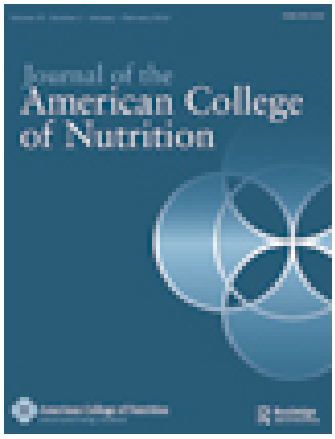

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Milk Products, Dietary Patterns and Blood Pressure Management

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Review

Milk Products, Dietary Patterns and Blood Pressure Management

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Key words: dairy foods, milk, blood pressure, hypertension, potassium, calcium, magnesium, DASH diet

High blood pressure (BP) is a major risk factor for heart disease, stroke, congestive heart failure, and kidney disease. Inverse associations between dairy product consumption and systolic blood pressure (SBP) and diastolic blood pressure (DBP) have been observed in cross-sectional studies; some studies, however, have reported an inverse association with only one BP parameter, predominantly SBP. Randomized clinical trials examining the effect of calcium and the combination of calcium, potassium and magnesium provide evidence for causality. In these studies, reductions in BP were generally modest (−1.27 to −4.6 mmHg for SBP, and −0.24 to −3.8 mmHg for DBP). Dairy nutrients, most notably calcium, potassium and magnesium, have been shown to have a blood pressure lowering effect. A low calcium intake increases intracellular calcium concentrations which increases 1,25-dihydroxyvitamin D_3 and parathyroid hormone (PTH), causing calcium influx into vascular smooth muscle cells, resulting in greater vascular resistance. New research indicates that dairy peptides may act as angiotensin converting enzyme (ACE) inhibitors, thereby inhibiting the renin angiotensin system with consequent vasodilation. A growing evidence base shows that dairy product consumption is involved in the regulation of BP. Consequently, inclusion of dairy products in a heart healthy diet is an important focal point to attain BP benefits.

Key teaching points

- Hypertension (≥ 140/90 mm Hg) is responsible for more deaths than any other risk factor for CVD and is predicted to become the leading cause of death and disability worldwide by 2020 [1–3].
- Epidemiologic studies have shown reductions in BP following 3 servings dairy/d, with greater benefits achieved when included in a low saturated fat diet, and using low-fat dairy products. Other cross-sectional studies however have found no decrease in blood pressure even with dairy intakes >5 servings/d.
- More robust evidence from a meta-analysis of randomized controlled studies reported a reduction in blood pressure with a mean 1200 mg calcium intake compared with intakes of <800 mg. Greater benefits in blood pressure lowering were observed from dairy foods vs. supplements, and in special populations such as African Americans.
- A meta-analysis of randomized controlled trials also reported that potassium supplementation (≥60 mmol/d) lowered systolic and diastolic BP by 4.4 mmHg and 2.5 mmHg in hypertensive subjects and by 1.8 mmHg and 1.0 mmHg in normotensive subjects. This effect also was greater in trials in which at least 80% of the subjects were black.
- The multi-center, Dietary Approaches to Stop Hypertension study (DASH), reported that 8 weeks consumption of a diet high in fruits, vegetables and fiber that also contained 2.7 servings of dairy products/d, and that was lower in total fat and saturated fat, lowered SBP and DBP by 5.5 and 3.0 mmHg greater than the control diet, whereas the fruits-and-vegetables diet (i.e. without dairy foods) produced blood pressure reductions of roughly half that of the DASH diet (SBP −2.8 mmHg; DBP −1.1 mmHg).
- Lifestyle practices that include a reduction in body weight, the DASH eating plan, a reduction in sodium intake, and moderate alcohol consumption, also are critical for reducing BP (Refer to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure for a description of these practices in relation to blood pressure reductions) [4].
- Emerging evidence indicates that dairy peptides also may act as ACE inhibitors thereby causing vasodilation and improving blood pressure.
- A better understanding on the mechanisms of dairy nutrients and dairy peptides will lead to more effective strategies through nutriceutical or pharmacological interventions to reduce hypertension, a major risk factor for cardiovascular disease.

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INTRODUCTION

High blood pressure (BP) is highly prevalent in the U.S. and is a major risk factor for heart disease, stroke, congestive heart failure, and kidney disease. According to the most recent National Health and Nutrition Examination Survey (NHANES) survey (1999–2004), 33.6% of adult Americans have hypertension (systolic BP ≥140 mm Hg, diastolic BP ≥90 mm Hg) or are taking BP lowering medications, and another 37.4% have prehypertension (systolic BP 120–139 mm Hg, diastolic BP 80–89 mm Hg) [5]. The relationship between BP and risk of cardiovascular (CVD) events is continuous, consistent, and independent of other risk factors [4]. No evidence of a BP threshold exists, i.e., the higher the BP, the greater is the chance of heart attack, heart failure, stroke, and kidney disease [6]. Data suggest that almost a third of BP-related deaths from coronary heart disease (CHD) occur in individuals with BP in the non-hypertensive range [7]. As the population ages, the prevalence of hypertension (HTN) will increase even further unless broad and effective preventive measures are implemented.

