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REVIEW PAPER

Drugs as anti-nutrients

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Abstract
Purpose: To collate evidence on nutrient deficiencies caused by drugs.
Design: Search of Medline and other databases, and published literature.
Materials and methods: Medline, Scirus and Google Scholar databases, journal articles and books.
Results: There is evidence that many drugs, medicinal or recreational, produce deficiencies in vitamins, minerals, fatty acids and/or amino acids. Some drugs cause multiple deficiencies. They may reduce conversion of vitamins to their active forms, or inhibit the production of important metabolites. By killing beneficial bacteria in the gut, they may cause vitamin deficiency. They may reduce absorption, or cause excretion of nutrients.
Conclusions: Many drugs have been identified, which appear to cause deficiencies in essential nutrients and their metabolites. Nutrients could be prescribed with drugs, to limit the damage done, provided that this does not undermine the action of the drugs. Further research is needed to confirm the results of those studies that have been carried out, and to find out about nutrient depletion from new drugs.

Key words: *drug–nutrient interaction, drug–vitamin interaction, drug–mineral interaction, nutrient deficiency, vitamin deficiency, mineral deficiency, coenzyme Q10 deficiency*

Introduction

Nutrients are amino acids, vitamins, elements and essential fatty acids that are required by the body in order to carry out its normal functions. Drugs act by bypassing the normal processes, and thus often cause side effects. Often drugs act as anti-nutrients, by causing deficiency in essential substances, or by interfering with their functions. People who are already deficient, or whose nutritional status is marginal are likely to be more susceptible to side effects of drugs. However, some drugs increase the levels of certain nutrients.

Drugs may affect nutritional status in different ways. They can alter intake, absorption, metabolism, utilisation or excretion [1,2]. Many people take several drugs at a time, and no one knows what the interactions of all these drugs are. These drugs may be medicinal, or recreational. Research on drug–nutrient interactions is very limited. I shall list here some of the information that has been reported so far, on possible deficiencies in nutrients, gut bacteria and hormones caused by drugs. Further research is needed in some cases, to check the findings. Research trials may produce conflicting information. Sometimes the research

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has been carried out into only one drug in a group, and we can only suspect that others have the same effect. Some individuals are more susceptible to loss of nutrients than others, and they are more likely to suffer from side effects. Research that has only been carried out on laboratory animals needs to be followed by studies on humans.

Prescription of drugs should be based on cost–benefit considerations. There are occasions where the side effects of a drug are acceptable, because of the gravity of the disease, and the lack of any other means of combating it effectively. However, there is no point in taking a drug if the expected side effects are worse than the disease or if the disease can be treated effectively without side effects. Short courses of drugs are usually less of a threat than long-term courses. Often illness is caused by nutrient deficiency, and unless the deficiency is treated, there may be more serious consequences later on. Using drugs to cover up deficiency symptoms can therefore be dangerous.

In some cases, side effects of drugs may be reduced by taking a supplement of a relevant nutrient. However, in other cases this is not recommended, as it may make the drug useless. For example, carbamazapine and phenobarbitone appear to lower folic acid levels [3], but giving too much folic acid may inactivate the drug [4].

Drugs have a generic name, and sometimes several other names given by different manufacturers. One manufacturer may use different names in different countries. This can make it difficult to check on drug–nutrient interactions.

It may be thought that people living in affluent countries are not subject to nutrient deficiencies. However, a combination of genetic diversity in nutrient requirements, unwise food selection or preparation, intensive exercise, infection, and the use of anti-nutrient drugs may lead to deficiency symptoms.

Materials and methods

A search was carried out of the literature on drug-nutrient interactions, using books and the Medline, Scirus and Google Scholar databases, to collect information on anti-nutrient drugs. 'Drug–nutrient interactions', 'Drug–vitamin interactions', and 'Drug–mineral interactions' were used as general search terms. Specific searches, for example for 'Statin, coenzyme Q10', or 'Seelig, magnesium deficiency' were also used.

Results

Many drugs were identified, which are thought to act as anti-nutrients (Table I). Deficiencies may be caused in many nutrients. Elements may be affected, including calcium, chlorine, copper, iron, magnesium, manganese, nitrogen, phosphorus, potassium, selenium, sodium and zinc. Vitamins A, B1, B2, B3, B6, B12, C, D, E and K, folic acid and biotin may also be affected, as well as carotene and coenzyme Q10. Amino acids involved may include L-carnitine, L-leucine, and the sulphur amino acids. Fat and carbohydrate are also mentioned in the literature, as well as beneficial gut bacteria. Hormones may be involved, including DHEA (dehydroepiandrosterone) and melatonin.

Discussion

A nutritional approach aims at finding out which biochemical systems are failing to work properly, and rectifying them. This is a very different process from the use of drugs or even herbs, which do not usually enhance an existing biochemical pathway. They are more likely to divert the body down a new pathway, which was not part of its design. This can lead to

Table I. Drugs that may reduce the absorption or activity of nutrients or normal body constituents.

Drug or type of drug	Possible deficiency or interference	Reference
Adriamycin (Doxorubicin)	Coenzyme Q10	[5]
	Vitamin B2	[6]
Aluminium hydroxide	Calcium	[7]
	Phosphorus	[8]
	Vitamin A	[8]
Aminoglycosides, e.g. Gentamycin	Calcium	[8]
	Magnesium	[9]
	Potassium	[8]
	Vitamins B1, B2, B3, B6,	[10]
	Vitamins B12 and K	[10]
Aminopterin	Folic acid	[8]
	Vitamin B12	[8]
Amitriptylene	Sodium	[8]
	Vitamin B2	[11,12]
Amoxicillin (Amoxil)	L-leucine	[13]
Amphotericin B (Fungizone)	Calcium	[10]
	Magnesium	[9,14]
	Potassium	[8]
Antacids	Folic acid	[15]
	Calcium	[7,16–19]
	Copper	[8]
	Phosphate	[8,10]
	Vitamin A	[8]
	Vitamin B12	[20]
Antibiotics	Beneficial gut bacteria	[4,21,22]
	Vitamin K	[4]
	L-leucine	[13]
	Biotin	[21–23]
Anticonvulsants	Biotin	[24,25]
	Folic acid	[3,25]
	Vitamins B2, B6, B12	[25]
	Vitamins D, E	[25]
	Vitamin K	[8]
	L-carnitine	[26]
Aspirin	Folic acid	[27]
	Iron	[10]
	Vitamin C	[8]
	Vitamin E	[10]
	Zinc	[4]
	Potassium	[10]
Atorvastatin	Coenzyme Q10	[28]
AZT (Zidovudine)	L-carnitine	[4]
	Copper	[29]
	Vitamin B12	[4]
	Zinc	[29]
Beta-adrenergic blocking agents	Coenzyme Q10	[5]
Bile acid sequestrants	Calcium	[4]
	Carotenoids	[30]
	Folic acid	[4]
	Vitamins A, D, E, K	[4]
	Zinc	[4]
Bisacodyl (Dulcolax, stimulant laxative)	Potassium	[31]
Boric acid	Riboflavin	[32,33]
Caffeine	Calcium	[34]

Table I. Continued.

