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Abbreviated Class Review: Vitamins and Electrolytes (Potassium, Magnesium, and Phosphate Supplementation)

Month/Year of Review: September 2014 **End date of literature search:** August 2014
PDL Class: None

Research Questions:

- Is there evidence to support and cover the use of specific products with good value?
- Are certain reformulations of vitamins more effective than safer than individual components or other formulations?
- Are there subpopulations that certain vitamins are more effective or safer than others?
- Is there evidence that supplementation improves clinical outcomes?

Conclusions:

- There is moderate to high quality evidence that increased potassium intake reduces blood pressure in adults and low quality evidence for reduced risk of stroke. [1] It is recommended to get potassium intake from dietary sources. There is additional evidence that potassium supplementation with oral potassium supplements has no significant effect on blood pressure. [2]
- Patients with drug-related hypokalemia (therapy with a diuretic) should receive potassium supplementation. Potassium chloride is the most effective for replacing acute potassium loss and is effective for the most common causes of potassium depletion.[10] All potassium formulations (liquid and tablets) are readily absorbed. Potassium phosphate is most commonly used to replace phosphate losses and potassium bicarbonate is recommended in the setting of metabolic acidosis.
- There is insufficient and conflicting evidence on the relationship of magnesium supplementation and blood pressure. There is insufficient evidence for any other benefit in magnesium supplementation, other than in nutritional deficiency.
- Mild to moderate hypophosphatemia in ambulatory patients can be treated with oral phosphate replacement therapy. There is no evidence of improved outcomes for routine supplementation in patients without hypophosphatemia

Recommendations:

- Evaluate comparative costs in executive session to list specific agents as preferred and non-preferred.
- Include a formulation of the different potassium salt supplements due to different clinical considerations.

- Designate KCl packets & Potassium Gluconate as NP. Make OTC K+ Not Covered.
- Make all Magnesium ER & DR non-preferred and all IR formulations preferred
- Designate all phosphorus products preferred.

Reason for Review:
In March, 2014, the multivitamins and antioxidant multivitamins were reviewed for clinical efficacy/effectiveness and safety. Prior authorization was proposed for multivitamins and antioxidant multivitamin supplements to approve for documented nutritional deficiency or diagnosis associated with nutritional deficiency. For mono vitamin supplements, including calcium, vitamin D, folic acid, vitamin B, and the ferrous salt formulations, specific agents were listed as preferred and non-preferred based on cost comparisons when no clinical advantage was identified. The additional minerals, electrolytes, and vitamins will be reviewed similarly.

Background:
Complementary and alternative medicine refers to preventive and therapeutic modalities not considered to be part of conventional medicine.[3] This includes dietary supplements and has increased dramatically in North America recently in general populations, as well as CVD populations. Evidence of both benefits and harms of adding supplements to medical treatments has been reported, and there remains debate concerning the efficacy and safety of dietary supplements [4] Safety concerns include the potential adverse effects, contamination of preparations, and mislabeling. Dietary supplements are regulated with much less rigor than prescription medications.[5] While randomized controlled trials are the gold standard for evidence based medicine, data on the efficacy and safety of dietary supplements is lacking, insufficient, or inconsistent. There is also a paucity of standardized guidelines for the use of these products. Even if there is guidance and/or evidence that a particular vitamin or dietary supplement may benefit patients, the question of which manufacturer or product to recommend is also raised. There are quality assessment programs available to ensure the quality of these products. This includes consumerlab.com, NSF International, and US pharmacopeia. Currently there are no specific vitamin policies under the Oregon Health Plan. A multivitamin with folic acid is included in the prevention table for pregnant patients.

Nutrient deficiencies are a public health concern in many countries in the world. RCTs in children in developing nations have shown that vitamin A supplementation decreases morbidity and all-cause mortality. However, the benefit of these supplements in nonpregnant adults in the US and other Western nations is less clear.[6] Malnutrition is both a cause and effect of poor health.[7] Factors contributing to disease related malnutrition include impaired intake (confusion, medication, poor appetite), impaired digestion and/or absorption (medical and surgical problems effecting the stomach, intestine, pancreas, and liver), altered requirements (increased metabolic demands), excess losses (vomiting, diarrhea, fistulae, stomas, burns). The National Institute for Health and Clinical Excellence recommends that all patients who have malnutrition due to one of the above reasons, in addition to sufficient calories, protein, and fluids, receive adequate electrolytes, minerals, micronutrients, and fiber if appropriate. [7] However, their evidence review found no data to support the routine use of vitamin and mineral supplements in either acute hospitalized patients or older residents in nursing homes. They recommend that if there is a concern about adequate micronutrient intake, a complete oral multivitamin and mineral supplement providing the reference nutrient intake should be considered by healthcare professionals.