Clinical trials have established that blood pressure reduction in people with HTN reduces risk for a variety of BP-related endpoints including CHD [8]. In addition to pharmacological interventions, adoption of a healthy diet and lifestyle that includes exercise, weight loss, moderate alcohol intake, sodium reduction, and a dietary pattern rich in fruits, vegetables, and low-fat dairy products, are important for the prevention and management of hypertension (HTN) [4,9].

Previous studies indicate that the intake of calcium from non-dietary and dietary sources (primarily from dairy foods) is inversely related to BP regulation [10–17] while studies also suggest an inverse relationship between dairy product intake and insulin resistance syndrome, type 2 diabetes [18], and CVD [19]. The potential benefits of dairy food on these conditions have generally been ascribed to the major nutrients provided by dairy including calcium, potassium, magnesium and more recently, vitamin D. Dairy products provide about 83% of the calcium in the diets of young children, 77% in adolescent females' diets, and between 65% and 72% in adults' diets [20]. Milk and milk products are the number one source of potassium and magnesium in the U.S. diet [21], contributing 16% of the potassium, 15% of the magnesium; and these products also are the major source of vitamin D in the U.S. diet [22]. In an analysis of the first NHANES I survey, comprising dietary data from more than 10,000 American adults, an inverse association was identified between dietary calcium and BP levels; dietary calcium intake >1000 mg was associated with a 40–50% reduction in HTN prevalence [23]. Since then numerous studies have assessed the effects of dairy food intake on blood pressure and HTN risk.

The purpose of this review is to describe the current understanding of the relationship between dairy food intake and BP, and HTN risk, based on results from population studies and randomized clinical trials and to review potential mechanisms of action.

RESULTS FROM OBSERVATIONAL STUDIES

Several observational studies have shown a relatively consistent inverse association between the intake of dairy foods and HTN risk and at least one parameter of BP, i.e. SBP and/or DBP (Table 1) [13,16,24–38], whereas other studies have reported equivocal or no inverse associations [39–41]. Many factors however appear to markedly influence the dairy-BP-HTN association including the type of dairy product and fat level, dietary mineral status, gender and HTN, and CVD risk status.

What Are the Effects of Dairy Intake on SBP and DBP?

In cross-sectional studies, significant inverse associations have been observed between dairy intake and both SBP and DBP [27,31,33,36], however these effects have been inconsistent since other studies have generally found significant inverse effects on only one BP parameter, predominantly SBP, but not both [24,28–30,34,37].

Dairy and SBP vs. DBP Findings. In a large cross-sectional study of the NHLBI Family Heart Study cohort involving 4,797 normal and high CVD risk, from the lowest to the highest quartile of dairy intake ranging from 0.4–3.1 servings of dairy/d and after multivariate adjustments, there was a graded inverse association between dairy intake and SBP (P_{trend} = 0.003) that corresponded to a 2.6 mmHg reduction in SBP whereas little effect was seen on DBP (−0.9 mmHg, P_{trend} = 0.09), when comparing the highest vs. lowest quartile of dairy intake [28]. The inverse dairy-SBP association was further enhanced (−3.5 mmHg lower SBP) in subjects whose saturated fat intake was below the population median of 11.2% of energy. In this same vein, other studies have examined the effects of dairy products on BP changes based on product type and fat level [27,34,37]. In a longitudinal analysis of older participants (55–80 yrs) at high CVD risk, after 12 months of follow-up, consumption of low-fat dairy products from the lowest to the highest intakes (3.1–631.6 g/d) was inversely associated with SBP (−4.2 mmHg, P_{trend} = 0.01) but not DBP (−1.8 mmHg, P_{trend} = 0.01), whereas no significant trends in SBP or DBP were observed with whole-fat dairy product intake [37]. Similarly, in a cross-sectional study from the French MONICA cohort consisting of 912 men that were treated or untreated for HTN, after multivariate adjustments, the intake of milk or milk + fresh cheese was inversely associated with lower SBP (P_{trend} 0.02 and 0.04, respectively), whereas intake of all dairy products with or without butter showed a non-significant inverse association with SBP (P_{trend} 0.08 and 0.06, respectively).

Table 1. Populations Studies Reporting Associations between Dairy Intake and Blood Pressure