Drug or type of drug	Possible deficiency or interference	Reference
Calomel	Phosphorus	[8]
Captopril (Capoten – ACE inhibitor)	Zinc	[35]
	Sodium	[8]
Carbamazepine	Folic acid	[3]
	Sodium	[8]
Carbenoxolone	Potassium	[8]
Cephalexin	L-leucine	[13]
Cephalosporins (Antibiotics)	Vitamin K	[8]
Chemotherapy	Magnesium	[36,37]
	Vitamin B2	[6]
	Taurine	[4]
	Many other nutrients	[4]
Chloramphenicol	Folic acid	[8]
Chloride	Calcium	[38]
	Magnesium	[38]
Chlorpromazine	Vitamin B2	[11,12,32,39,40]
Chlorpropamide	Sodium	[41]
	Potassium	[10]
Chlorthalidone (Chlortalidone)	Zinc	[42,43]
	Potassium	[10]
Cholestyramine	Carotenoids	[8]
	Fat	[8]
	Folic acid	[44]
	Calcium	[10,44]
	Iron	[44]
	Magnesium	[10]
	Phosphorus	[10]
	Zinc	[10]
	Vitamin A	[8]
	Vitamin B12	[44]
	Vitamins D, E	[8]
	Vitamin K	[45]
Cimetidine (Tagamet)	Iron	[4]
	Zinc	[46]
	Folic acid	[15]
	Vitamin B12	[4]
	Vitamin D	[47]
Cisplatin (Platinol)	Magnesium	[48]
Clofibrate (Atromid-S)	Vitamin B12	[4]
	Vitamin E	[8]
Clozapine	Selenium	[10]
Colchicine	Fat	[8]
	Beta carotene	[8]
	Potassium	[8]
	Sodium	[8]
	Vitamin B12	[8]
Colestipol (Colestid)	Beta carotene	[30]
	Folic acid	[44]
	Iron	[44]
	Vitamin A	[8]
	Vitamin B12	[44]
	Vitamins D, E and K	[8]
Conjugated oestrogens (Premarin)	Vitamin B6	[4]

Table I. Continued.

Drug or type of drug	Possible deficiency or interference	Reference
Corticosteroids	Calcium	[10]
	DHEA	[4]
	Magnesium	[10]
	Melatonin	[4]
	Potassium	[4]
	Folic acid	[49]
	Vitamin B6	[4]
	Vitamin B12	[49]
	Vitamins C, D, K	[4]
	Vitamin E	[10]
	Selenium	[8]
	Zinc	[10]
Cyclophosphamide (Cytoxan, Neosar)	Sodium	[8]
Cycloserine (Seromycin)	Calcium	[4]
	Folic acid	[4]
	Magnesium	[4]
	Vitamins B6, B12, K	[4]
Cyclosporin (Sandimmune, Neoral)	Magnesium	[50–52]
Dicoumarol	Vitamin K	[8]
Digitalis (Digoxin, Lanoxin, Digitoxin)	Magnesium	[48,53]
	Calcium	[8]
	Sodium	[53]
	Potassium	[48,53]
Disopyramide phosphate	Magnesium	[8]
Distal tubule diuretics	Zinc	[42,43]
	Magnesium	[54–58]
Diuretics	Magnesium	[48,54,55–59,61–64]
	Potassium	[48,59,60]
	Zinc	[42,43]
	Vitamin B1	[65]
L-dopa (Levodopa, Dopar, Larodapa)	Vitamin B6	[8]
	Potassium	[60,66]
Doxycycline	Vitamin K	[4]
Dymelor	Coenzyme Q10	[8]
Edetate calcium disodium (EDTA)	Calcium	[8,10]
	Zinc	[8,10]
Erythromycin	Calcium	[4]
	Magnesium	[4]
	Folic acid	[4]
	Vitamins B6 and B12	[4]
Ethacrynic acid	Calcium	[8]
	Magnesium, potassium	[8]
Ethanol	Vitamin A	[10]
	Vitamin B1	[10]
	Vitamin B2	[67]
	Vitamin B6	[10]
	Iron, zinc	[10]
Ethionamide	Vitamin B6	[8]
Etodolac (Lodine)	Iron	[4]
Famotidine (Pepcid – antacid)	Copper	[4]
	Folic acid	[4]
	Calcium, iron	[10]
	Vitamin B12	[4]

Table I. Continued.

Drug or type of drug	Possible deficiency or interference	Reference
Fibric acid derivatives	Folic acid	[68]
5-Fluorouracil (5-FU, Efudex, Fluoroplex)	Vitamin B1	[8]
Fluoxetine (Prozac – SSRI)	Melatonin	[69]
	Potassium	[10]
	Sodium	[70]
Furosemide (Frusemide, loop diuretic)	Calcium	[8]
	Magnesium	[9,61]
	Potassium	[8]
	Vitamin B1	[8]
	Vitamins B6 and C	[71]
Gemfibrozil (lipid regulator)	Coenzyme Q10	[5]
Gentamycin (Garamycin)	Calcium	[10]
	Magnesium	[72]
	Potassium	[72]
	Vitamin B6	[4]
Glutethimide	Vitamin D	[8]
Glyburide (Glibenclamide, Diabeta, Micronase)	Coenzyme Q10	[8]
Gold	Selenium	[8]
Haloperidol (Haldol)	Iron, potassium, sodium	[4]
Heparin	Vitamin D	[73]
Histamine H_2-antagonists	Iron	[74]
	Zinc	[46]
	Folic acid	[10]
	Vitamin B12	[74]
Hydralazine (Apresoline)	Vitamin B6	[75]
Hydrazine	Vitamin B6	[8]
Ibuprofen (Advil, Motrin, Nuprin)	Iron	[4]
Imipramine	Vitamin B2	[11,12]
Indapamide	Chloride	[76]
	Sodium, potassium	[76]
Indomethacin (Indocin)	Calcium	[4]
	Iron	[77]
	Folic acid	[10]
	Vitamin C	[4]
	Phosphate	[10]
Isoniazid (INH, Laniazid, Rifamate, Rimactane)	Calcium	[10]
	Folic acid	[4]
	Magnesium	[10]
	Vitamins B3, B6	[10]
	Vitamin B12	[4]
	Vitamin D	[47]
	Vitamins E, K	[4]
Lansoprazole (Prevacid, proton pump inhibitor)	Beta carotene	[4]
	Vitamin B12	[4]
	Calcium	[10]
Laxatives	Potassium	[31,60,78]
Lithium carbonate	Sodium	[79]
Loop diuretics	Magnesium	[48,55–58,61,62]
	Potassium	[48]
	Vitamins B1, B6, E	[10]

Table I. Continued.

Drug or type of drug	Possible deficiency or interference	Reference
Losartan (Cozaar, angiotensin-II receptor antagonist)	Calcium	[80]
	Chloride	[80]
	Magnesium	[80]
	Potassium	[80]
	Sodium	[80]
	Phosphate	[80]
Lovastatin (Mevacor)	Coenzyme Q10	[81,82]
Magnesium hydroxide (Milk of Magnesia)	Iron	[10]
	Phosphate	[10]
	Folic acid	[15]
Mannitol	Sodium	[8]
Metformin (Glucophage)	Folic acid	[4]
	Vitamin B12	[10]
Methotrexate (Folex, Rheumatrex)	Calcium	[10]
	Folic acid	[83]
Methyldopa (Aldomet)	Vitamin B12	[4]
Mineral oil	Beta carotene	[84]
	Calcium, phosphorus	[10]
	Potassium	[10]
	Vitamins A, K	[10]
	Vitamins D, E	[4]
Neomycin	Carbohydrate	[4]
	Beta carotene	[4]
	Fats	[4]
	Folic acid	[4]
	Calcium	[10]
	Iron	[10]
	Magnesium,	[8]
	Potassium	[8]
	Nitrogen	[8]
	Sodium	[8]
	Vitamin A	[10]
	Vitamin B6	[4]
	Vitamin B12	[10]
	Vitamin D	[4]
	Vitamin K	[8]
Nicotinamic acid (niacin)	Folic acid	[68]
Nitrous oxide	Folic acid	[85]
	Vitamin B12	[85–87]
Non-steroidal anti-inflammatory analgesics	Folic acid	[88]
	Iron	[89]
Omeprazole (Prilosec – proton pump inhibitor)	Beta carotene	[90]
	Vitamin B12	[91]
Oral contraceptives	Magnesium	[92]
	Manganese	[4]
	Zinc	[10]
	Folic acid	[93]
	Vitamins B1	[4]
	Vitamin B2	[10]
	Vitamin B3	[4]
	Vitamin B6	[94]
	Vitamin B12	[10]
	Vitamin C	[4]

Table I. Continued.

