Introduce physiological functioning requires optimal nutrition, which needs to be in balance to prevent potential detrimental interactions, especially when administered at pharmacological dosages. Many nutrients function in harmony to complement digestive function and assimilation. Some may hinder these processes and compete for uptake, while others may also be required in tandem to assist in metabolism which may ultimately affect a number biochemical cycles.

Many similar synergistic and antagonistic functions exist within human physiology and should be considered, particularly in the health and research arenas, where positive outcomes may be more likely if nutrient preparations are formulated with assistant supplementary nutrients, while nutrient related confounders need also to be accounted for. A variety of these are discussed in detail, with emphasis on relationships in health and disease.

Introduction

Appropriate physiological functioning requires optimal nutrition, which need to be in balance to prevent potential detrimental interactions, especially when taken at pharmacological dosages. Many micronutrients function in harmony to complement digestive function and assimilation such as the requirement of adequate vitamin D for calcium absorption. Others may hinder these processes and compete for uptake, for instance the effect of zinc on copper or iron on zinc absorption. Folate and vitamin B12 are also required, in tandem, to assist in metabolism which ultimately affects a number biochemical cycles such as methylation, transulfuration and one-carbon metabolism, the later also requiring vitamins B2 and B6.
Zinc is required in sufficient amounts to maintain vitamin A status due to its regulatory role in vitamin A transport via synthesis of retinol-binding protein. Zinc is also an indispensable enzyme cofactor for the vitamin A metabolic pathway which requires oxidative conversion from retinol to retinaldehyde, as commonly described in the visual cycle of the retina.

Many similar synergistic and antagonistic functions exist within human physiology and ought to be considered, particularly in the health and research arenas, where positive outcomes may be more likely if nutrient preparations are formulated with assistant supplementary nutrients. Antagonistic confounders need also be considered to improve the quality and precision of both clinical treatments and research findings.

A variety of other factors may influence micronutrient status and therefore should be taken into account if a particular deficiency is suspected or a specific condition present, in order to optimise a patient’s health. Aside from the effect of other nutrients on micronutrient status, a number of disease conditions and food substances can increase the need for a particular nutrient, while others may interfere with absorptive or excretion capacity. Other considerations such as medications and other drug usage, which subsequently affect the nutrition and biochemistry in human subjects, have been added as a drug–nutrient interaction table at the conclusion of the chapter The influence of gut microbiota, also warrants consideration and further investigation.

Calcium and Vitamin D

The most well established synergism which exists between calcium and vitamin D is that of the latter being required for the synthesis of the calcium transport protein calbindin, which facilitates the uptake of calcium through the intestinal mucosa. Its absorption also occurs passively, although to a lesser degree and is positively associated with intake [1]. Despite this mechanism, it is difficult to acquire enough calcium solely through passive transport, therefore adequate vitamin D is necessary for the function of the active transport mechanisms [1]. Even with an increase in calcium absorption, elicited from parathyroid hormone in response to its insufficiency, quantitatively this mechanism is not sufficient to ameliorate a deficiency in the absence of adequate vitamin D [2].

Calcium also plays a role in vitamin D metabolism, which is hypothesised to be due to the fact that high calcium decreases calcitriol levels, which is known to shorten the half life of 25(OH)D, and as such lowers vitamin D status due to an upregulation of degradative mechanisms [3]. A study on healthy adults by Berlin and Bjorkhem, provided subjects with 2000mg supplemental calcium and resulted in a 20% decrease in serum 1,25(OH)2D and 30% increase in 25(OH)D [4]. Here it appears that the change in serum 1,25(OH)2D intercedes the change in 25(OH)D metabolism [3].

The positive skeletal effects of adequate calcium and vitamin D have been well established. In such studies, a number of additional variables may exist and if not considered, potentially confound results.

These include sexual maturity, race and skin colour, genetics, lean mass and season, as well as dietary intakes of these nutrients, proteins and sodium [5]. During adolescence, bone accretion peaks around the time of the pubertal spurt, with majority tending to occur over a
period of approximately 2 years, either side of peak height velocity. In these instances it is necessary to account for stage of sexual maturity, although precise estimates of this mechanism relating to peak bone mineral content accrual is not definitive [6].

