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Dietary minerals and modification of cardiovascular risk factors

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Abstract

High serum cholesterol, hypertension and obesity are major risk factors for cardiovascular diseases, and together with insulin resistance form a deadly disorder referred to as the metabolic syndrome. All the aspects of this syndrome are strongly related to dietary and lifestyle factors; therefore, it would be reasonable to look for dietary approaches to their modification. Mineral nutrients, such as calcium, potassium and magnesium, lower blood pressure, and especially calcium has beneficial effects also on serum lipids. Recent evidence suggests that increased intake of calcium may help in weight control as well. This review summarizes previous literature on the effects and use of dietary minerals on serum lipids, blood pressure and obesity, with specific focus on the effects of calcium. Calcium and magnesium as divalent cations can form insoluble soaps with fatty acids in the intestine and thus prevent the absorption of part of the dietary fat. Decreased absorption of saturated fat leads to reduction in serum cholesterol level via decreased production of VLDL and increased intake of LDL in the liver. Dietary calcium may also bind bile acids, which increases the conversion of cholesterol to bile acids in the liver. Furthermore, calcium appears to enhance the cholesterol-lowering effect of plant sterols. Thus, dietary combination of the mineral nutrients and plant sterols provides a promising novel approach to the modification of cardiovascular risk factors.

1. Introduction

Despite very impressive recent advances in coronary risk factor identification and modification, heart attack remains the most common cause of death in Western societies. Major risk or even causative factors for heart attack, as well as other cardiovascular diseases, are elevated blood pressure and serum cholesterol levels and obesity [1–3]. These disorders are often associated with insulin resistance and other disturbances in carbohydrate metabolism; together they comprise the notorious metabolic syndrome, also referred to as syndrome X or Reaven syndrome [4], and multiply the risk of cardiovascular complications and death [4,5].

The increasing prevalence of the metabolic syndrome and related disorders in the industrialized populations is an enormous challenge to preventive public health efforts [6–9]. While medical treatment of these conditions is expensive and the results often unsatisfactory, increased exercise and certain changes in dietary habits would benefit almost everyone. Results of recent studies and public health policy statements emphasize abundant intake of fruits and vegetables, as well as fat-free and low-fat dairy products with increased intake of potassium, magnesium, calcium, fiber, and protein [6,10–13]. They also emphasize reduced intake of sodium salts, total fats, saturated fats, and cholesterol. Unfortunately, population-wide implementation of any effective dietary intervention to combat the above-mentioned disorders has proven problematic.

Enrichment of salt or other widely used food items has been the method of choice for a population-wide supplementation of iodine, various vitamins, iron and other mineral nutrients. A marked increase in the levels of potassium and magnesium in a variety of food items has been produced by using potassium- and magnesium-enriched salt alternatives instead of common salt [14,15]. The use of such foods produces lowering of elevated blood pressure and also other beneficial effects both in hypertensive animals and in man [16–21]. Recently, the protective effects of dietary calcium in osteoporosis and hypertension have been widely publicized [22,23]; however, the possible cholesterol-lowering effects of calcium have created much less interest. This review summarizes current knowledge on the effects and use of these dietary minerals on serum lipids, blood pressure and obesity, with specific focus on the effects of calcium.

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Table 1
Effects of dietary calcium on serum lipids in animals

Species	Diet; treatments; duration	Results	Reference
Rat	20% fat, 1% cholesterol, 0.3% cholic acid; [Ca] 0.2, 0.6 or 1.2%, [Mg] 0.02 or 0.2%; 4 weeks	TC ↓ PL ↓	Vitale et al. 1959 [38]
Rat	20% fat, 2% cholesterol; [Ca] 0.08, 0.2, 1.2 or 2%; 5 months	TC ↓ TG ↓ Fecal fat, bile acids and sterols ↑	Fleischman et al. 1967 [39]
Rat	20% fat, 2% cholesterol; [Ca] 0.08, 0.2 or 1.2%; 3 weeks	TC ↓ TG ↓ Fecal fat, bile acids and sterols ↑	Yacowitz et al. 1967 [40]
Rat	20% fat, 2% cholesterol; [Ca] 2.0% ± vitamin D2; 3 weeks	TC ↓ TG ↓ Fecal fat and sterols ↑	Fleischman et al. 1972 [41]
Rat	Low-fat, 1% cholesterol [Ca] 0.2, 0.8 or 2.1%; 8 weeks	TC ↓ LDL ↓ HDL ↑ Cholesterol synthesis and absorption ↑	Vaskonen et al. 2002 [42]
Rabbit	Low-fat; [Ca] 0.02, 0.8 or 1.6%; 3 months	TC ↓ TG ↔	Iacono 1974 [43]
Rabbit	25% butter, 25% casein; [Ca] 0.3 or 0.9%, [Mg] 0.04 or 0.4%; 6 months	TC ↓ HDL-C ↔ TG ↓ Atherosclerosis ↓	Renaud et al. 1983 [44]
Rabbit	10% fat, 21% casein; [Ca] 0.8 or 1.4%; 7 weeks	TC ↓ PL ↔ Fecal fat ↑	Van der Meer et al. 1985 [45]
Rabbit	11% fat, 20% casein, cod, or soy protein; [Ca] 0.7 or 1.4%; 4 weeks	TC ↓ LDL-C ↓ HDL-C ↔ VLDL-C ↓ TG ↔ Fecal fat ↓	Jacques et al. 1995 [46]
Pig	19% fat, 0.05% cholesterol; [Ca] 0.7 or 2.1% ± vitamin D; 6 weeks	No changes in TC, VLDL-C, LDL-C, HDL-C, or TG	Foley et al. 1990 [47]
Pig	10% butter, 0.5% cholesterol; [Ca] 0.7 or 1.4%; 15 days	TC ↓ LDL-C ↓ HDL-C ↔ Serum bile acids ↓	De Rodas et al. 1996 [48]
Goat	Fat and cholesterol supplemented goat milk; [Ca] 0.1% or 0.2%; 20 weeks	No changes in TC, VLDL-C, LDL-C, HDL-C, or TG	Diersen-Schade et al. 1984 [49]
Goat	Normal goat milk; [Ca] 0.1% or 0.2% ± vitamin D3; 20 weeks	TC ↓ Atherogenesis ↓ Fecal fat ↔	Hines et al. 1985 [50]