Drug or type of drug	Possible deficiency or interference	Reference
Orlistat	Fat	[95]
	Vitamin E	[95]
Pancreatic extract	Folic acid	[96]
Para-aminosalicylic acid	Fat	[8]
	Folic acid, vitamin B12	[8]
Paracetamol (acetaminophen)	Sulphur amino acids	[97]
	Phosphate	[98]
Paroxetine (Paxil – SSRI)	Sodium	[70]
D-Penicillamine (Cuprimine, Depen)	Copper, sodium	[4]
	Vitamin B6	[99]
	Zinc	[99]
	Magnesium	[99]
Pentamidine	Calcium	[10]
	Folic acid	[8]
Phenelzine (Nardil)	Vitamin B6	[100]
Phenformin	Coenzyme Q10	[8]
	Vitamin B12	[8]
Phenobarbital (Phenobarbitone)	Calcium	[10]
	Folic acid	[3]
	Vitamin D	[8]
Phenolphthalein	Calcium, potassium	[8]
	Vitamin D	[8]
Phenothiazines	Coenzyme Q10	[8]
	Vitamin B2	[10]
Phenylbutazone	Folic acid	[8]
Phenytoin (Epanutin)	Calcium	[10]
	Folic acid	[101]
	Vitamins B1, B12, K	[10]
	Vitamin D	[8]
Potassium chloride	Vitamin B12	[8]
Potassium sparing diuretics	Folic acid	[10]
Pravastatin (Pravachol)	Coenzyme Q10	[82,102]
Prednisone	Calcium	[103]
Prednisolone	Potassium	[10]
Primidone	Folic acid	[8]
	Vitamin D	[8]
Probucol	Carotenoids	[8]
	Vitamin E	[8]
Procarbazine	Vitamin B6	[8]
Progesterone	Folic acid	[8]
	Vitamin B6	[8]
Propranolol (Inderal)	Coenzyme Q10	[4]
Pyrazinamide	Vitamin B6	[8]
Pyrimethamine (anti-malarial)	Folic acid	[8]
Quinidine sulphate	Magnesium	[8]
Ranitidine (Zantac)	Iron	[46]
	Zinc	[46]
	Vitamin B12	[8]
Selective Serotonin Reuptake Inhibitors (SSRIs)	Sodium	[70,104]
	Melatonin	[69]
Sennoside	Potassium	[31]
Simvastatin (Zocor)	Coenzyme Q10	[105]
	Vitamin E	[105]
	Beta carotene	[105]

Table I. Continued.

Drug or type of drug	Possible deficiency or interference	Reference
Sodium bicarbonate	Folic acid	[8]
	Iron	[4]
	Potassium	[10]
Sodium sulphate	Potassium	[8]
Spironolactone (Aldactone)	Potassium, sodium	[8]
Stanozolol (Winstrol)	Iron	[4]
Statins (HMG-CoA Reductase Inhibitors)	Selenium	[106]
	Coenzyme Q10	[5,82,102,105]
	Vitamin E	[105]
	Beta carotene	[105]
Strophanthin	Calcium	[8]
Sulfamethoxazole (Gantanol)	Calcium	[4]
	Folic acid	[4]
	Magnesium	[4]
	Vitamins B6, B12, and K	[4]
Sulfasalazine (Azulfidine – sulphonamide)	Folic acid	[83,107]
Sulphonamides	Calcium, magnesium, iron	[10]
	Vitamins B1, B3, B6, B12	[10]
	Vitamin K	[10]
Tetracyclines (Achromycin, Sumycin – antibiotic)	Potassium	[8]
	Magnesium	[10]
	Folic acid	[4]
	Vitamins B2, B6, B12	[10]
	Vitamin C	[4]
	Vitamin K	[10]
	Beneficial gut bacteria	[4]
	L-leucine	[13]
Theophylline (Slo-Bid, Slo-phyllin, Theo-dur)	Magnesium, potassium	[4]
	Vitamin B1	[108]
	Vitamin B6	[108,109]
Thiazide diuretics	Magnesium	[62]
	Potassium, sodium	[8]
	Zinc	[42,43]
Thiosemicarbizide	Vitamin B6	[8]
Thyroid hormones	Calcium	[4]
Tobacco	Zinc	[8]
	Beta carotene	[8]
	Folic acid, vitamins B6, C, E	[8]
Tobramycin (AKTob, Nebicin, Tobrex – antibiotic)	Calcium	[110]
	Magnesium, potassium	[110]
	Vitamin K	[4]
Tolazamide	Coenzyme Q10	[8]
Tolbutamide	Sodium	[8]
Triamterene (Dyrenium)	Calcium	[10]
	Folic acid	[8]
Triazinate	Folic acid	[8]
Tricyclic antidepressants	Coenzyme Q10	[8]
	Vitamin B2	[8]
Trientine hydrochloride	Iron	[8]
Trimethoprim (Proloprim, Trimpex)	Folic acid	[8]
	Calcium, magnesium	[4]
	Vitamins B6, B12, K	[4]

Table I. Continued.

Drug or type of drug	Possible deficiency or interference	Reference
Valproic acid (Depakene)	L-carnitine	[111,112]
	Copper	[4,10]
	Selenium	[10]
	Zinc	[10]
	Folic acid	[8,10]
Ventolin (Albuterol/Salbutamol/Proventil)	Calcium	[4,10]
	Magnesium	[4,10]
	Phosphate	[4,10]
	Potassium	[4,10]
Vincristine	Sodium	[8]
	Potassium	[10]
Warfarin (Coumadin)	Vitamin K	[8]
Xipamide	Magnesium	[64]
	Zinc	[43]

side effects, sometimes because of causing nutrient deficiencies. Nutrients also interact with each other, often cooperatively, but sometimes in competition with each other.

Research already carried out suggests that deficiencies are caused by large numbers of drugs. This is not likely to be a popular topic for sponsoring research. So we probably know only a small proportion of these interactions.

Diuretics are commonly used drugs, which can cause deficiency of magnesium, potassium and vitamin B1. There is evidence that magnesium protects against potassium deficiency, vitamin B1 deactivation, hypertension, intravascular coagulation, diabetes, congestive heart failure, hyperlipidaemia, atherosclerosis, arrhythmia, myocardial infarction, preeclampsia, asthma, kidney and liver damage, migraine, multiple sclerosis, glaucoma, Alzheimer's disease, recurrent bacterial infection of cavities, fungal infection, premenstrual syndrome, hypochlorhydria, behavioural disorders, osteoporosis, mood swings, dental caries, hearing loss, cramps, muscle weakness, impotence, aggression, cancer, and iron accumulation. A person presenting with what may be temporary hypertension may find that the drug prescribed makes the condition permanent, as well as leading to other disastrous consequences [113–126]. Hypertension could be treated with magnesium, taurine and coenzyme Q10, salt reduction and the avoidance of liquorice. Alternatively, diuretics could be used together with magnesium and potassium.