The inverse association between intakes of calcium and vitamin D with both breast cancer and mammographic densities [7, 8] has been shown to be significant. Many studies are now available linking low vitamin D status to increase cancer risk [9] as well as high calcium intakes and reduced cancer risk, mainly that of colorectal cancer [10]. Aside from the synergistic effects between the 2 nutrients, the effect of high calcium diets in colon cancer is also thought to be due to its binding of cancer promoters within the digestive tract [11], as well as systemically via its role in modulating intercellular adhesion [12].

And Protein

Low protein diets can affect calcium absorption [13] and further contribute to a decrease in bone mineral density [14]. On the other hand, diets high in protein increase the urinary excretion of calcium, which is not compensated by increased calcium absorption [15] and is thought to occur due to an increased acid load. Research has shown that utilising supplemental bicarbonate or citrate [16], reduces urine calcium losses via the correction of the metabolic acidosis [17] induced by sulphur amino acids and the typical Western Diet [18]. A study by Hannan et al demonstrated lower protein intakes in elderly significantly related to changes in bone loss over a 4 year period, after controlling for known confounders [14] In healthy menopausal women, increasing dietary protein from 10% to 20% of energy, improved calcium absorption from a low-calcium diet and increased serum insulin-like growth factor I without affecting parathyroid hormone [19]. Caffeine and sodium have also been shown to increase urinary calcium losses, which displayed a greater effect in black than white female adolescents [20].

And Other Foods

Calcium absorption in the intestine also may be inhibited by the presence of oxalate, which is found in a variety of vegetables such as spinach, beets, celery, eggplant, greens, okra and squash, as well as fruits such as strawberries, blackberries, blueberries, gooseberries, currants, pecan nuts, peanuts, beverages such as tea, Ovaltine and cocoa. Oxalate chelates calcium and increases fecal excretion of the complex, although may be inactivated by heating [21] Phytates and tannins found in a variety of foods similarly complex with calcium reducing its absorption [22].

And Other Micronutrients

Divalent cations such as magnesium and calcium compete for intestinal absorption whenever an excess of either is in the gastrointestinal tract, while diets high in phosphorus
relative to calcium have also been shown to impair calcium balance [21]. Calcium deficiency may also occur in response to a deficiency in magnesium [23].

**And Conditions**

Hypoparathyroidism [24], hypomagnesemia [25], phosphate supplementation and impaired vitamin D synthesis, are also associated with depression of serum calcium levels [23]. Calcium absorption may also be decreased with age, diabetes, chronic renal failure, nontropical sprue and primary biliary cirrhosis [24]. Malabsorption is also associated with gastrointestinal diseases such as Crohn’s and coeliac disease, intestinal resection or bypass [21]. Contrary, hyperparathyroidism is the most common cause of hypercalcemia [24], while may also be associated with hyperthyroidism, sarcoidosis and when large parts of the body are immobilised, as well as in patients with kidney stones and during vitamin D intoxication, the latter usually due to excessive absorption [26].

Vitamin D deficiency may be exacerbated by nephrotic syndrome, advanced renal failure, chronic liver diseases and severe small-bowel disease, Fanconi syndrome, neonatal hypocalcaemia, osteomalacia, osteoporosis, renal osteodystrophy [27], bowel resection, celiac disease, inflammatory bowel disease, malabsorption, pancreatic insufficiency or thyrotoxicosis [28]. Lack of exposure to UV light combined with a bad diet [27], may the greatest contributor in the general population. Increased vitamin D levels occur in primary hyperparathyroidism associated with hypophosphatemia, vitamin D-dependent rickets type II or sarcoidosis [27]. In all, attempting to separate the beneficial effects of both calcium and vitamin D may be inappropriate, as their synergism far outweighs a reductionist scientific approach to establish value of each as a separate entity [1].

**Iron**

Unlike other minerals iron status is regulated solely by absorption and is influenced both positively and negatively by a number of factors [29].

**And Vitamin C**

Ascorbic acid is by far the most effective synergist for iron absorption, particularly in meals containing antagonists, due to it facilitating the reduction of ferric to ferrous iron. This role in iron chemistry highlights the fact that these nutrients should to be consumed together to confer absorptive benefits [30]. With low to medium levels of other antagonists, ascorbate is required at a molar ratio of 2:1, for example 20mg ascorbate:3 mg iron, due to its greater molecular weight, while during high level competition the ratio needs to be in excess of 4:1 [31].