[Ca] = total calcium content; TC = total cholesterol; VLDL-C, LDL-C, HDL-C = very low, low, high density lipoprotein cholesterol; TG = triglycerides; PL = phospholipids

2. Calcium

Calcium is an essential nutrient, quantitatively the most abundant of the body's minerals and a vital electrolyte. Besides structural support, calcium is required for critical biological functions like nerve conduction, muscle contraction, cell adhesiveness, mitosis, and blood coagulation. An average adult body contains about 1,5 kg of calcium, 99% of it in the skeleton (for a review, see [24]. Calcium in blood is divided among protein-bound, complexed, and ionized or free fractions. The ionized fraction is the focus of metabolic control, especially through parathyroid hormone (PTH) and vitamin D, and it is kept constant at 1.0 to 1.2 mmol/L by processes that continuously add and remove calcium.

The Recommended Dietary Allowance (RDA) for calcium has long been 800 mg/day. Recognition of the many health benefits of calcium has led to increases in dietary calcium recommendations up to 1500 mg/day, depending on sex and age group [22,25]. Inadequate intake of calcium is a global problem, especially in aging populations, and it has been associated with several medical disorders, such as osteoporosis, hypertension, colon cancer, breast cancer, and kidney stones (for review, see [26]. Based on recent research, increased dietary intake of calcium is currently recommended for the general population to lower the risk of these chronic diseases [13,27].

2.1. Calcium and serum lipids

Considering the ever-growing amount of calcium-related research, particularly around hypertension and osteoporosis, it is surprising how little attention has been called upon the possible lipid-lowering effects of an increased intake of calcium.

Epidemiological evidence in favor of the hypothesis of calcium as a lipid-lowering agent is undeniably scarce. Higher calcium intake rather seems to correlate with higher serum cholesterol levels and incidence of coronary heart disease [28–30]. This might be due to the fact that dietary calcium usually comes from milk products that often con-

Table 2
Effects of dietary calcium on serum lipids in humans

Subjects	Design, duration	Intervention	Result	Reference
13 healthy adults	Cross-over, 3 weeks	Ca 890 mg/d	TC ↓ TG ↓ Fecal fat ↑	Yacowitz et al. 1965 [51]
12 healthy men	Cross-over, 4 × 2 weeks	SAFA/PUFA 90g+Ca 2 g/d	TC ↓ Fecal fat and C ↑	Bhattacharyya et al. 1969 [52]
16 HC patients	Cross-over with placebo, single-blind, 4+8 weeks	Ca 2 g/d	TC ↓ TG ↔	Carlson et al. 1971 [53]
20 HC patients	Randomized, open, 12 months	Ca 800 mg/d	TC ↓ TG ↓	Bierenbaum et al. 1972 [54]
30 HC patients	Cross-over with placebo, single-blind, 16 months	Clofibrate + Ca 800 mg/d	VLDL-C ↓ LDL-C ↓ HDL-C ↔ TG ↔	Lehtonen & Viikari 1979 [55]
50 FHC children	Cross-over with placebo, double-blind, 10+10 weeks	Ca 400 mg/d	LDL-C ↓ Apo-AI ↑	Groot et al. 1980 [56]
43 hypertensive 27 normotensive	Randomized, double-blind, cross-over, 8+8 weeks	Ca 1 g/d	TC, VLDL-C, LDL-C, HDL-C, and TG: ↔	Karanja et al. 1987 [60]
200 healthy adults	Open, 6 months	Ca 1,4 g/d	TC ↓ HDL ↔ TG ↔	Bierenbaum et al. 1987 [58]
56 HC patients	Randomized, double-blind, cross-over, 6+6 weeks	AHA Step-1 + Ca 1,2 g/d	LDL-C ↓ HDL-C ↑	Bell et al. 1992 [57]
13 healthy men	Randomized, single-blind, cross-over, 10+10 days	Ca 1,8 g/d	TC ↓ LDL-C ↓ Apo-B ↓ TG ↔ HDL-C ↔ Apo-A1 ↔ Fecal fat ↓ bile acids ↔	Denke et al. 1993 [59]
130 hypertensive 196 normotensive	Randomized, parallel, placebo-controlled, 12 weeks	Ca 1 g/d	TC, VLDL-C, LDL-C, HDL-C, and TG: ↔	Karanja et al. 1994 [61]
10 healthy men	Randomized, double-blind, cross-over, 2+2 weeks	Ca 900 mg/d	LDL-C ↓ HDL-C ↔ TG ↔ Fecal fat and bile acids ↑	Shahkhalili et al. 2001 [62]
223 elderly women	Randomized, placebo-controlled, 1 year	Ca 1 g/d	TC ↓ LDL-C ↓ HDL-C ↑ TG ↔	Reid et al. 2002 [63]

(F)HC = (familial) hypercholesterolemia; Ca = supplemental elementary calcium; SAFA/PUFA = saturated/polyunsaturated fatty acids; C = cholesterol; TC = total cholesterol; LDL-C, VLDL-C, HDL-C = low, very low, high density lipoprotein cholesterol; Apo = apolipoprotein; TG = triglycerides

tain lots of saturated fat and cholesterol, which may override the effects of calcium. Conversely, low-fat and low-cholesterol diets, which lower serum lipid levels, often contain less calcium [31,32]. One fairly large cross-sectional study in 5 394 men and 4 800 women found a linear increase of both total cholesterol and HDL cholesterol with serum calcium levels, independent of confounding factors such as age, blood pressure, body weight, fat and cholesterol intake [33]. Recently, no association between milk consumption and coronary or all cause mortality was found in a 25-year prospective study on a cohort of 5 765 men in Scotland [34]. In a large cohort study of 34 486 postmenopausal women, higher intake of calcium, but not of vitamin D or milk products, was associated with reduced ischemic heart disease mortality [35]. On the other hand, several studies indicate that milk and milk products have hypolipidemic and anti-atherogenic effects [36,37], which could be related to calcium, but may also be due to other bioactive substances in milk.