A healthy person, with total cholesterol within the reference range, and an excellent HDL:LDL ratio may be advised to take a statin (HMG-CoA reductase inhibitor) drug, or choose to buy one over the counter. These drugs cause deficiency of coenzyme Q10, a nutrient which has been found to protect the heart against stress, and in particular, oxidative stress [127–128]. Coenzyme Q10 levels tend to drop with age. There is evidence that coenzyme Q10 protects against arrhythmia and heart failure, and that deficiency can cause ataxia [129–133]. It may reduce the pro-inflammatory cytokines, TNF-alpha and IL-6 [134], increase exercise capacity [130] or reduce high blood pressure [130]. It has been suggested that coenzyme Q10 be administered before cardiac surgery [135]. It may be taken together with statin drugs, without making them ineffective [136]. The bioavailability of coenzyme Q10 supplements may depend on their form [137]. As alternatives to statins, cholesterol may be reduced with sterols in macadamia nuts and oil, glycation of cholesterol could be reduced by avoiding milk, fruit juice and sugar [138], and anti-oxidants could be

used to reduce oxidation of glycated cholesterol [139]. Nicotinic acid, magnesium, chromium, lecithin and L-carnitine could be used to improve the total cholesterol:high density lipoprotein ratio [140–144].

Deficiencies that may be caused by drugs can have diverse effects. Riboflavin (vitamin B2) deficiency may be caused by adriamycin, amitriptylene, anticonvulsants, boron, chlorpromazine, ethanol, and oral contraceptives. Riboflavin is needed for electron transport, which is part of energy production [145–146]. It is also needed for production of sulphate, which is used in detoxification of amines and phenols [147]. Amitriptylene prescribed for a person with ME may intensify the exhaustion, unless riboflavin is supplemented. People with ME often have poor sulphate conjugation [147], and amitriptylene is likely to make this worse. Riboflavin is also needed to activate vitamin B6 [148–149]. People may have fits because of lack of activated vitamin B6 [150–152]. Anticonvulsants may worsen this, unless riboflavin is supplemented.

Vitamin D deficiency may be caused by many drugs (Table II), and excessive vitamin A. Epileptics in Sweden, who may have little exposure to sunlight, and whose food is fortified with much vitamin A [153], may have their risk of osteoporosis increased by taking phenytoin.

Polypharmacy may cause increased problems. Magnesium deficiency may cause anxiety [154], hypertension [119,155] and osteoporosis [156–157]. The patient may be prescribed drugs for each of these results of magnesium deficiency, resulting in a variety of further deficiencies. These may lead to further symptoms and the provision of more drugs.

Lifestyle may affect responses to drugs. Alcohol is detoxified mainly by alcohol dehydrogenase, followed by aldehyde dehydrogenase, and oxidase. High alcohol consumption also requires cytochrome P450 2E1 [158]. An alcoholic may have five times the normal CYP2E1 [158]. When drinking heavily, processing of other chemicals by CYP2E1 may be competitively inhibited. However, if admitted to hospital, and unable to obtain alcohol, he/she may cope very well with medicinal drugs, as the CYP2E1 is still available to process them [158]. A teetotaller may have a worse reaction to the same drugs.

People who are ill are likely to have nutritional deficiencies that contributed to the illness. Their responses to drugs will be affected by their genes, their food intake, their use of other

Table II. Drugs which may cause vitamin D deficiency.

Drug	Reference
Anticonvulsants	[25]
Bile acid sequestrants	[4]
Cholestyramine	[8]
Cimetidine	[47]
Colestipol	[8]
Corticosteroids	[4]
Glutethimide	[8]
Heparin	[73]
Isoniazid	[47]
Mineral oil	[4]
Neomycin	[4]
Phenobarbital	[8]
Phenolphthalein	[8]
Phenytoin	[8]
Primidone	[8]

drugs, recreational or medicinal, their age and gender, and the stresses to which they are subject.

Diets vary greatly in nutritional content. People who are already deficient will be more susceptible to the effects of drugs. Those already on drugs causing the same deficiencies, will be more at risk and those with genetic problems causing deficiency will also be at risk. People may have atypical forms of enzymes, which are less effective. An example of biochemical individuality involves the three siblings who consumed much chicken liver pâté. One died of vitamin A toxicity, one was very ill, and the third was apparently unaffected [159]. Stresses, like pregnancy, grief, infection, surgery, and excessive exercise contribute to deficiencies. Nutrients are lost in chronic or acute diarrhoea, or excessive sweating.

In order to avoid causing nutrient deficiencies when treating or trying to prevent disease, the following strategies could be considered:

a. Use non-drug treatments when these are available and effective; for example, supplementing nutrients that are already deficient and making changes to diet and exercise.
b. Manufacture drugs together with relevant nutrients where this is possible, so as to avoid causing deficiency.
c. Prescribe nutrients together with drugs, in separate containers, to avoid causing deficiency; for example, probiotics could be prescribed at a different time of day from antibiotics.
d. Prescribe smaller quantities of drugs, together with nutrient supplements, where they will act synergistically.
e. Label drugs clearly, and provide information in drug handbooks, so that the person prescribing them knows what deficiencies are likely to be produced, whether the relevant nutrients may be supplemented, and whether there is a level of supplementation that would inactivate the drug.
f. Require drug companies to fund research on deficiencies caused by their products.
g. Require medical schools to teach nutrition in greater depth, and to emphasize the nutritional deficiencies which may be caused by drugs.

Conclusion

Many drugs (including some commonly used, some used in combinations, and some available over the counter) cause deficiencies in nutrients, which can compromise health. The value of a drug treatment can be weighed against the consequences of deficiencies that may be caused. Drugs could be prescribed together with relevant nutritional supplements, where the supplements do not prevent the drug from working [160]. More research needs to be done, to identify deficiencies caused by drugs, in order to protect the public. This research could be taught to medical students and to doctors as part of their continuing professional development.

It is sometimes assumed that people whose diet provides recommended amounts of all the nutrients will not have deficiencies. Many people in affluent countries take one or more drugs for long periods of time, and may well have deficiencies in specific nutrients, or combinations of nutrients. Such deficiencies can lead to life-threatening conditions.

Those whose diets are deficient in essential nutrients, from lack of knowledge, cooking skills, money or inclination, may well experience side effects from drugs, when better nourished individuals do not.