Other organic acids may only act synergistically in ratios in excess of 100 molar, such that the presence or addition of 1g of citric acid would be needed to enhance 3mg of iron. At these levels, fortification vehicles are limited to condiments or beverages, although fermented
foods which naturally have high levels of organic acids would also be suitable [31]. While ascorbic acid enhances the absorption of non-haeme iron from foods consumed at the same meal, absorption of haem iron is not affected by vitamin C intake [32]. Ascorbic acid suffers from issues with stability and is sensitive to heat, light, oxygen, copper, excessive iron and tin [33], therefore can suffer diminishing values during food processing and preparation. It appears that temperature and length of cooking time is positively associated with ascorbate losses [31]. Vitamin C status may also be reduced physiologically via the use of pharmaceutical preparations particularly if chronically ingested. These include oral contraceptive agents [26] and aspirin containing compounds [34]. Deficiency can occur secondary to some disease states such as liver disease, cancer, hyperthyroidism, rheumatoid disease and GI disorders [28]. Cigarette smoking, alcohol and other environmental exposures increase its usage, while acute infection and stress may increase urinary excretion [26].

**And Food Constituents**

Phytates and polyphenols are great antagonists of iron absorption, particularly at low levels [31]. 2 mg of phytate has been shown to decrease absorption by approximately 18% [35] while 12mg of tannic acid displayed 30% reduction [36]. These are of particular importance when attempting to improve iron nutrition or researching the effects of iron supplementation, due to their high level propensity for antagonism.

Many grain products contain phytates which have been shown to act dose dependently, starting at very low concentrations and depending on whether additional synergists are also present. An estimated molar ratio for phytate to iron, in the presence of an enhancer such as vitamin C needs to be less than 6:1, while without less than 1:1 to maximise iron absorption within a meal [37]. Processes such as milling, heating, soaking or fermenting can degrade phytates to varying extents [38]. Phenolic compounds exist in a large range of foods and beverages, such as tea, coffee, berries and fruits. When released during digestion, these substances complex with iron in the intestines rendering it unabsorbable. Unlike phytates, both the quantity and type of polyphenol, influences the level of antagonism on iron absorption. For example a study conducted in Thailand found chilli, but not turmeric, formed iron complexes despite the latter containing higher levels of phenols [39]. In relation to beverages, black tea, coffee and peppermint tea display the strongest inhibition properties, ranging from 79-94%, while to a lesser extent pennyroyal 73%, cocoa 71%, vervain 59%, lime flower 52% and chamomile tea 47% also bind iron molecules in the intestinal lumen [40]. Polyphenol rich vegetables such as spinach and eggplant have also been negatively associated with iron absorption which is reported to be related to content [42].

**And Proteins**

The consumption of muscle tissue possesses synergistic effects on iron absorption from non-haem sources, where 30g of muscle tissue has been found to be equivalent to 25mg ascorbic acid [42]. It is thought that cysteine containing peptides within the myofibrillar proteins both reduce and chelate iron, similar to ascorbate [43]. Other mechanisms have also been hypothesized [29]. Despite animal tissues containing the more easily absorbable form of
haem iron and enhancing the effects of non-haem iron, animal proteins such as whey and casein from milk and dairy products, as well as egg proteins and albumin [44], have all demonstrated iron antagonism in humans. Soy protein has also been shown to inhibit iron absorption. Despite majority of iron inhibition caused by its high level of phytates, their removal still lead to decreases in iron absorption to levels by half that of the egg white control [45].

And B2

Riboflavin and iron are co-dependent, whereby iron metabolism is hindered in the presence of riboflavin deficiency [46] and correction if this deficiency has also been shown to improve response to iron supplements [47]. A study conducted on Gambian men and children with poor haematological status, demonstrated after 6 weeks of supplementation with iron, iron and riboflavin or placebo, improvements in the 2 supplemented groups. The additional riboflavin did however confer extra benefit, especially in those with the lowest levels of baseline haemoglobin [48]. Conditions such as alcoholism [49], diabetes mellitus, thyroid and adrenal insufficiency, liver disease and gastrointestinal or biliary obstruction [26] affect B2 status. Caffeine and saccharin have been shown to form chelates or complexes that may affect its bioavailability [50]. PEM leads to increased urinary losses of B2, while exercise increases requirements [51].