However, there are intervention studies both with animals (Table 1) and humans (Table 2) that have explored the effects of dietary calcium on serum lipids.

In rats supplemented with dietary fat and cholesterol [38–41], consistent decreases in serum total cholesterol and triglycerides with increased calcium intakes were observed. The level of serum total cholesterol in rats fed 1.2% dietary calcium was about 30 to 40% lower and with 2.0% calcium up to 60% lower than in the controls fed low-calcium diets. Calcium was hypolipidemic during both saturated and polyunsaturated fat supplementation, but the effects were more pronounced in the presence of saturated fat [40]. Cholic acid enhanced the diet-induced hyperlipidemia and even abolished the effects of calcium [38], but vitamin D had no significant effect on either direction [41]. In New Zealand

white rabbits fed a low-fat diet, calcium supplementation lowered serum total cholesterol and reduced the accumulation of cholesterol in heart, kidney and muscles, but the tissue triglyceride levels were increased [43]. In a six-month experiment with butterfat-supplemented rabbits, Renaud et al. [44] found that calcium and magnesium, in addition to lowering of cholesterol and triglycerides, also reduced platelet aggregation, the severity of atherosclerosis and accumulation of cholesterol in the aorta. Casein and cod protein -induced hypercholesterolemia in rabbits was effectively counteracted by 1.4% dietary calcium, while soy protein did not raise serum lipid levels at all [45,46]. In fat- and cholesterol-supplemented pigs the effects of calcium were less unanimous. Tripling the dietary calcium intake had no effect on cholesterol or triglyceride concentrations in plasma or their partitioning among plasma lipoproteins [47]. The levels of both dietary and plasma cholesterol in this study, though, were only a fraction of those in the other pig study [48], where the lowering of serum total and LDL cholesterol after dietary cholesterol supplementation was enhanced by a diet containing 1.4% calcium. Another species where findings seem to differ is young goat. Diersen-Schade et al. [49] found no effect of dietary fat or calcium on plasma and lipoprotein cholesterol concentrations, but a year later Hines et al. [50] reported calcium-induced lowering of cholesterol in plasma and tissues in a similar setting. High intake of vitamin D, however, reversed the beneficial effects of calcium, resulting in a marked increase in lipid accumulation in the aorta. Recently, in our own laboratory, dietary calcium dose-dependently decreased serum total and LDL cholesterol and increased HDL cholesterol levels in obese Zucker rats during both low-fat [42] and high-fat (Vaskonen, unpublished observation) diets.

The first clinical studies in the 1960's and 1970's were rather small but well conducted and showed a consistent serum cholesterol- and triglyceride-lowering effect of increased dietary calcium intake. In healthy adults on normal diets, a moderate 890 mg/day calcium supplementation produced a mean 15.4 mg/dL (0.4 mmol/L) decrease in serum total cholesterol and 32.2 mg/dL (0.83 mmol/L) decrease in triglycerides [51]. The decreases were greater, up to 15 to 30% in those whose baseline lipid levels were elevated. Calcium counteracted the rise of serum cholesterol induced by saturated fat; polyunsaturated fat supplementation did not raise the cholesterol levels [52]. In hyperlipidemic patients, Carlson et al. [53] found a 10% decrease in serum chole-sterol during calcium treatment, but no change in triglycerides; Bierenbaum et al. [54] reported a calcium-induced decrease in all serum lipids over 12 months; and Lehtonen and Viikari [55] showed that calcium supplementation was able to enhance the lipid-lowering effect of clofibrate. In children with familial hypercholesterolemia, calcium supplementation in addition to a low-fat and low-cholesterol diet produced a rather small but significant 4% decrease in serum LDL cholesterol and a 4% increase in serum apolipoprotein A1, which is the main protein in HDL [56]. Similar results were achieved in adults with only 400 mg/day increase in calcium intake, in addition to the low-fat, low-cholesterol diet [57]. Bierenbaum et al. [58] had 200 volunteers drink one liter of calcium-fortified milk per day for six months and reported, in addition to 7/6 mmHg decrease in blood pressure, a slight decrease in serum total cholesterol. Two smaller studies have examined the effects of dietary calcium fortification on serum and fecal lipid contents. Increased intake by 1800 mg/day resulted in decreases of 6% in total and 11% in LDL cholesterol and doubled the saturated fat excretion [59], and supplementation of 900 mg/day of calcium in chocolate markedly reduced the absorption of cocoa butter, and lowered plasma LDL cholesterol by as much as 15% [62]. Very recently, a 1 g/day calcium supplemen-tation was reported to produce a 7% increase in HDL cholesterol and 6% decrease in LDL cholesterol in a study on 223 healthy postmenopausal women – the group most commonly using calcium supplements [63]. However, not all studies have demonstrated any hypolipidemic effects for calcium. Two fairly large intervention studies by the same group [60, 61] found that hypertensive patients at baseline consumed less calcium, magnesium and potassium than normotensive patients and had significantly lower HDL cholesterol and higher LDL cholesterol levels, but no changes occurred in plasma lipids or lipoproteins with either calcium supplementation or counseling to increase dietary calcium intake.

2.2. Mechanisms of the effects

The possible hypolipidemic mechanisms of calcium include 1) inhibition of the intestinal absorption of cholesterol [39–41,49,52], 2) inhibition of absorption of bile acids [39,40,48,62], and 3) inhibition of absorption of fat [39–41,45,46,51,52,59,62].

In a recent study in obese Zucker rats [42], calcium dose-dependently increased both the intestinal absorption and endogenous synthesis of cholesterol; yet, at the same time, serum cholesterol was decreased. This apparently paradoxical effect can be explained by a calcium-induced increase in the excretion of bile acids. The catabolism of cholesterol to bile acids is an important route for the elimination of cholesterol from the body, accounting for approximately 50% of the cholesterol eliminated daily [64]. Increased fecal loss of bile acids results firstly in decreased absorption of fat and cholesterol and secondly in increased conversion of cholesterol to bile acids in the liver. Even if *de novo* synthesis of cholesterol is increased, it may not be sufficient for the replacement bile acid synthesis, and cholesterol must be taken from the circulation via LDL-receptors, which leads to lowering of serum LDL cholesterol. In fact, this same mechanism has been previously utilized in treatment of hypercholesterolemias with cholestyramine and other resins [65].