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References

1. Trovato A, Nuhlicek DN, Midtling JE. Drug–nutrient interactions. Am Fam Physician 1991;44(5):1651–8.
2. White R, Ashworth A. How drug therapy can affect, threaten and compromise nutritional status. J Hum Nutr Diet 2000;13(2):119–129.
3. Kishi T, Fujita N, Eguchi T, Ueda K. Mechanism for reduction of serum folate by antiepileptic drugs during prolonged therapy. J Neurol Sci 1997;145(1):109–12.
4. Lininger SW, Gaby AR, Austin S, et al. A–Z Guide to Drug–herb–vitamin Interactions. Roseville, CA, USA: Healthnotes. Prima Publishing, 1999.
5. Sarter B. Coenzyme Q10 and cardiovascular disease: A review. J Cardiovasc Nurs 2002;16(4):9–20.
6. Pinto J, Raiczyk GB, Huang YP, Rivlin RS. New approaches to the possible prevention of side effects of chemotherapy by nutrition. Cancer 1986;58(8Suppl):1911–14.
7. Spencer H, Kramer L, Osis D, Wiatrowski E. Effects of aluminium hydroxide on fluoride and calcium metabolism. J Environ Pathol Toxicol Oncol 1985;6(1):33–41.
8. Werbach MR. Foundations of Nutritional Medicine: A Sourcebook of Clinical Research. Tarzana, CA, USA: Third Line Press, 1997.
9. Tsau YK, Tsai WY, Lu FL, Tsai WS, Chen CH. Symptomatic hypomagnesemia in children. Zhonghua Min Guo Xiao Er Ke Yi Xue Hui Za Zhi 1998;39(6):393–7.
10. Boullata JI, Armenti VT (eds). Handbook of Drug–Nutrient Interactions. Totowa, New Jersey, USA: Humana Press, 2004.
11. Pinto J, Huang YP, Rivlin RS. Inhibition of riboflavin metabolism in rat tissues by chlorpromazine, imipramine and amitryptyline. J Clin Invest 1981;67(5):1500–506.
12. Pinto J, Huang YP, Pelliccione N, Rivlin RS. Cardiac sensitivity to the inhibitory effects of chlorpromazine, imipramine and amitriptyline upon formation of flavins. Biochem Pharmacol 1982;31(21):3495–9.
13. Barcina Y, Ilundain A, Larralde J. Effect of amoxicillin, cephalexin, and tetracycline-HCl on intestinal L-leucine transport in the rat in vivo. Drug Nutr Interact 1988;5(4):283–8.
14. Marcus N, Garty BZ. Transient hypoparathyroidism due to amphotericin B-induced hypomagnesemia in a patient with beta-thalassemia. Ann Pharmacother 2001;35(9):1042–4.
15. Russell RM, Golner BB, Krasinski SD, Sadowski JA, Suter PM, Braun CL. Effect of antacid and H2 receptor antagonists on the intestinal absorption of folic acid. J Lab Clin Med 1988;112(4):458–63.
16. Spencer H, Kramer L. Osteoporosis, calcium requirement, and factors causing calcium loss. Clin Geriatr Med 1987;3(2):389–402.
17. Spencer H, Kramer L. The calcium requirement and factors causing calcium loss. Fed Proc 1986;45(12):2758–62.
18. Spencer H, Kramer L. Osteoporosis: Calcium, fluoride, and aluminium interactions. J Am Coll Nutr 1985;4(1):121–8.
19. Spencer H, Kramer L, Norris C, Osis D. Effect of small doses of aluminium-containing antacids on calcium and phosphorus metabolism. Arch Intern Med 1983;143(4):657–9.
20. Baik HW, Russell RM. Vitamin B12 deficiency in the elderly. Annu Rev Nutr 1999;19:357–77.
21. Dugina NN, Chebotareva TV, Mitrokhin SD. Large intestine dysbacteriosis and therapy efficacy in patients with respiratory tract tuberculosis in sanatoria. Antibiot Khimioter 2004;49(4):35–8.
22. Šušković J, Kos B, Goreta J, Matošić S. Role of lactic acid bacteria and bifidobacteria in synbiotic effect. Food Technol Biotechnol 2001;39(3):227–235.
23. Noda H, Akasaka N, Ohsugi M. Biotin production by bifidobacteria. J Nutr Sci Vitaminol (Tokyo) 1994;40(2):181–8.
24. Mock DM, Mock NI, Nelson RP, Lombard KA. Disturbances in biotin metabolism in children undergoing long-term anticonvulsant therapy. J Pediatr Gastroenterol Nutr 1998;26(3):245–50.
25. Krause KH, Bonjour JP, Berlit P, Kynast G, Schmidt-Gayk H, Schellenberg B. Effect of long-term treatment with antiepileptic drugs on the vitamin status. Drug Nutr Interact 1988;5(4):317–43.
26. Zelnik N, Fridkis I, Gruener N. Reduced carnitine and antiepileptic drugs: Cause relationship or co-existence? Acta Paedriatr 1995;84(1):93–5.

27. Lawrence VA, Loewenstein JE, Eichner ER. Aspirin and folate binding: in vivo and in vitro studies of serum binding and urinary excretion of endogenous folate. J Lab Clin Med 1984;103(6):944–8.
28. Rundek T, Naini A, Sacco R, Coates K, DiMauro S. Atorvastatin decreases the coenzyme Q10 level in the blood of patients at risk for cardiovascular disease and stroke. Arch Neurol 2004;61(6):889–92.
29. Baum MK, Javier JJ, Mantero-Atienza E, et al. Zidovudine-associated adverse reactions in a longitudinal study of asymptomatic HIV-1-infected homosexual males. J Aquir Immune Defic Syndr 1991;4(12):1218–26.
30. Probstfield JL, Lin TL, Peters J, Hunninghake DB. Carotenoids and vitamin A: The effect of hypocholesterolemic agents on serum levels. Metabolism 1985;34(1):88–91.
31. Ritsema GH, Eilers G. Potassium supplements prevent serious hypokalaemia in colon cleansing. Clin Radiol 1994;49(12):874–6.
32. Pinto JT, Rivlin RS. Drugs that promote renal excretion of riboflavin. Drug–Nutrient Interactions 1987;5:143–51.
33. Pinto J, Huang YP, McConnell RJ, Rivlin RS. Increased urinary riboflavin excretion resulting from boric acid ingestion. J Lab Clin Med 1978;92(1):126–34.
34. Harris SS, Dawson-Hughes B. Caffeine and bone loss in healthy postmenopausal women. Am J Clin Nutr 1994;60(4):573–8.
35. Golik A, Modai D, Averbukh Z, et al. Zinc metabolism in patients treated with captopril versus enalapril. Metabolism 1990;39(7):665–7.
36. Atkinson SA, Halton JM, Bradley C, Wu B, Barr RD. Bone and mineral abnormalities in childhood acute lymphoblastic leukemia: Influence of disease, drugs and nutrition. Int J Cancer 1998;11:35–9.
37. Guo CY, Halton JM, Barr RD, Atkinson SA. Hypomagnesemia associated with chemotherapy in patients treated for acute lymphoblastic leukemia: Possible mechanisms. Oncol Rep 2004;11(1):185–9.
38. Kaup SM, Greger JL. Effect of various chloride salts on the utilisation of phosphorus, calcium, and magnesium. J Nutr Biochem 1990;1(10):542–8.
39. Pinto J, Huang YP, Rivlin RS. Inhibition by chlorpromazine of thyroxine modulation of flavin metabolism in liver, cerebrum and cerebellum. Biochem Pharmacol 1985;34(1):93–5.
40. Pelliccione N, Pinto J, Huang YP, Rivlin RS. Accelerated development of riboflavin deficiency by treatment with chlorpromazine. Biochem Pharmacol 1983;32(19):2949–53.
41. Hirokawa CA, Gray DR. Chlorpropamide-induced hyponatremia in the veteran population. Ann Pharmacother 1992;26(10):1243–4.
42. Reyes AJ, Olhaberry JV, Leary WP, Lockett CJ, van der Byl K. Urinary zinc excretion, diuretics, zinc deficiency and some side-effects of diuretics. S Afr Med J 1983;64(24):936–41.
43. Reyes AJ, Leary WP, Lockett CJ, Alcocer. Diuretics and zinc. S Afr Med J 1982;62(11):373–5.
44. Leonard JP, Desager JP, Beckers C, Harvengt C. In vitro binding of various biological substances by two hypocholesterolaemic resins. Cholestyramine and colestipol. Arzneimittelforschung 1979;29(7):979–81.
45. Vroonhof K, van Rijn HJ, van Hattum J. Vitamin K deficiency and bleeding after long-term use of cholestyramine. Neth J Med 2003;61(1):19–21.
46. Sturniolo GC, Montino MC, Rossetto L, et al. Inhibition of gastric acid secretion reduces zinc absorption in man. J Am Coll Nutr 1991;10(4):372–5.
47. Bengoa JM, Bolt MJ, Rosenburg IH. Hepatic vitamin D 25-hydroxylase inhibition by cimetidine and isoniazid. J Lab Clin Med 1984;104(4):546–52.
48. Whang R, Whang DD, Ryan MP. Refractory potassium repletion. A consequence of magnesium deficiency. Arch Intern Med 1992;152(1):40–5.
49. Frequin ST, Wevers RA, Braam M, Barkhof F, Hommes OR. Decreased vitamin B12 and folate levels in cerebrospinal fluid and serum of multiple sclerosis patients after high-dose intravenous methylprednisolone. J Neurol 1993;240(5):305–8.
50. June CH, Thompson CB, Kennedy MS, Loughran TP Jr, Deeg HJ. Correlation of hypomagnesemia with the onset of cyclosporine-associated hypertension in marrow transplant patients. Transplantation 1986;41(1): 47–51.
51. Thompson CB, June CH, Sullivan KM, Thomas ED. Association between cyclosporin neurotoxicity and hypomagnesaemia. Lancet 1984;2(8412):1116–20.
52. June CH, Thompson CB, Kennedy MS, Nims J, Thomas ED. Profound hypomagnesemia and renal magnesium wasting associated with the use of cyclosporine for marrow transplantation. Transplantation 1985;39(6):620–24.
53. Whang R, Oei TO, Watanabe A. Frequency of hypomagnesemia in hospitalized patients receiving digitalis. Arch Intern Med 1985;145(4):655–6.
54. Leary WP, Reyes AJ. Prophylaxis and treatment of magnesium depletion. S Afr Med J 1983;64(8):281–2.