And Copper

Copper binds to either albumin or a2-macroglobulin for delivery to the liver in portal blood from enterocytes. Here, levels of copper have an inverse relationship to iron status for unknown reasons [52]. A study looking at levels of trace elements in infant formulas found higher levels of iron caused negative effects on copper status [53]. The utilisation of iron for the formation of haemoglobin by bone marrow is copper dependent. Therefore anaemia may occur in the presence of normal serum iron levels [54]. Copper deficiency has been shown to reduce iron absorption in animal models, which is believed to be due to intestinal iron transports being copper dependent [52].

And Other Micronutrients

High levels of zinc decrease iron bioavailability, but it is not entirely clear whether this is a direct effect or is mediated indirectly through the copper effect on iron metabolism [55]. Intakes at a ratio of 3:1 iron to zinc is desirable to prevent competitive interference [56]. Vitamin A is involved in several stages of iron metabolism including erythropoiesis and its release from ferritin stores [57]. Therefore in vitamin A deficiency, anaemia can occur which cannot be corrected with iron supplementation alone [28]. Carotenoids such as lycopene, lutein and zeaxanthin have been demonstrated to increase iron absorption 2-3 fold, when 2-4mg was added as a flour fortificant [58]. Calcium has demonstrated dose-dependent
antagonistic effects of both haem and non-haem iron, with maximal inhibition of 60%, occurring at calcium doses of 300-600mg [59]. This inhibition is now thought to occur during uptake into enterocytes [60], despite being originally thought to occur during membrane transport. The effect is shown to be prominent in single-meal studies, with limited effects in multi-meal studies containing a wide variety of foods [61].

High levels of manganese interfere with iron metabolism as shown by decreased haemoglobin concentrations and reversal by dietary iron supplementation [55]. Copper deficiency can also diminish iron status, via influencing iron metabolism and absorption [32].

And Conditions

Lead poisoning may also be associated with iron deficiency as absorption of lead may be increased under these conditions. As lead and iron share a common absorptive mechanism, lead uptake is enhanced in iron deficiency [62]. Obesity has been demonstrated to increase inflammation and decrease iron absorption, independent of iron status [63], while overweight children have also been documented to have lower iron levels than those children within their weight for height range, despite intakes being similar [64]. Achlorhydria originating either endogenous or exogenous by long-term use of gastric acid suppressant medications, can lead to iron deficiency anaemia via the reduced ability to solubilise nonhaem iron from foods. An inverse relationship between gastric pH and percentage of iron absorption has been established [65].

Zinc

Zinc homeostasis is regulated by the intestines, with both absorption and saturation kinetics of the zinc transporters into and across the enterocytes playing a role. Regulation of absorption via body zinc status only plays a minor role [66], while maximal saturation in adults is approximately 6mg per day [67]. At high intakes, paracellular zinc absorption is thought to occur [21]. Zinc status and recent intake regulates levels of intestinal excretion, to maintain an adequate whole body zinc pool [68].

In relation to supplements, the solubility of the zinc salt determines its absorptive capacity. Zinc sulphate and chloride have the highest solubility and zinc acetate is freely soluble, while zinc carbonate and oxide are mostly insoluble [69]. Gastric pH was also found to be a confounding factor. In the presence of a low pH <3, plasma zinc was 40% higher for zinc acetate supplements, than for zinc oxide. When pH was >5, zinc acetate absorption was reduced by 28% and zinc oxide by 82%, no healthy volunteers [70].

And Phytates

Majority of dietary zinc inhibition is known to occur with co-consumption of phytates, with daily zinc requirements doubling in its presence of 1000mg per day [68]. A major factor contributing to zinc deficiency in developing countries are plant based diets with high phytate
to zinc ratios [71]. An endogenous resorption mechanism which exists in the small bowel, to assist with the maintenance of zinc status, may suffer interference by the presence of certain dietary factors such as phytate or unabsorbed fat. This mechanism has been demonstrated in infants with fat malabsorption disorders [72]. Fibre is often implicated in antagonising zinc, although this is due to the high phytate content of most fibre containing foods. Fibre itself has little effect on zinc absorption [73]. The consumption of tea, coffee may also affect absorption via containing tannins which bind with zinc, forming insoluble complexes [74].

And Proteins

Total protein in a single meal is positively associated with zinc absorption [75]. Casein, however, has been shown to have a negative effect, thought likely to be due to phosphorylated serine and threonine residues of partially undigested casein binding to zinc and reducing its bioavailability, similar to that of iron [76].

Amino acid chelator histidine binds to zinc, enhances its absorption and hence increases plasma levels [77]. Despite this benefit, high levels of histidine has been shown to increase its urinary excretion [78], therefore molar ratios of the two substances is vitally important.