Increased fecal loss of fat, especially saturated fat, is also important because saturated fatty acids, when absorbed, will increase serum cholesterol levels. This effect of saturated fat

has been known for decades, but its mechanism is still not completely understood; probably the saturated fatty acids inhibit the receptor-mediated uptake of LDL into liver cells, thereby decreasing the clearance of LDL particles from the circulation [66,67]. Consequently, decreased absorption of saturated fat would lead to a decrease in serum cholesterol. Calcium and other divalent cations may bring about this effect through precipitation of saturated fatty acids from the solution. This concept of formation of non-absorbable calcium and magnesium soaps in the intestine was first proposed by Givens in 1917 [68], and has since been confirmed in both animal and human studies [69, 70]. The bile and fatty acid binding properties of calcium are also utilized in the prevention of colorectal neoplasia [71,72].

In summary, despite some controversy and lack of large epidemiological and intervention studies, the existing evidence strongly suggests that calcium does have beneficial effects on serum lipids, in animals as well as in humans. Larger-scale prospective clinical trials need to be conducted to define the scope and significance of this effect.

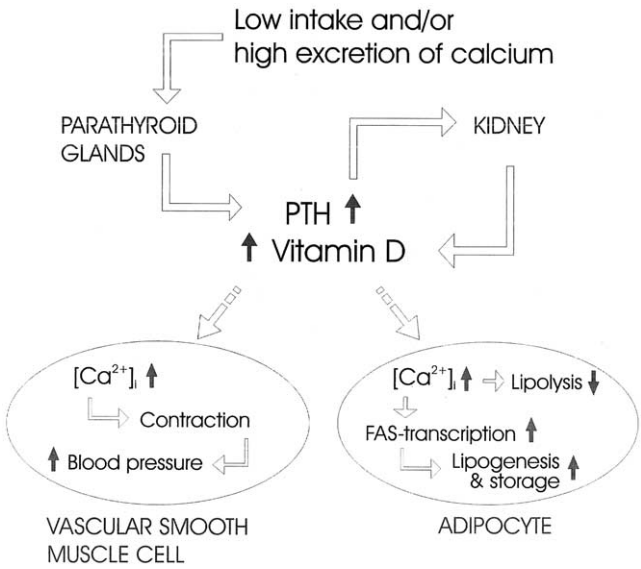

Fig 1. Suggested mechanism of the effects of dietary calcium on blood pressure and obesity [87].

2.3. Calcium and blood pressure

After 20 years of intense investigation in the area of dietary calcium and blood pressure, a consensus is at hand: a large body of recent data consistently and clearly prove the antihypertensive effect of increased intake of calcium (for review, see [23]. The association between higher dietary calcium intake and lower prevalence of high blood pressure was first reported by McCarron et al. [73] in the analysis of the first National Health and Nutrition Examination Survey (NHANES I). Since then, more than 30 well-designed epidemiological studies assessing the calcium-blood pressure relationship have been published. A meta-analysis of 23 observational studies estimated that each 100 mg increase in daily calcium intake would produce a lowering of 0.39 mmHg in systolic and 0.35 mmHg in diastolic blood pressure [74].

Studies in various strains of hypertensive rats and their normotensive counterparts have largely confirmed the initial hypothesis that an increase in dietary calcium intake reduces blood pressure, and provided some insight into its possible mechanisms of action (for reviews, see [75,76]. Calcium may act concurrently through several physiological mechanisms, including reduced membrane permeability and intracellular calcium, changes in calcium-regulating hormones, modulation of the sympathetic nervous system, and altering the metabolism of other electrolytes [77]. Pörsti [78] found that the urinary excretion of sodium increased and the action of deoxycorticosterone on sodium balance was prevented [79], and that the activity of erythrocyte cell membrane calcium-ATPase was increased, platelet intracellular free calcium reduced, vascular smooth muscle relaxation improved and contractile responses attenuated by a high-calcium diet in spontaneously hypertensive rats [80,81]. These results were later confirmed, and complemented by new observations indicating that the augmented endothelium-dependent vasorelaxation could be explained by enhanced hyperpolarization, mediated via opening of calcium-activated potassium channels, increased sensitivity to nitric oxide in arterial smooth muscle, and decreased production of superoxide and vasoconstrictor prostanoids [82–84]. Furthermore, the enhanced vasodilation and lowering of blood pressure, at least in experimental models, could be related to the lipid-lowering action of calcium, as hyper-lipidemia *per se* is known to induce endothelial dysfunction [85,86].

The antihypertensive effect of increased dietary calcium intake might also be mediated via suppression of the calcitrophic hormones PTH and vitamin D [87]. These hormones increase vascular smooth muscle intracellular calcium, which leads to increased peripheral resistance and blood pressure (Fig. 1). Dysregulation of calcium homeostasis may also be a fundamental factor linking together hypertension and obesity [87].

More than 60 calcium intervention trials in humans have been reported, and as with all nutrient modification trials, the results have been heterogeneous [88]. However, a most carefully conducted and recent meta-analysis of 43 randomized controlled studies found that both dietary and supplemental increase in calcium intake to more than 1000 mg/day for at least two weeks leads to a significant reduction in blood pressure [89]. Pooled estimates across all studies, comprising 3500 subjects altogether, showed decreases of 1.44 mmHg in systolic and 0.84 mmHg in diastolic blood pressure. The decreases tended to be greater and less heterogeneous in dietary calcium studies as compared with those that employed non-food sources of calcium [89]. Perhaps the most important recent study in this area is the Dietary Approaches to Stop Hypertension (DASH) trial [11]. The DASH diet, rich in calcium, magnesium, potassium and fiber, produced up to 11.4/5.5 mmHg reductions in

blood pressure and, when analyzed statistically for calcium effect, the observed reductions in blood pressure correspond remarkably with those revealed by meta-analyses of both epidemiological and clinical intervention trials [23]. On the whole, these data support the role of the combination of the mineral nutrients as an independent factor that significantly contributes to the lowering of hypertension risk.