55. Reyes AJ, Leary WP. Diuretic therapy, magnesium deficiency and lipid metabolism. S Afr Med J 1983;64(10):355–6.
56. Reyes AJ, Leary WP. Magnesium deficiency provoked by diuretics. S Afr Med J 1983;63(11):410–12.
57. Reyes AJ, Leary WP. Cardiovascular toxicity of diuretics related to magnesium depletion. Hum Toxicol 1984;3(5):351–71.
58. Leary WP, Reyes AJ. Diuretic-induced magnesium losses. Drugs 1984;28 Suppl 1:182–7.
59. Dorup I, Skajaa K, Thybo NK. Oral magnesium supplementation restores the concentrations of magnesium, potassium and sodium–potassium pumps in skeletal muscle of patients receiving diuretic treatment. J Intern Med 1993;233(2):117–23.
60. Steen B. Hypokalemia—clinical spectrum and etiology. Acta Med Scand 1981;647:61–6.
61. Cohen N, Almoznino-Sarafian D, Zaidenstein R, et al. Serum magnesium aberrations in furosemide (frusemide) treated patients with congestive heart failure: Pathophysiological correlates and prognostic evaluation. Heart 2003;89(4):411–6.
62. Martin BJ, Milligan K. Diuretic-associated hypomagnesemia in the elderly. Arch Intern Med 1987;147(10):1768–71.
63. Reyes AJ, Leary WP. Pathogenesis of arrhythmogenic changes due to magnesium depletion. S Afr Med J 1983;64(9):311–12.
64. Reyes AJ, Leary WP. The magnesiuric effects of several single doses of xipamide in healthy adults. Braz J Med Biol Res 1984;17(3–4):285–91.
65. Brady JA, Rock CL, Horneffer MR. Thiamin status, diuretic medications, and the management of congestive heart failure. J Am Diet Assoc 1995;95(5):541–4.
66. Granerus AK, Jagenburg R, Svanborg A. Kaliuretic effect of L-dopa treatment in parkinsonian patients. Acta Med Scand 1977;201(4):291–7.
67. Pinto J, Huang YP, Rivlin RS. Mechanisms underlying the differential effects of ethanol on the bioavailability of riboflavin and flavin adenine dinucleotide. J Clin Invest 1987;79(5):1343–8.
68. Desouza C, Keebler M, McNamara DB, Fonseca V. Drugs affecting homocysteine metabolism: Impact on cardiovascular risk. Drugs 2002;62(4):605–16.
69. Childs PA, Rodin I, Martin NJ, et al. Effect of fluoxetine on melatonin in patients with seasonal affective disorder and matched controls. Br J Psychiatry 1995;166(2):196–8.
70. Strachan J, Shepherd J. Hyponatraemia associated with the use of selective serotonin re-uptake inhibitors. Aust N Z J Psychiatry 1998;32(2):295–8.
71. Mydlik M, Derzsiova K, Zemberova E. Influence of water and sodium diuresis and furosemide on urinary excretion of vitamin B(6), oxalic acid and vitamin C in chronic renal failure. Miner Electrolyte Metab 1999;25(4–6):352–6.
72. Shetty AK, Rogers NL, Mannick EE, Aviles DH. Syndrome of hypokalemic metabolic alkalosis and hypomagnesemia associated with gentamicin therapy: Case reports. Clin Pediatr (Phila) 2000;39(9):529–33.
73. Aarskog D, Aksnes L, Markestad T, Ulstein M, Sagen N. Heparin-induced inhibition of 1,25-dihydroxyvitamin D formation. Am J Obstet Gynecol 1984;148(8):1141–2.
74. Aymard JP, Aymard B, Netter P, Bannwarth B, Trechot P, Streiff F. Haematological adverse effects of histamine H2-receptor antagonists. J Med Toxicol Adverse Drug Exp 1988;3(6):430–48.
75. Vidrio H. Interaction with pyridoxal as a possible mechanism of hydralazine hypotension. J Cardiovasc Pharmacol 1990;15(1):150–56.
76. Reyes AJ, Leary WP, Van der Byl K. Urinary magnesium output after a single dose of indapamide in healthy adults. S Afr Med J 1983;64(21):820–22.
77. Ganchev T, Negrev N, Mileva V. Effects of indomethacin on erythropoiesis and plasma iron in rats. Acta Physiol Pharmacol Bulg 1989;15(2):53–7.
78. Fleming BJ, Genuth SM, Gould AB, Kamionkowski MD. Laxative-induced hypokalemia, sodium depletion and hyperreninemia. Effects of potassium and sodium replacement on the renin–angiotensin–aldosterone system. Ann Intern Med 1975;83(1):60–62.
79. Mercado R, Michelis MF. Severe sodium depletion syndrome during lithium carbonate therapy. Arch Intern Med 1977;137(12):1731–3.
80. Burnier M, Rutschmann B, Nussberger J, et al. Salt-dependent renal effects of an angiotensin II antagonist in healthy subjects. Hypertension 1993;22(3):339–47.
81. Folkers K, Langsjoen P, Willis R, Richardson P, Xia L-J, Ye C-Q, Tamagawa H. Lovastatin decreases coenzyme Q levels in humans. Proc Natl Acad Sci USA 1990;87:8931–4.
82. Mortensen SA, Leth A, Agner E, Rohde M. Dose-related decrease of serum coenzyme Q10 during treatment with HMG-CoA reductase inhibitors. Mol Aspects Med 1997;18(Suppl):S137–44.