And Vitamin A

Zinc plays an indispensible role in vitamin A metabolism, where it regulates vitamin A transport which is believed to occur via its role in protein synthesis [79]. Retinol dehydrogenase is a zinc-dependent enzyme and is needed for the important metabolic conversion of retinol to retinal [80]. Zinc deficiency has also been shown to affect the absorption of vitamin A via impairing biliary secretion and hence the formation of chylomicrons necessary to uptake fats and fat soluble vitamins [81].

Zinc absorption is also affected by vitamin A status and as such is necessary to maintain adequate zinc status. Research has demonstrated reduced zinc uptake by 40% throughout the small intestine and 57% in the ileum, in vitamin deficient animal models. Supplementation of retinyl acetate increased ileal zinc uptake 3-fold and was believed to be modulated via vitamin A dependent synthesis of a zinc binding protein in the ileal mucosa [82].

The interdependent relationship between zinc and vitamin A also requires adequate protein, while protein metabolism requires both zinc [79] and vitamin A [83]. This latter relationship is a particularly important confounding variable in malnourished populations, where interventions with these nutrients may be carried out without protein energy considerations within the population.

Pre-existing conditions which may affect vitamin A status include abetalipoproteinaemia, carcinoid syndrome, chronic infections, cystic fibrosis, disseminated tuberculosis, hypothyroidism [28], liver disease or a systemic inflammatory response [84]. Diseases which cause fat malabsorption, including impaired pancreatic and/or biliary secretions such as Crohn’s and celiac disease, radiation enteritis, ileal resection or damage affect vitamin A absorption [85]. Pre-term infants are generally considered to be at risk of deficiency because their plasma retinol concentrations are usually low [24].
And Other Micronutrients

Riboflavin in this form or in its activated form flavin adenine dinucleotide or FAD, has been shown to act as an organic ligand which complexes with zinc, protecting it from precipitation into an insoluble form and thus acts as a synergist [86].

The absorption of copper is thought to be modulated via intake concentrations, where lower intakes have a higher percentage of utilization [87]. High levels of zinc have been shown to act as a copper antagonist, affecting uptake from both the stomach and duodenum [88]. A study in chicks demonstrated there was a significant increase in mortality and decrease in growth in copper deficient compared to control animals when administered high levels of zinc due to the exacerbation of the copper deficiency [89].

Studies have demonstrated high levels of iron supplementation at doses ranging between 164-395mg to antagonise zinc, as demonstrated by reduced plasma zinc levels during pregnancy [90] and reduced absorption during lactation [91]. However, Harvey et al. showed that 100mg/d of iron consumed with meals had no observable effects on zinc metabolism [92]. In another study, a molar ratio of iron to zinc intake of 25:1 displayed antagonism, while a ratio of 2.5:1 did not in a water solution, however no inhibitory effect at either doses was seen when added to a meal [93].

And Conditions

Malabsorption syndromes such as Crohn’s disease, short bowel syndrome and cystic fibrosis have been shown to affect zinc status [94]. Increased urinary losses occur during alcohol consumption and infections, while also occurs with liver cirrhosis, diabetes mellitus, renal tubular diseases, anorexia, starvation, burns, dialysis, pregnancy and oral contraceptive use [51]. Gastric acid secretion inhibition and disease processes such as infection, surgery, pancreatic insufficiency and alcoholism, may alter zinc absorption in humans [74].

As albumin appears to be the major portal carrier for newly absorbed zinc, changes in the systemic level of albumin, such as inflammation or protein deficiency may also alter zinc balance [74], while excessive levels of protein intake enhance urinary excretion [15].

Sodium and Potassium

The high sodium levels in convenience and processed foods [95] warrants consideration as high sodium diets have been associated with increased risk of bone demineralisation, stomach cancer and kidney stones [96], as well as the large body of evidence linking high intakes with hypertension and cardiovascular diseases [97]. Studies have outlined processed meats and commercially prepared sauces and spreads, as well as breads as containing levels of sodium above reasonable standards [98]. In contrast high potassium intakes have demonstrated blood pressure lowering effect and are also associated with a decreased risk of cardiovascular disease, bone demineralisation and kidney stones, potentially negating the harmful effects of high sodium intakes [96, 99]. The positively associated effect of sodium
and negative effect of potassium on blood pressure have been confirmed in meta-analyses of clinical trials, the latter independent of sodium intake.