2.4. Calcium and obesity

Obesity is the common denominator in several comorbid conditions, including hypertension, hyperlipidemia and type II diabetes, and its prevalence is increasing rapidly all over Western world [90]. While it is known that weight reduction would be one of the most effective means of lowering the risk of cardiovascular diseases – even a few per cent decrease in body weight is associated with significant lowering of blood pressure and improvement of glucose tolerance and blood lipid profile [90] – the treatment of obesity in practice has proven extremely difficult.

Reductions in body weight gain were observed in several of the previously cited experimental calcium supplementation studies [39,40,47,80,82]. There are two plausible explanations: dietary calcium may form soaps with fatty acids and thereby prevent the absorption of some of the fatty acids released during lipid digestion, and/or dietary calcium may bind bile acids, which would decrease micelle formation and thus reduce lipid absorption and digestible energy of the diet. Many of these studies also reported increases in fecal fat excretion, which supports these assumptions.

Among the clinical studies addressing the effect of calcium on serum lipids, Carlson et al. [53] reported a significant 0.55 kg weight loss by calcium supplementation of 2 g/day for eight weeks, and Karanja et al. [61] found a small but significant decrease in body weight by 1 g/day calcium supplementation in both men and women in 12 weeks. In the same study, counseling to increase dietary calcium through food consumption to 1.5 g/day resulted in substantial increase in energy intake, yet body weight was not significantly altered. Neither did Shahkhalili et al. [62] find any significant changes in body weight during two weeks' consumption of calcium-fortified chocolate. The other studies listed in Table 2 did not report body weights. In a clinical trial investigating the antihypertensive effect of calcium in obese African-Americans, an increase in calcium intake from about 400 to 1000 mg/day for one year resulted in as much as 4.9 kg reduction in body fat [91]. A recent reevaluation of five clinical studies, designed with a primary skeletal end point on a total of 780 women in their 3rd, 5th and 8th decades, showed significant negative associations between calcium intake and body weight in all age groups across nearly four years of observation [92]. Estimates of the relationship indicated that a 1000 mg daily calcium intake difference is associated with as much as 8 kg difference in body weight and that calcium intake explains approximately 3% of the variance in body weight.

Epidemiological analysis of both the NHANES I [73] and NHANES III databases [91] have revealed an inverse association with body weight and dietary calcium intake. Moreover, calcium adjusted for energy intake had a negative relationship with two-year changes in total body weight and body fat in young women in a prospective analysis of an exercise intervention study [93]. Also a recent longitudinal study in preschool children showed that higher intake of calcium was associated with lower body fat [94].

Recently, a new theory about regulation of intracellular calcium as a fundamental factor linking together obesity, insulin resistance and hypertension has been presented [87,95]. It was discovered that increasing intracellular calcium concentration stimulates the expression and activity of fatty acid synthase (FAS) and inhibits lipolysis in human and murine adipocytes via a calcium-dependent mechanism [96,97]. Moreover, vitamin D and PTH were shown to produce sustained increases in adipocyte intracellular calcium and a corresponding inhibition of lipolysis [91]. This phenomenon may also contribute to the high body weight and fat mass reported in primary hyperparathyroidism [98]. Increased intracellular calcium in fat and muscle cells may even interfere with signal transduction and attenuate insulin response [95]. The levels of PTH and vitamin D are elevated during low intakes of calcium. An increase in dietary calcium intake should, accordingly, suppress these calcitrophic hormones and thereby reduce intracellular calcium concentration and lipid storage in adipocytes; these effects together with reduction in body weight were indeed observed in calcium supplemented obese mice [99].

In conclusion, the possible role of calcium in the regulation of adiposity is a fairly novel idea and not usually quoted in calcium-related reviews. It has a plausible physiological basis and a good deal of experimental as well as some recent clinical and population data to support it. However, larger intervention studies should be performed to define the true significance of this action.

2.5. Adverse effects of calcium

Dietary calcium intake up to 2000 mg/day is generally recognized as safe [25]. However, no research data in humans are available about the long-term risks or benefits of consuming higher amounts. Clinical toxicity of excessive calcium intakes could rise from development of hypercalcemia; symptoms may include confusion, fatigue, irritability, in severe cases even cardiac arrhythmias and, particularly with associated hyperphosphatemia, soft tissue calcification and renal damage [100]. True life-threatening toxicity is rare: there are about 30 case reports from the last two decades of the milk-alkali syndrome, and most of them had a predisposing factor, such as thiazide diuretic treatment or concurrent high alkali intake [101]. High calcium intake has also been thought to cause kidney stones, for which hypercalciuria is an important risk factor [101]. However,

more recent studies suggest that increased dietary calcium may actually reduce the risk of nephrolithiasis [102]. Although dietary calcium increases urine calcium, it also binds phosphate and oxalic acid in the intestine, thereby reducing the formation of calcium oxalate and calcium phosphate crystals in the kidney. A normal rather than low calcium intake provided protection against recurrent stones even in patients with idiopathic hypercalciuria [103]. Moreover, with long-term consistent increase in calcium intake, intestinal adaptation mechanisms reduce the fractional calcium absorption, which already is highly dependent on the dietary source [104]. On the other hand, while reducing the likelihood of adverse effects, this adaptation may also reduce the expected benefits of calcium supplementation.

Another possible adverse effect of excessive calcium intake is the interaction with the absorption of other essential minerals, such as iron, magnesium, and zinc [101]. The interaction between calcium and iron has been extensively studied. Calcium clearly inhibits iron absorption in a dose-dependent manner and, surprisingly, even heme iron absorption is inhibited [105]. A recent review, however, concluded that while this is true in short-term absorption studies, long-term consumption of calcium supplements does not affect overall iron status [106]. Calcium supplements may also affect the magnesium status of the body. It has been proposed that a dietary calcium to magnesium ratio greater than five may pose a risk for magnesium deficiency, partly because of reduced absorption but also because of increased excretion [107]. This emphasizes the importance of adequate or increased magnesium intake concurrently with calcium supplementation. In practice, though, high-calcium diets have not been demonstrated to affect magnesium retention in the long-term, probably due to the powerful compensatory function of the kidneys to decrease magnesium excretion [101]. As for zinc, early animal studies indicated that high-calcium diets decrease its bioavailability, but most later studies in humans have not found any effect of calcium on either the absorption or whole-body retention of zinc [101].