83. Baggott JE, Morgan SL, Ha TS, Alarcon GS, Koopman WJ, Krumdieck CL. Antifolates in rheumatoid arthritis: A hypothetical mechanism of action. Clin Exp Rheumatol 1993;11(Suppl 8):S101–105.
84. Clark JH, Russell GJ, Fitzgerald JF, Nagamori KE. Serum beta-carotene, retinol, and alpha-tocopherol levels during mineral oil therapy for constipation. Am J Dis Child 1987;141(11):1210–12.
85. Koblin DD, Tomerson BW, Waldman FM, Lampe GH, Waulk LZ, Eger El 2nd. Effect of nitrous oxide on folate and vitamin B12 metabolism in patients. Anesth Analg 1990;71(6):610–17.
86. Flippo TS, Holder WD Jr. Neurologic degeneration associated with nitrous oxide anesthesia in patients with vitamin B12 deficiency. Arch Surg 1993;128(12):1391–5.
87. Ermens AA, Refsum H, Rupreht J, et al. Monitoring cobalamin inactivation during nitrous oxide anesthesia by determination of homocysteine and folate in plasma and urine. Clin Pharmacol Ther 1991;49(4):385–93.
88. Baggott JE, Morgan SL, Ha T, Vaughn WH, Hine RJ. Inhibition of folate-dependant enzymes by non-steroidal anti-inflammatory drugs. Biochem J 1992;282(1):197–202.
89. Bjarnason I, Macpherson AJ. Intestinal toxicity of non-steroidal anti-inflammatory drugs. Pharmacol Ther 1994;62(1–2):145–57.
90. Tang G, Serfaty-Lacrosniere C, Camilo ME, Russell RM. Gastric acidity influences the blood response to a beta carotene dose in humans. Am J Clin Nutr 1996;64(4):622–6.
91. Marcuard SP, Albernaz L, Khazanie PG. Omeprazole therapy causes malabsorption of cyanocobalamin (vitamin B12). Ann Intern Med 1994;120(3):211–15.
92. Blum M, Kitai E, Ariel Y, Schnierer M, Bograd H. Harefuah 1991;121(10):363–4.
93. Girdwood RH. Drug-induced anaemias. Drugs 1976;11(5):394–404.
94. Masse PG, van den Berg H, Duguay C, Beaulieu G, Simard JM. Early effect of a low dose (30 micrograms) ethinyl estradiol-containing Triphasil on vitamin B6 status. A follow-up study on six menstrual cycles. Int J Vitam Nutr Res 1996;66(1):46–54.
95. Melia AT, Koss-Twardy SG, Zhi J. The effect of orlistat, an inhibitor of dietary fat absorption, on the absorption of vitamins A and E in healthy volunteers. J Clin Pharmacol 1996;36(7):647–53.
96. Russell RM, Dutta SK, Oaks EV, Rosenberg IH, Giovetti AC. Impairment of folic acid absorption by oral pancreatic extracts. Dig Dis Sci 1980;25(5):369–73.
97. Reicks M, Calvert RJ, Hathcock JN. Effects of prolonged acetaminophen ingestion and dietary methionine on mouse liver glutathione. Drug Nutr Interact 1988;5(4):351–63.
98. Jones AF, Harvey JM, Vale JA. Hypophosphataemia and phosphaturia in paracetamol poisoning. Lancet 1989;2(8663):608–9.
99. Seelig MS. Auto-immune complications of D-penicillamine—a possible result of zinc and magnesium depletion and of pyridoxine inactivation. J Am Coll Nutr 1982;1(2):207–14.
100. Heller CA, Friedman PA. Pyridoxine deficiency and peripheral neuropathy associated with long-term phenelzine therapy. Am J Med 1983;75(5):887–8.
101. Seligmann H, Potasman I, Weller B, Schwartz M, Prokocimer M. Phenytoin–folic acid interaction: A lesson to be learned. Clin Neuropharmacol 1999;22(5):268–72.
102. Hanaki Y, Sugiyama S, Ozawa T, Ohno M. Coenzyme Q10 and coronary artery disease. Clin Invest 1993;71(8 Suppl):S112–5.
103. Lems WF, Van Veen GJ, Gerrits MI, et al. Effect of low dose prednisone (with calcium and calcitriol supplementation) on calcium and bone metabolism in healthy volunteers. Br J Rheumatol 1998;37(1):27–33.
104. Bouman WP, Pinner G, Johnson H. Incidence of selective serotonin reuptake inhibitor (SSRI) induced hyponatraemia due to the syndrome of inappropriate antidiuretic hormone (SIADH) secretion in the elderly. Int J Geriatr Psychiatry 1998;13(1):12–15.
105. Jula A, Marniemi J, Huupponen R, Virtanen A, Rastas M, Rönnemaa T. Effects of diet and simvastatin on serum lipids, insulin, and antioxidants in hypercholesterolemic men: A randomised controlled trial. JAMA 2002;287(5):598–605.
106. Moosmann B, Behl C. Selenoprotein synthesis and side-effects of statins. Lancet 2004;363(9412):892–4.
107. Baum CL, Selhub J, Rosenberg IH. Antifolate actions of sulfasalazine on intact lymphocytes. J Lab Clin Med 1981;97(6):779–84.
108. Shimizu T, Maeda S, Arakawa H, Mochizuki H, Tokuyama K, Morikawa A. Relation between theophylline and circulating vitamin levels in children with asthma. Pharmacology 1996;53(6):384–9.
109. Delport R, Ubbink JB, Serfontein WJ, Becker PJ, Walters L. Vitamin B6 nutritional status in asthma: The effect of theophylline therapy on plasma pyridoxal-5′-phosphate and pyridoxal levels. Int J Vitam Nutr Res 1988;58(1):67–72.
110. Slayton W, Anstine D, Lakhdir F, Sleasman J, Neiberger R. Tetany in a child with AIDS receiving intravenous tobramycin. South Med J 1996;89(11):1108–10.

