat intake *Trans* fatty acids

slightly lower level of certainty, evidence level B. Of course much morbidity and mortality in type 2 diabetes stems from cardiovascular and renal disease, thus recommendations to reduce the risk of such conditions also need to be taken into account when making recommendations for people with type 2 diabetes.

Carbohydrates or *cis*-unsaturated fatty acids as replacement for saturated fatty acids

The question as to whether carbohydrates or *cis*-unsaturated fatty acids should replace saturated fatty acids is relevant to people with diabetes as well as recommendations for the population at large. The suggestion that *cis*-monounsaturated fatty acids might be preferable stems from epidemiological observations (the potential benefits of the Mediterranean diet and lifestyle) as well as experimental studies suggesting higher levels of triglyceride and very low density lipoprotein as well as lower high-density lipoproteins on high carbohydrate diets (Fig. 1).[19,20]

However, in the experimental studies quoted about 50% of the total carbohydrate was derived from mono- and disaccharides or readily digested starches so the findings are hardly surprising. However, studies of different dietary patterns suggest that various dietary patterns, including those traditionally high in carbohydrates are compatible with a cardioprotective effect but they and confirmatory experimental studies suggest that under such circumstances carbohydrates are more appropriately derived from vegetables, fruits and wholegrain cereals and not food sources especially rich in mono- and disaccharides.[21–24] In this instance evidence-based nutrition provides evidence that there is more than one way in which to achieve cardioprotective effects.

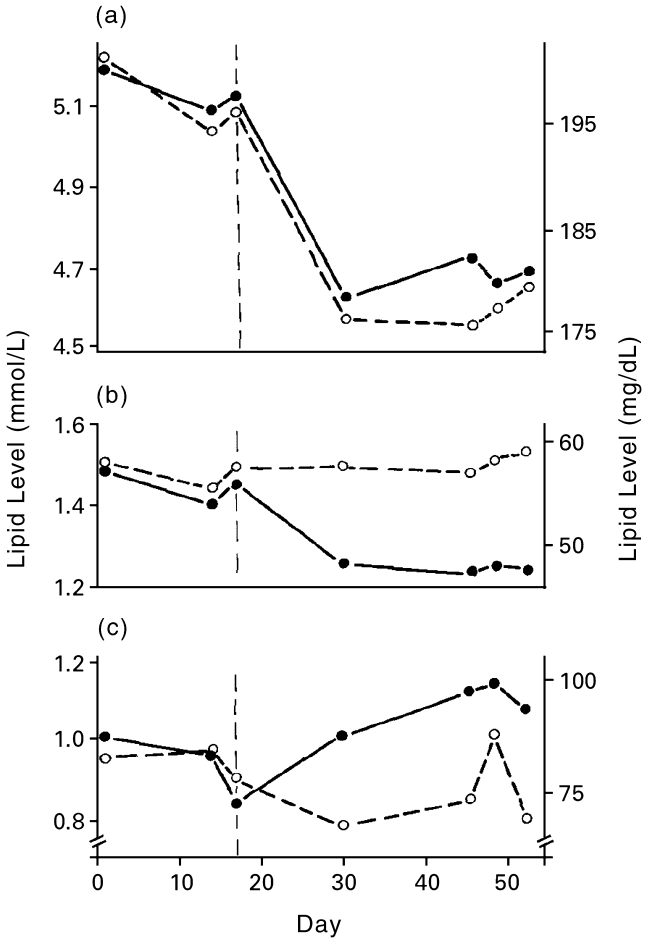

Figure 1. Effects on blood lipids of diet high in olive oil (--○--) versus high in carbohydrate and fibre and low in fat (—●—).[23] (a) Total cholesterol; (b) HDL cholesterol; (c) Triglycerides.

Conclusions

When considering potential health claims and probably also when making decisions about fortification and supplementation it is generally appropriate to require evidence of benefit from 'conventional' randomised controlled trials (i.e. those with 'hard' clinical endpoints). However, in many situations convincing evidence sufficient for nutritional recommendations may be derived from consistent appropriate epidemiological studies together with appropriate experimental evidence. It is imperative, though, that the nature of the experimental evidence is specified. Some situations do require special consideration. Practical measures aimed at stemming the tide of the obesity epidemic should perhaps be exempt from the strict criteria suggested here. For example, there has been a phenomenal increase in energy dense foods and in particular in serving sizes of such foods from fast food outlets. It seems self evident that any measures aimed at reducing over consumption of such foods or enhancing energy output do not require the same level of assessment as

individual nutritional recommendations. However, in such situations evaluation of programs aimed at achieving change in eating habits warrants assessment before widespread implementation.

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