Particularly calcium supplements can produce gastrointestinal side effects like bloating and constipation; they can also diminish the effectiveness of some medications such as alendronate, used to treat osteoporosis, or the antibiotic tetracycline, and should therefore not be consumed at the same time [27].

In conclusion, little evidence exists for any general toxicity of calcium intakes of even more than 2 g/day, especially if consumed with food when most of the calcium is not even absorbed. However, patients with hypercalcemia, thiazide treatment, or propensity to hypercalciuric stone formation should be more careful to keep to the recommended range.

3. Magnesium

Magnesium is the most abundant intracellular divalent cation. It is an essential cofactor for a multitude of enzymatic reactions that are important for the generation of energy from ATP and for physiologic processes including neuromuscular function and maintenance of cardiovascular tone (for review, see [108]).

The serum concentration of magnesium is tightly regulated within a narrow range of 0.7 to 1.1 mmol/L as a result of the efficient absorption of dietary magnesium by the small intestine and conservation of magnesium in the kidney. The current RDA for magnesium is 400 mg/day. About 30% of dietary magnesium is absorbed in the small intestine, but this fraction can be substantially increased when intake is reduced. Approximately 96% of filtered magnesium is reabsorbed along the nephron, and only 4% is excreted into the urine. Hypercalcemia and hypercalciuria decrease tubular reabsorption of magnesium. Also excessive sodium intake and certain drugs, particularly thiazide diuretics, increase magnesium loss into the urine. There appears to be no specific and direct endocrine control of magnesium balance, similar to what exists for calcium, sodium and potassium. The calcitrophic hormones PTH, vitamin D and calcitonin, however, have similar actions for calcium and magnesium [108].

Magnesium deficiency may play an important role in the pathogenesis of several cardiovascular diseases, including cardiac arrhythmias, ischemic heart disease, congestive heart failure, vascular complications of diabetes, hypertension and stroke [109,110]. Current dietary recommendations include the maintenance of adequate intake of magnesium, along with calcium and potassium, in order to lower the risk of cardiovascular diseases [13].

3.1. Magnesium and lipids

Several studies have evaluated the effects of dietary magnesium on serum and tissue lipids. In an early study in rats, 0.2% magnesium supplementation had no effect on serum cholesterol, but it effectively reduced tissue calcification and vascular lipid accumulation [38]. In a six-month experiment with cholesterol-fed rabbits [44], 0.4% dietary magnesium markedly lowered serum total cholesterol and reduced the accumulation of cholesterol as well as the severity of atherosclerosis in the aorta. Another study in rabbits [111] showed no changes in cholesterol levels but, again, additional magnesium dose-dependently decreased both the area of aortic lesions and the cholesterol content in the aortas. Altura et al. [112] demonstrated up to 40% lowering of cholesterol and triglyceride levels along with marked attenuation of the atherosclerotic process by magnesium supplementation in cholesterol-fed rabbits. Recently, increased magnesium intake was reported to reduce both cholesterol and triglyceride levels and inhibit athero-

genesis in apo-E deficient mice receiving a low-fat diet [113].

In humans, two similar randomized, single-blinded, controlled studies with 430 [114] and 400 patients [115] showed about 10% decreases in serum total and LDL cholesterol and triglyceride concentrations as a result of an increase in dietary magnesium intake from about 400 to 1000 mg/day. HDL cholesterol remained mostly unchanged, however, in originally hypomagnesemic subjects the dietary change induced an 11% increase in serum HDL cholesterol together with the decrease in the other lipids [114]. A 500 mg/day oral magnesium supplementation lowered serum triglycerides but had no positive effect on cholesterols in a study with 69 hyperlipidemic patients on a low-fat, low-cholesterol diet [116]. Recently, magnesium supplementation was found to reduce both serum total and LDL cholesterol levels and insulin-stimulated glucose uptake in patients with type I diabetes [117].

Thus, in the light of current knowledge, increased intake of dietary magnesium is likely to have beneficial effects on serum lipids. Moreover, experimental data suggest that it may attenuate the development of atherosclerosis even without major changes in the lipoprotein levels, especially in magnesium-deficient subjects. Magnesium deficiency is not uncommon, although it is often clinically latent, because less than 1% of total body magnesium is present in blood, and assessment of tissue magnesium status is problematic [118]. The mechanisms of the lipid-lowering effect of magnesium are poorly understood. In theory, as a divalent cation similar to calcium, it could bind fatty acids and bile acids in the intestine, reduce the absorption of saturated fat, and increase the excretion of cholesterol as bile acids from the liver. One of the above-mentioned studies [44] reported a magnesium-induced increase in fecal fat excretion, but currently no data are available on concomitant effects on bile acid excretion and serum lipids or atherogenesis.

3.2. Magnesium and blood pressure

Magnesium may also have a beneficial effect on blood pressure. No quantitative analyses are available, but qualitative overviews on epidemiological studies point to an inverse relationship between dietary magnesium intake and blood pressure [119,120]. The large cross-sectional Atherosclerosis Risk in Communities (ARIC) study on 15 000 middle-aged Americans showed a negative correlation of dietary and serum magnesium levels to both systolic and diastolic blood pressure [121]; on the other hand, no such relationship was found in the NHANES III [122]. Data from clinical studies are also inconsistent. Dietary magnesium supplementation has been shown to lower blood pressure in many [123–125] but not in all [126–128] intervention studies.

3.3. Magnesium and obesity

Little is known about the effects of dietary magnesium on obesity, and no reductions of body weight attributable to increased magnesium intake were reported in any of the studies referred to above. Theoretically, magnesium could have an anti-obesity effect similar to calcium, because it too can form soaps with fatty acids in the intestine and thus reduce the digestible energy content of the diet [68,69].

Furthermore, there is both experimental [129] and epidemiological evidence [130] that magnesium may attenuate the development of insulin resistance and type II diabetes, and insulin response has been reported to be improved by magnesium administration [131]; this should also eventually affect adiposity. Interestingly, in a recent study obese persons were found more insulin-resistant and had lower magnesium concentrations in their serum and erythrocytes than nonobese controls [132]. Also the ARIC study reported an inverse relation between serum magnesium concentration and body mass index at baseline [130].