111. Opala G, Winter S, Vance C, Vance H, Hutchison HT, Linn LS. The effect of valproic acid on plasma carnitine levels. Am J Dis Child 1991;145(9):999–1001.
112. Kendler BS. Carnitine: An overview of its role in preventive medicine. Prev Med 1986;15(4):373–90.
113. Johnson S. The multifaceted and widespread pathology of magnesium deficiency. Med Hypotheses 2001;56(2):163–70.
114. Rylander R, Arnaud MJ. Mineral water intake reduces blood pressure among subjects with low urinary magnesium and calcium levels. BMC Public Health 2004;4(1):56.
115. Yokota K, Kato M, Lister F, et al. Clinical efficacy of magnesium supplementation in patients with type 2 diabetes. J Am Coll Nutr 2004;23(5):506S–509S.
116. Gums JG. Magnesium in cardiovascular and other disorders. Am J Health Syst Pharm 2004;61(15):1569–76.
117. Maier JA, Malpuech-Brugere C, Zimowska W, Rayssiguier Y, Mazur A. Low magnesium promotes endothelial cell dysfunction: Implications for atherosclerosis, inflammation and thrombosis. Biochim Biophys Acta 2004;1689(1):13–21.
118. Touyz RM. Magnesium in clinical medicine. Front Biosci 2004;9:1278–93.
119. Touyz RM. Role of magnesium in the pathogenesis of hypertension. Mol Aspects Med 2003;24(1–3):107–36.
120. Carlin Schooley M, Franz KB. Magnesium deficiency during pregnancy in rats increases systolic blood pressure and plasma nitrite. Am J Hypertens 2002;15(12):1081–6.
121. Touyz RM, Pu Q, He G, et al. Effects of low dietary magnesium intake on development of hypertension in stroke-prone spontaneously hypertensive rats: role of reactive oxygen species. J Hypertens 2002;20(11):2221–32.
122. Chakraborti S, Chakraborti T, Mandal M, Mandal A, Das S, Ghosh S. Protective role of magnesium in cardiovascular diseases: A review. Mol cell Biochem 2002;238(1–2):163–79.
123. Walti MK, Zimmermann MB, Spinas GA, Jacob S, Hurrell RF. Dietary magnesium intake in type 2 diabetes. Eur J Clin Nutr 2002;56(5):409–14.
124. Innerarity S. Hypomagnesemia in acute and chronic illness. Crit Care Nurs Q 2000;23(2):1–19.
125. Fox C, Ramsoomair D, Carter C. Magnesium: Its proven and potential clinical significance. South Med J 2001;94(12):1195–201.
126. Seelig MS. Increased need for magnesium with the use of combined oestrogen and calcium for osteoporosis treatment. Magnes Res 1990;3(3):197–215.
127. Rosenfeldt F, Miller F, Nagley P, et al. Response of the senescent heart to stress: Clinical therapeutic strategies and quest for mitochondrial predictors of biological age. Ann N Y Acad Sci 2004;1019:78–84.
128. Lee CK, Pugh TD, Klopp RG, et al. The impact of alpha-lipoic acid, coenzyme Q10 and caloric restriction on life span and gene expression patterns in mice. Free Radic Biol Med 2004;36(8):1043–57.
129. Chung MK. Vitamins, supplements, herbal medicines, and arrhythmias. Cardiol Rev 2004;12(2):73–84.
130. Rosenfeldt F, Hilton D, Pepe S, Krum H. Systematic review of effect of coenzyme Q10 in physical exercise, hypertension and heart failure. Biofactors 2003;18(1–4):91–100.
131. Mortensen SA. Overview on coenzyme Q10 as adjunctive therapy in chronic heart failure. Rationale, design and end-points of 'Q-symbio'—A multinational trial. Biofactors 2003;18(1–4):79–89.
132. Berman M, Erman A, Ben-Gal T, et al. Coenzyme Q10 in patients with end-stage heart failure awaiting cardiac transplantation: a randomised, placebo-controlled study. Clin Cardiol 2004;27(5):295–9.
133. Naini A, Lewis VJ, Hirano M, DiMauro S. Primary coenzyme Q10 deficiency and the brain. Biofactors 2003;18(1–4):145–52.
134. Singh RB, Kartik C, Otsuka K, Pella D, Pella J. Brain–heart connection and the risk of heart attack. Biomed Pharmacother 2002;56 (Suppl 2):257s–265s.
135. Rosenfeldt F, Marasco S, Lyon W et al. Coenzyme Q10 therapy before cardiac surgery improves mitochondrial function and in vitro contractility of myocardial tissue. J Thorac Cardiovasc Surg 2005;129(1):25–32.
136. Langsjoen PH, Langsjoen AM. The clinical use of HMG CoA-reductase inhibitors and the associated depletion of coenzyme Q10. A review of animal and human publications. Biofactors 2003;18(1–4):101–11.
137. Kurowska EM, Dresser G, Deutsch L, Bassoo E, Freeman DJ. Relative bioavailability and antioxidant potential of two coenzyme q10 preparations. Ann Nutr Metab 2003;47(1):16–21.
138. Colaco CALS (ed.). The Glycation Hypothesis of Atherosclerosis. Austin, Texas: Chapman & Hall, 1997.
139. Leonarduzzi G, Sottero B, Verde V, Poli G. Oxidized products of cholesterol: Toxic effects. In: Preedy VR, Watson RR, editors. Reviews in Food and Nutrition Toxicity, Volume 3. Boca Raton, Florida: CRC Press, 2005.

140. Aronov DM, Keenan JM, Akhmedzhanov NM, Perova NV, Oganov RY, Kiseleva NY. Clinical trial of wax-matrix sustained-release niacin in a Russian population with hypercholesterolemia. Arch Fam Med 1996;5(10):567–75.
141. Press RI, Geller J, Evans GW. The effect of chromium picolinate on serum cholesterol and apolipoprotein fractions in human subjects. West J Med 1990;152(1):41–5.
142. Rosanoff A, Seelig MS. Comparison of mechanism and functional effects of magnesium and statin pharmaceuticals. J Am Coll Nutr 2004;23(5):501S–505S.
143. Diaz M, Lopez F, Hernandez F, Urbina JA. L-Carnitine effects on chemical composition of plasma lipoproteins of rabbits fed with normal and high cholesterol diets. Lipids 2000;35(6):627–32.
144. Brook JG, Linn S, Aviram M. Dietary soya lecithin decreases plasma triglyceride levels and inhibits collagen- and ADP-induced platelet aggregation. Biochem Med Metab Biol 1986;35(1):31–9.
145. Salway JG. Metabolism at a Glance. Oxford: Blackwell Science, 1994.
146. Berg JM, Tymoczko JL, Stryer L. Biochemistry. 5th edition. New York: W.H. Freeman and Co, 2002. p 518.
147. Moss M, Waring RH. The plasma cysteine/sulphate ratio: A possible clinical biomarker. J Nut Env Med 2003;13(4):215–229.
148. Abraham GE, Rumley RE. Role of nutrition in managing the premenstrual tension syndromes. J Reprod Med 1987;32(6):405–22.
149. Linder MC. Nutrition and metabolism of vitamins. In: Linder MC, editor. Nutritional Biochemistry and Metabolism with Clinical Applications. 2nd edition. East Norwalk, Connecticut: Prentice-Hall International, 1991. p 129.
150. Sheth RD, Stafstrom CE, Hsu D. Nonpharmacological treatment options for epilepsy. Semin Pediatr Neurol 2005;12(2):106–13.
151. Topcu I, Yentur EA, Kefi A, Ekici NZ, Sakarya M. Seizures, metabolic acidosis and coma resulting from acute isoniazid intoxication. Anaesth Intensive Care 2005;33(4):518–20.
152. Ramachandrannair R, Parameswaran M. Prevalence of pyridoxine dependent seizures in South Indian children with early onset intractable epilepsy: A hospital based prospective study. Eur J Paediatr Neurol 2005;9(6):409–13.
153. Michaëlsson K, Lithell H, Vessby B, Melhus H. Serum retinol levels and the risk of fracture. N Engl J Med 2003;348(4):287–94.
154. Seelig MS, Berger AR, Spielholz N. Latent tetany and anxiety, marginal magnesium deficit, and normocalcemia. Dis Nerv Syst 1975;36(8):461–5.
155. Rosanoff A. Magnesium and hypertension. Clin Calcium 2005;15(2):255–60.
156. Rude RK, Gruber HE. Magnesium deficiency and osteoporosis: animal and human observations. J Nutr Biochem 2004;15:710–716.
157. Matsuzaki H. Prevention of osteoporosis by foods and dietary supplements. Magnesium and bone metabolism. Clin Calcium 2006;16(10):59–64.
158. Lucas D. Dietary Alcohol and xenobiotics. In: Preedy VR, Watson RR, editors. Reviews in Food and Nutrition Toxicity, Volume 1. London: Taylor and Francis, 2003, pp 284–304.
159. Carpenter TO, Pettifor JM, Russell RM, et al. Severe hypervitaminosis A in siblings: Evidence of variable tolerance to retinol intake. J Pediatr 1987;111(4):507–12.
160. Seelig MS, Alba A, Berger AR, Rudez A, Tarlau M. Pilot study of D-penicillamine, vitamins and minerals in multiple sclerosis. J Clin Psychiatry 1978;39(2):1702–4.