It is well known that electrolyte disorders are common in hospitalized patients and are associated with increased morbidity and mortality.[8] However, chronic and mild electrolyte disorders also occur in the general population and can be associated with adverse outcomes. A recent epidemiological study in subjects 55 years of age or older found that the most common electrolyte disorders were hyponatremia and hypernatremia, and there were significant interactions between increasing age and prevalence. Overall, 15% of subjects had at least 1 electrolyte disorder. Overall, major risk factors for electrolyte disorders were diabetes for hyponatremia (OR 1.98; 95% CI 1.47 to 2.68) and hypomagnesaemia (OR 3.32; 95% CI 2.0-5.50), and diuretics for hypokalemia (OR 7.68; 95% CI 4.92 to 11.98).

The authors concluded that an interventional study comparing correction with supplements vs. no correction is needed to prove that this is beneficial. Low potassium intake has been associated with hypertension, cardiovascular disease (CVD), chronic kidney stones, and low bone-mineral density.[9]

Methods:
A Medline literature search ending June 2013 for new systematic reviews, clinical guidelines, and randomized controlled trials (RCTs) for the following dietary and vitamin groups was conducted: potassium, phosphate, and magnesium formulations. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, Clinical Evidence, Up To Date, Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts, and the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. The primary focus of the evidence is on high quality systematic reviews and evidence based guidelines for this class update. RCTs will be emphasized if evidence is lacking or insufficient from those preferred sources.

Potassium: Increasing dietary potassium may be sufficient for asymptomatic patients with hypokalemia without underlying cardiac disease and serum potassium levels above 3 mEq/L. Otherwise, potassium replacement is recommended. Potassium salts include potassium chloride, potassium phosphate, and potassium bicarbonate. Potassium chloride is the most effective for replacing acute potassium loss and is effective for the most common causes of potassium depletion.[10] All potassium formulations (liquid and tablets) are readily absorbed. Potassium phosphate is most commonly used to replace phosphate losses and potassium bicarbonate is recommended in the setting of metabolic acidosis.

Systematic Reviews:

1. A high quality systematic review was done to evaluate potassium intake and cardiovascular (CV) risk factors and disease.[1] RCTs and cohort studies studying the effects of potassium intake on blood pressure, renal function, blood lipids, mortality, CV disease, stroke, and coronary heart disease (CHD) were included. The review as conducted according to the Cochrane methodology. Twenty one RCTs showed that increased potassium intake reduced systolic blood pressure (SBP) by 5.93 (95% CI 1.70 to 10.15) mm Hg and diastolic blood pressure (DBP) by 3.78 (1.43 to 6.13) mm Hg. Heterogeneity was significant for both analyses (I2=96% and I2=93%). When removing studies to reduce the heterogeneity (65% and 55%), increased potassium intake was shown to reduce SBP by 3.49 (1.82 to 5.15) mm Hg and DBP by 1.96 (0.86 to 3.06 mm Hg). Nine cohort studies demonstrated a protective effect of high potassium intake on risk of strike (RR 0.76; 95% CI 0.66 to 0.89). There was a non-significant relation with CV disease and CHD. There was insufficient evidence to evaluate effects on all-cause mortality. Subgroup analysis demonstrated that a decrease in SBP was seen when potassium was increased through a supplement or through dietary advice and changes. There were no adverse effects seen on blood lipid concentrations, catecholamine concentrations, or renal function.

   Based on this evidence review, the World Health Organization (WHO) recommends an increase in potassium intake from food to reduce blood pressure and risk of CVD, stroke, and CHD in adults (Strong recommendation).[9] WHO suggests potassium intake of at least 90 mmol/day. WHO suggests an increase in potassium intake from food to control blood pressure in children as well, but this is a conditional recommendation not based on strong evidence. Although the evidence comes from studies evaluating supplements and dietary sources, WHO recommends replacement of potassium through food consumption, as there have been reports of acute toxicity from extremely high potassium intake in supplement form, but not from consumption in food. WHO attempted to

detect differences in the effect of increased potassium according to type of intervention (supplements or food) and type of potassium supplement (potassium citrate, potassium chloride, etc.). The analysis of 19 studies using potassium supplements showed high quality evidence of a decrease in SBP of 3.31 mmHg (95% CI 1.55 to 5.07) and the three studies using dietary changes showed a decrease in 4.19 mmHg (95% CI 1.92 to 6.46).