3.4. Adverse effects of magnesium

The therapeutic window of magnesium is wide and severe toxic effects are extremely rare (for review, see [108]. Oral magnesium supplementation has a laxative effect that is even utilized in treatment of constipation, but large doses may also cause diarrhea and abdominal cramps. Signs of magnesium toxicity are vomiting, hypotension, bradycardia and other arrhythmias, somnolence, and weakness; these usually occur at plasma levels of four to five times higher than normal, and have only been observed during intravenous magnesium treatment. Magnesium toxicity is increased in patients with hypocalcemia, hyperkalemia and renal failure. Calcium gluconate is clinically used as an antidote for magnesium; therefore, with concurrent dietary supplementation of calcium and magnesium, any adverse effects attributable to magnesium are unlikely.

4. Potassium

Potassium is the principal intracellular cation and mainly involved in membrane potential and electrical excitation of nerve and muscle cells. The extracellular concentration of potassium is kept constant at 4 to 5 mmol/L by active ion transport systems, which are usually coupled with the regulation of sodium concentration and excretion as well. Until recently, from an evolutionary point of view, humans consumed a diet low in sodium (about 0.5 to 1 g/day) and high in potassium (8 to 10 g/day), but these days the relation has often turned the other way around, largely as a result of the increasing consumption of industrially processed foods [133,134].

In addition to its widely accepted role in the prevention and treatment of Hypertension high intake of potassium may also have other beneficial effects that are independent of blood pressure – for example, reduction of the risk of stroke, prevention of renal vascular, glomerular and tubular damage, and improvement in glucose intolerance (for review, see [135]. In the Scottish Heart Health Study, findings included an unexpectedly powerful protective relation of dietary potassium to all cause mortality [136]. Potassium also decreases urinary calcium excretion and thereby has many effects comparable to increased calcium intake, such as reduced risk of osteoporosis and kidney stones. Increasing potassium intake and reducing sodium intake have an additive effect in most of these conditions [135].

4.1. Potassium and lipids

There appears to be no direct evidence of any effect of dietary potassium on serum lipid levels in humans or in animals. However, potassium may protect against atherosclerosis by modifying lipid properties even without significant changes in their concentrations. In cholesterol-fed rabbits, increasing dietary potassium from 0.4% to 1.5% did not produce any differences in plasma cholesterol or body weight in six weeks, yet substantially reduced atherosclerotic lesions in coronary arteries [137]. Other experimental studies have provided explanations for possible mechanisms by which increased intake of potassium may protect against cardiovascular diseases. Potassium has been shown to 1) inhibit free radical formation from vascular endothelial cells and macrophages [138], which could also affect LDL oxidation and thereby the development of atherosclerosis; 2) inhibit proliferation of vascular smooth muscle cells [139]; and 3) inhibit platelet aggregation and arterial thrombosis [140]. Recently, a high level of dietary potassium was shown to inhibit neointimal proliferation after balloon angioplasty in the rat carotid artery [141] as well as in a swine coronary artery [142].

4.2. Potassium and blood pressure

The important role of potassium intake in regulating blood pressure in both the general population and people with high blood pressure has been repeatedly shown in epidemiological as well as clinical studies, and is today well established [12,143]. For instance, pooled data from a meta-analysis of 33 trials (2609 patients) on the effects of potassium supplementation showed highly significant net decreases of 4.5 mmHg in systolic and 2.5 mmHg in diastolic blood pressure with a median dose of 1.9 g/day [144]. Very recently, an analysis of the NHANES III database on 17030 subjects again confirmed that higher potassium intake is associated lower systolic and diastolic blood pressure [122].

The blood pressure-lowering effect has been particularly prominent in patients and animals with salt-sensitive hypertension [134,145]; thus, the action of potassium could be related to facilitation of natriuresis and decrease in volume load. However, the antihypertensive effect is most likely multifactorial; suggested mechanisms include reduced sympathetic nervous activity [146] and decreased pressor response to noradrenaline and angiotensin II [147]. Experimental studies with a potassium-enriched mineral salt have supported the volume load theory [17], but also indicated that potassium may attenuate the vascular contractile responses and improve both endothelium-dependent and -independent relaxation [19]. Recently, Tolvanen et al. [83] showed that dietary potassium supplementation improved endothelium-dependent arterial relaxation in spontaneously hypertensive rats by mechanisms involving enhanced hyperpolarization, increased smooth muscle sensitivity to nitric oxide and decreased production of vasoconstrictor prostanoids. Increased intake of calcium together with potassium was more effective than either one alone in reducing blood pressure and restoring arterial tone. In another recent study, the most effective protection against hypertension induced by cyclosporin toxicity was achieved when dietary potassium and magnesium supplementations were combined [148].

4.3. Potassium and obesity

There are no reports in the literature that would closely link together dietary potassium and obesity, and only sparse references to point to even a distant connection. However, as with magnesium, type II diabetes might be the common link: improvements in carbohydrate metabolism in response to potassium administration have been reported [149–151]. Furthermore, decreased skeletal muscle potassium and increased sodium to potassium ratios have been measured in obese and glucose intolerant men [152,153]. A recent study demonstrated that insulin and leptin, hormones that reduce food intake and body weight in lean but not obese Zucker rats, hyperpolarize hypothalamic glucose-responsive neurons by opening ATP-sensitive potassium channels, suggesting that this potassium channel is involved in the physiological regulation of energy homeostasis [154]. There is no evidence to date about any effect of dietary potassium on the function of this channel, but knowing that potassium supplementation can enhance hyperpolarization in vascular smooth muscle cells via its action on potassium channels [83], this kind of a mechanism could be speculated.

4.4. Adverse effects of potassium

The renal mechanisms for potassium excretion adapt efficiently to increases in the rate of potassium influx to

extracellular fluid, particularly from dietary sources. Hence acute or chronic hyperkalemia due to exogenous potassium intake is uncommon, but usually occurs as a result of either potassium release from cells or decreased renal excretion [155]. However, iatrogenic hyperkalemia may result from excessive parenteral potassium replacement, in patients with renal insufficiency, or with certain drugs like potassium-sparing diuretics and ACE-inhibitors. Particularly potassium supplements may be hazardous, and case reports of even severe hyperkalemia following abundant ingestion of potassium chloride either as salt substitutes or tablets have been published [156–158]. Moreover, potassium chloride is irritating to the gastrointestinal tract, even to the extent of causing perforation.