Potassium intakes have also been positively correlated with bone mineral density in a cohort of well-nourished, calcium replete 8 year old children, independent of lean body mass. This effect of potassium has been attributed to alterations in renal handling of electrolytes, namely increasing calcium resorption and sodium excretion. Likewise, potassium deficiency can increase calcium excretion. Studies in adults suggest both potassium and magnesium intake may be important in maintaining bone mass, believed to be through decreasing potential metabolic acidosis.

And Magnesium

Potassium depletion and hypophosphatemia stimulates magnesium excretion. Magnesium also shares a common renal reabsorption pathway with sodium, therefore increased sodium results in magnesium status, while intakes of protein 30g/d may also reduce magnesium absorption. High dietary fibre, phytate, oxalate and phosphate intakes reduce Mg absorption by binding its cations. CVD, myocardial infarction, toxæmia of pregnancy, hypertension or post-surgical complications, excessive vomiting and diarrhea and burns, protein malnutrition, malabsorption syndromes, endocrine disorders such as diabetes mellitus, parathyroid disease, hyperparathyroidism with hypercalcemia, hyperthyroidism and hyperaldosteronism, have all been shown to affect magnesium. Alcoholism, chronic glomerulonephritis, haemodialysis, pancreatitis, severe loss of body fluids as in diarrhoea, sweating and laxative abuse are also confounding variables, while pregnancy and lactation may require increased magnesium intakes. On the contrary, magnesium levels be increased in Addison’s disease, adrenocortical insufficiency, severe diabetic acidosis, multiple myeloma, overuse of antacids, renal insufficiency, SLE and tissue trauma, while may also occur as a result of increased PTH, hypocalcemia, fluid depletion and hypothyroidism which inhibits magnesium excretion.

Folate and Vitamin B12

Folate and vitamin B12 play an indispensable role in the methylation cycle, which is the sole methyl group donor in numerous biochemical reactions within the central nervous system and elsewhere, such as neurotransmitter synthesis, hepatocellular detoxification, nerve myelination and DNA stabilization. This cycle is also needed to be functioning adequately for one-carbon metabolism which facilitates purine and thymidylate formation, hence in DNA synthesis and replication needed for cell repair, growth and development.

Methylation dysfunction may occur in the presence of vitamin deficiencies such as vitamin B12 and folate, as well as abnormalities in their metabolism. B12 deficiency may induce a secondary folate deficiency by reducing methionine synthase (MS) enzyme activity, which activates folate. Studies have reported that supplemental folate accrues in
a B12 deficiency [112], via MS inactivity and therefore compromises the ability to utilise intracellular folate [113].

And Conditions

Hyperthyroidism, pregnancy, haemolytic anaemia, need for intensive care or any other sustained metabolic drain, may increase folate need up to six-to-eight fold [114]. Malabsorption of folate, secondary to an infection with Giardia Lamblia and bacterial overgrowth has also been documented [26]. Achlorhydria, oral contraceptive agents [115], oral oestrogen and antacids [116] may affect folate absorption or metabolism. Inadequate peptic digestion and gastric acid [117], pancreatic insufficiency [85] and alcoholism may result in B12 deficiency due to inadequate digestion and absorption, as well as enhanced utilization and excretion [118]. Its uptake occurs through receptor sites in the ileum and requires an alkaline pH and the presence of calcium [26]. Bacterial overgrowth [119], tropical or non-tropical sprue, Crohn’s disease, inflammatory bowel disease may cause decreased B13 levels [28], as the commensal bacteria found in an adequately functioning bowel contribute to the synthesis of some of the bodies B12.

Drug – Nutrient Interactions

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<td>Gentamicin</td>
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<td>Digoxin</td>
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<tr>
<td>Calcium</td>
<td>Synthetic thyroid hormone</td>
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<td></td>
<td>H2 blockers</td>
<td>[137]</td>
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<td>Aminoglycosides</td>
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<td>Zinc</td>
<td>ACE Inhibitors – captopril, enalpril</td>
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<td>Oral contraceptives</td>
<td>[139]</td>
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<td>H2 blockers</td>
<td>[121]</td>
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<tr>
<td>Iron</td>
<td>NSAID’s</td>
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<td>Calcium channel blockers</td>
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<td>Selenium</td>
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<td>Iodine</td>
<td>Bacterial products of Escherichia coli in drinking water</td>
<td>[122]</td>
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