2. In contrast, a Cochrane Collaboration Systematic review found that potassium supplementation has no significant effect on blood pressure.[2] Only RCTs including oral potassium supplements were included in the review; dietary changes were not evaluated. A total of 6 RCTs (n=483) met inclusion criteria, most being of poor quality. Five were able to be combined in a meta-analysis that showed potassium supplementation resulted in a large but no statistically significant reduction in SBP)mean difference -11.2; 95% CI -25.2 to 2.7) and DBP (mean difference -5.0; 95% CI -12.5 to 2.4). There was significant heterogeneity between trials I2=98%) that could not be accounted for by potassium dose, trial quality or baseline blood pressure. The significant heterogeneity along with the short duration of follow-up and small number of participants makes it difficult to draw conclusions based on this evidence. The authors concluded that further high quality RCTs are required to clarify results. No trials reported death or CV events. An older systematic review and meta-analysis of RCTs from 1995 found that potassium supplementation was associated with a significant reduction in mean SBP and DBP of -3.11 mm Hg (95% CI -1.91 to -4.31) and -1.97 mm Hg (-0.52 to -3.42), respectively.[11]

3. The National Council on Potassium in Clinical Practice provided guidelines for potassium replacement therapy.[10] However, the quality of the guidelines is low as they are not evidenced based and do not provide detail of the methodology or how they came to such conclusions. Main conclusions regarding potassium replacement are as following:
    - Potassium replacement is recommended for individuals who are sensitive to sodium or who are unable or unwilling to reduce salt intake for the benefit in blood pressure reduction
    - Potassium replacement is recommended for individuals who are subject to nausea, vomiting, diarrhea, bulimia, or diuretic/laxative abuse. Potassium chloride has been shown to be the most effective.
    - Potassium supplements are best administered orally in a moderate dosage over a period of days.
    - Potassium supplementation regimens should be as uncomplicated as possible to help optimize long-term compliance.
    - A dosage of 20 mmol/day is generally sufficient for the prevention of hypokalemia, and 40 to 100 mmol/day sufficient for its treatment.
    - Patients with drug-related hypokalemia (therapy with a diuretic) should receive potassium supplementation.
    - In patients with asymptomatic hypertension, an effort should be made to achieve and maintain normal serum potassium levels.
    - Potassium replacement should be routinely considered in patient with congestive heart failure (CHF).

Randomized Controlled Trials:

1. A 12-week double-blind, placebo-controlled RCT was done to determine the effects of potassium supplementation on endothelial function, CV risk factors, and bone turnover and to compare potassium chloride with potassium bicarbonate.[12] Adults with no previous treatment for elevated blood pressure with SBP of 140 to 170 mmg HG or DBP of 90 to 105 mm HG, and who were already on a relatively low-salt and high –potassium diet were included in the study. Patients were randomized to placebo, potassium chloride, or potassium bicarbonate (n= 46). Compared with placebo, there was no significant difference in BP with either potassium chloride or potassium bicarbonate. Paired comparison showed that SBP was slightly lower with potassium chloride compared to potassium bicarbonate. Both potassium chloride and bicarbonate significantly improved endothelial function. Authors concluded that the 2 potassium salts

appear to have similar effects on most of the CV parameters with small differences in effects on calcium and bone metabolism and urinary albumin excretion.

2. A double-blind, placebo-controlled 8 week RCT evaluated the effects of potassium chloride and potassium citrate in young healthy normotensive on change in mean arterial pressure (n=114).[13] Mean blood pressure was not significantly different among the three groups at baseline and throughout the duration of the study. At the end of 6 weeks, mean blood pressure decreased significantly from baseline in both potassium groups, while no change was observed in the placebo group. No significant differences were found between the two potassium treatments, but the difference was statistically significant between placebo and the two potassium groups.

Magnesium:

Studies have shown that magnesium is effective in eclampsia and preeclampsia (intravenous), arrhythmia (intravenous), severe asthma (intravenous, and migraine (oral). Other uses have been explored, including lowering the risk of metabolic syndrome, improving glucose and insulin metabolism, relieving symptoms of dysmenorrhea, and alleviating leg cramps in women who are pregnant. Although limited evidence to support its use, magnesium is often used for constipation.[14] This review will focus on the evidence of efficacy and safety of oral supplementation of magnesium. Magnesium supplements are available in a variety of forms, including magnesium oxide, citrate, and chloride. All have poor bioavailability and sustained release preparations are more slowly absorbed and minimize renal excretion. Low magnesium intake or excessive losses due to certain health conditions, chronic alcoholism, and/or the use of certain medications can lead to magnesium deficiency. Magnesium deficiency is most common in those with gastrointestinal diseases, alcohol dependence, type 2 diabetes and older adults. There is insufficient evidence that magnesium supplementation is effective in preventing migraines. [18]

Patients with symptomatic hypomagnesaemia should receive intravenous magnesium with cardiac monitoring. Asymptomatic outpatients can be given oral replacement.