Since the resting membrane potential is related to the ratio of the intracellular to extracellular potassium concentration, hyperkalemia partially depolarizes the cell membrane. Prolonged depolarization impairs membrane excitability and is manifested as weakness, which may progress to flaccid paralysis and hypoventilation if the respiratory muscles are involved. The most serious effect of hyperkalemia is cardiac toxicity. Electrocardiographic changes include increased T-wave amplitude, prolonged PR interval and QRS duration, and atrioventricular conduction delay, which may eventually lead to ventricular fibrillation or asystole [155].

In general, a moderate increase in dietary potassium intake is not likely to produce any toxic effects, unless its renal excretion is severely compromised. The regulatory mechanisms of the human body have evolved to save sodium and actively excrete potassium; the current high dietary sodium intake, especially in ratio to potassium, goes against this adaptation and is much more likely to cause problems [134].

5. Combinations of dietary minerals

Recently, a marked increase in the levels of potassium and magnesium in a variety of food items has been produced by using potassium- and magnesium-enriched salt alternatives instead of common salt. The beneficial effects of such a combination of dietary minerals have been well documented in an experimental model of essential hypertension, the spontaneously hypertensive rat [17,19,159–161]. The mineral salt lowers blood pressure, reduces left ventricular hypertrophy, and enhances the effect of various antihypertensive drugs, even when dietary sodium content is intentionally kept constant [20,21]. Potassium and magnesium appear to facilitate renal sodium excretion, although reduction in dietary sodium intake is also important, especially in humans. In fact, this is part of the rationale in using a mineral salt: sodium intake is automatically reduced when part of it is replaced with potassium and magnesium. The taste or technical properties do not necessarily differ from common salt, and the use of the mineral salt in food preparation has been shown to lower blood pressure in clinical studies as well [18,20,21].

Probably the most important recent study applying concurrent increases in the intake of several recommended nutrients, including the minerals calcium, potassium and magnesium, was the DASH trial. In this study, 459 adults with normal or moderately elevated blood pressure were assigned to receive for eight weeks a control diet, a diet rich in fruits and vegetables, or a “combination” diet rich in fruits, vegetables, and low-fat dairy products. Sodium intake and body weight were maintained at constant levels. Dietary changes produced remarkable decreases in blood pressure: in the group with the highest dietary mineral content the average decrease was 11.5 mmHg in systolic and 5.5 mmHg in diastolic blood pressure [11], which is statistically more than would be possible to achieve with either calcium or potassium alone. The combination diet also resulted in significant decreases in serum total and LDL cholesterols [162]. However, because the DASH diets consisted of “natural” changes in dietary patterns and not supplements, the changes in the intakes of other nutrients than minerals may also have contributed to the observed effects.

In obese Zucker rat, an experimental model of the metabolic syndrome, the effects of mineral supplements alone and in combination with plant sterols have been extensively studied. Supplementation of a high-fat diet with calcium, magnesium and potassium effectively lowered serum cholesterol levels, and even enhanced the effect of dietary plant sterols [163]. Plant sterols and stanols lower serum cholesterol by inhibiting the intestinal cholesterol absorption; this effect in patients with mild hypercholesterolemia is well established [164], and food products containing these compounds have been widely accepted as part of a healthy antiatherogenic diet [165]. From a mechanistic point of view, a positive interaction between plant sterols and the minerals could be expected, and was indeed found in this experimental study. However, this enhancement effect was confined to calcium and magnesium, whereas sodium and potassium had no independent effects on serum cholesterol [163]. Increased intake of dietary calcium and magnesium, both with and without potassium, also reduced the development of obesity during the four to seven week experiments [163].

In a long-term (up to two years) experiment, fortification of normal rat food with butter, cholesterol and common salt resulted in severe hyperlipidemia, hypertension and death in 6 to 12 months, apparently due to heart infarctions and kidney damage [166]. Addition of plant sterols and replacing the sodium chloride in this atherogenic diet partially with calcium, magnesium and potassium salts effectively prevented the diet-induced increases in total and LDL cholesterols and 24-hr systolic and mean blood pressures, and markedly improved endothelium-mediated vasorelaxation [166]. The combination of plant sterols and minerals also protected against cardiovascular and renal damage and considerably extended the life span of the rats [166].

Quite recently, the first clinical trial confirmed the cholesterol-lowering effect of a similar combination of natural plant sterols and recommended doses of the mineral nutrients calcium, magnesium and potassium [167]. Further research in humans is thus warranted to find out if a long-term use of foods enriched with this kind of combination of mineral nutrients and plant sterols is able to produce any of the other beneficial effects that were seen in the experimental setting.

6. Conclusion

Hyperlipidemia, hypertension, obesity and type II diabetes are strongly interrelated conditions and form a serious health hazard particularly to modern western populations. Dietary and lifestyle factors are most important causes behind these risk determinants; therefore, it would be reasonable to look for dietary approaches for their modification. Reduced intake of sodium and increased intakes of calcium, magnesium and potassium have proven antihypertensive in several studies in humans, and are currently recommended for even the general population by health organizations and officials worldwide. Furthermore, calcium is considered important in prevention of some other chronic diseases, primarily osteoporosis. Recent experimental, epidemiological and clinical evidence strongly suggests that increased intake of calcium is also useful in controlling the serum levels of harmful lipids, and possibly even obesity. Plant sterols and stanols are also recommended and useful for lowering of elevated blood cholesterol levels. The DASH study, in particular, has shown the practical relevance of combination diets low in sodium, fat and cholesterol, and high in calcium, magnesium, potassium, and plant fiber in treatment of elevated blood pressure and even in lowering serum lipid levels. Also a novel combination of mineral nutrients and plant sterols incorporated into various food items appears a promising approach to concurrent modification of several diet-induced cardiovascular risk factors.

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