Systematic Reviews:

1. A comparative effectiveness review by AHRQ evaluated the evidence of benefits and harms of adding a dietary supplement to cardiovascular drugs routinely prescribed in outpatient settings.[3] A total of 69 studies contributed to the meta-analysis; no systematic reviews were identified. Most of the evidence was graded as insufficient and most had low statistical power due to short-term efficacy design. Strict inclusion criteria excluded patients with uncontrolled comorbidities and acute ischemic events, limiting the generalizability of the results. The authors concluded that the many limitations of the evidence made it difficult to make meaningful conclusions for most supplement-drug combinations. Low-strength evidence suggests benefits of omega-3 fatty acids (incremental improvement of triglyceridemia), vitamin K, (stabilization of INR with warfarin therapy) and garlic administration (improved HDL) only on those specific intermediate outcomes. Evidence on harms was inconclusive. No evidence on clinical effectiveness outcomes was found for Echinacea, garlic, ginseng, niacin, red yeast, vitamin A, or vitamin D supplementation coadministered with a CV drug. No evidence on intermediate outcomes was identified for effects of vitamin A or vitamin D supplementation in combination with CV drugs. No study analyzed statistical interactions between a supplement and a CV drug in terms of clinical outcomes. Additional specific conclusions based on supplement type are as followed:

Magnesium: There was insufficient evidence of no difference in myocardial infarction between oral magnesium + beta-blockers compared to beta-blockers alone. Three RCTs evaluated intermediate outcomes with magnesium in combination with hydrochlorothiazide or beta-blockers in participants with

hypertension. In two trials, systolic blood pressure (SBP) and diastolic blood pressure (DBP) did not differ significantly between the magnesium hydrochlorothiazide combinations versus hydrochlorothiazide-alone groups (insufficient evidence). There was also no significant difference with the combination of magnesium plus beta-blockers versus beta-blockers alone (insufficient evidence).

2. A Cochrane Collaboration systematic review evaluated magnesium supplementation for the management of essential hypertension in adults. [15] A total of 12 RCTs were included and overall those receiving magnesium supplements compared to control did not significantly reduce SBP (mean difference -1.3 mmHg; 95% CI -4.0 to 1.5, I^2=67%), but did statistically significantly reduce DBP (mean difference -2.2 mm Hg, 95% CI -3.4 to -0.9; I^2=47%). There was significant heterogeneity between trials and subgroup analysis could not explain it by magnesium dose, baseline blood pressure or proportion of males. Studies were also of poor quality. The author concluded that any association seen between magnesium supplementation and blood pressure reduction is week and probably due to bias as the quality of the studies was poor. The trials were too short and small to show any effect on CV outcomes such as death, heart attack or stroke.

3. A more recent meta-analysis also evaluated the effect of magnesium supplementation on blood pressure. [16] A literature search through July 2010 identified 22 trials to be included in the analysis. Again, the quality of many of the trials was poor and can overestimate the effect of treatment. Meta-analysis showed an overall effect of 0.36 and 0.32 for DBP and SBP, respectively (95% CI 0.27-0.44 for DBP and 0.23-0.41 for SBP) and this increased with increasing dose. This analysis resulted in a very small decrease in blood pressure, with a high risk of bias included in the trials.

4. The combination of calcium, magnesium and potassium supplementation was evaluated in the management of primary hypertension in adults by the Cochrane Collaboration. [17] Only 3 RCTs were included, evaluating 3 combinations of minerals (potassium-magnesium, calcium-magnesium, and calcium-potassium). The potassium-magnesium combination compared to control resulted in non-significant reductions in both SBP (mean difference -4.6 mmHg; 95% CI -9.9 to 0.7) and DBP (mean difference -3.8 mm Hg; 95% CI -9.5 to 1.8), with significant heterogeneity. The authors concluded that there is not robust evidence that supplements with any combination of potassium, magnesium or calcium reduces mortality, morbidity, or BP in adults.

Phosphates:

Patients most affected by hypophosphatemia are hospitalized patients with malnutrition, alcoholism, sepsis, and diabetic ketoacidosis. Certain medications may also predispose patients to hypophosphatemia, including insulin, diuretics, sucralfate, and antacids.[19] Mild to moderate hypophosphatemia in ambulatory patients can be treated with oral phosphate replacement therapy (1000-2000 mg/day). There is no evidence of improved outcomes for routine supplementation in patients without hypophosphatemia. No systematic reviews or high quality clinical guidelines on supplementation were found. Oral phosphate supplements contain varying ratios of sodium and potassium phosphate. An oral phosphate supplement should be selected with consideration of its potassium and sodium content and dosed according to millimoles of phosphate. Phosphates can also be used clinically to treat hypercalcemia and calcium based kidney stones. No high quality systematic reviews or clinical guidelines were identified evaluating phosphates on clinical outcomes.

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