Author, year [Ref.]	Age, mean or range (yr)	Gender	Design, Cohort Total/no. cases (follow-up, yrs)	Outcome (measure)	Dairy predictor, (range, or category or lowest and highest amount)	Results	Adjustments
Ackley, 1983 [24]	30–79	M	Cross-sectional Normotensives, borderline and hypertensives N = 541	SBP/DBP (correlation coefficient)	Total dairy Ca or Whole milk Ca, (NR)	Total dairy intake inversely correlated with DBP ($r = -0.067$; $p < 0.05$) but not SBP. Whole milk intake inversely correlated with SBP ($r = -0.067$, $p < 0.05$) but not DBP.	Age, obesity, alcohol
Alonso, 2005 [25]	37	M/F	Prospective, SUN N = 5,880 (2.25 yrs)	HTN risk (Hazard Ratio)	Dairy intake (g/d), Low-fat: 47 and 474 Whole-fat: 108 and 324 Total: 156 and 799	Low-fat: HR = 0.46 (0.26–0.84; P_{trend} 0.02) Whole-fat: HR = 1.37 (0.77–2.42, P_{trend} 0.44) Total dairy: HR = 0.75 (0.45–1.27; P_{trend} 0.12)	Age, sex, BMI, exercise, energy intake, smoking, fruit, fiber, caffeine, Na, Mg, K, MUFA, SAFA
Ascherio, 1996 [39]	38–63	F	Prospective, Nurses' Health Study N = 41,541	SBP/SBP	Dairy intake (g/d) Amounts NR	Intakes of low-fat and high-fat dairy products not significantly associated with SBP or DBP	Age, BMI, energy and alcohol intake, eight food groups added simultaneously
Azadbakht, 2005 [26]	18–74	M/F	Cross-sectional, Tehranian adults N = 827	Elevated BP (Odds Ratio)	Dairy Intake: milk, yogurt, cheese <1.7 and >3.1 servings/d	Total dairy inversely correlated with hypertension: OR = 0.83 (0.69–0.99; $P < 0.05$, P_{trend} <0.03 (all adjustments)	Age, BMI, BP and estrogen drugs, smoking, exercise, intake of energy, fat, food groups, calcium, protein
Beydoun, 2008 [27]	≥18	M/F	Cross-sectional NHANES 14,464	SBP/DBP	Fluid milks (servings/d) Yogurt (servings/d) Cheese (servings/d)	All milk: inversely associated with SBP and DBP, $P < 0.05$ Yogurt: inversely associated with SBP and DBP, $P < 0.05$ Cheese: positively associated with SBP and DBP, $P < 0.05$	Age, sex, ethnicity, SES, energy intake, exercise
Djousse, 2006 [28]	52	M/F	Cross-sectional, NHLBI FHS N = 4,797/728	HTN prevalence (Odds Ratio, SBP and DBP)	Dairy intake (servings/d) 0.4 and 3.1 servings/d	Dairy: inversely associated with HTN prevalence: OR = 0.64 (0.46–0.90; P_{trend} 0.01 Dairy: inversely associated with SBP, P_{trend} 0.01 Dairy: has little relation to DBP, P_{trend} 0.09	Age, sex, BMI, exercise, energy intake, smoking, CHD, diabetes, intake of fruit, vegetables, fiber, Na, Mg, K, caffeine, MUFA, n-6 PUFA, SAFA, alcohol
Elwood, 2004 [29]	45–59	M	Prospective, Caerphilly N = 2,512/678 20–24	Ischemic heart disease, Ischemic stroke	Milk intake: (pint/d) None and >1 pint/d	Milk: inversely associated with SBP, P_{trend} 0.02 Milk: Has no relation to DBP, P_{trend} 0.11	Energy intake
Iso, 1991 [30]	40–69	M	Cross-sectional Japanese populations N = 1,928	SBP/DBP (correlation coefficient)	Dairy calcium intake (change mmHg/100 mg increased/d)	Dairy Ca: inversely associated with SBP ($r = -1.12$; $p < 0.001$) Dairy Ca: inversely associated with DBP ($r = -0.40$; NS)	Age, BMI, intake of alcohol, sodium

Table 1. Continued

Author, year [Ref.]	Age, mean or range (yr)	Gender	Design, Cohort Total/no. cases (follow-up, yrs)	Outcome (measure)	Dairy predictor, (range, or category or lowest and highest amount)	Results	Adjustments
Joffres, 1987 [31]	NR	M	Cross-sectional Honolulu Heart Study N = 1,379/615	SBP/DBP (correlation coefficient)	Milk intake, (NR)	Milk: inversely associated with SBP ($r = -1.12$; $p < 0.01$)	Age, BMI
Jorde, 2000 [49]	25–69	M/F	Cross-sectional Tromso Study N = 15,596	SBP/DBP	Dairy intake	Milk: inversely associated with DBP ($r = -1.12$; $p \leq 0.01$)	
Pereira, 2002 [32]	18–30	M/F	Prospective CARDIA N = 3,157 (10 yrs)	HTN (% incidence)	Dairy intake (times/wk) 0–<10 and ≥35 times/wk	Dairy: associated with lower incidence of HTN (%): BMI ≥25, $P_{trend} < 0.001$ BMI <25, $P_{trend} < 0.06$	Age, sex, race, BMI, energy intake, study center
Reed, 1985 [33]	NR	M	Cross-sectional Honolulu Heart Study N = 6,496	SBP/DBP (regression coefficient)	Milk intake (oz/d)	Milk: inversely associated with SBP ($r = -0.04$; $p < 0.001$) Milk: inversely associated with DBP ($r = -0.04$; $p < 0.01$)	Age, BMI, exercise, alcohol intake
Ruidavets, 2006 [34]	45–64	M	Cross-sectional French MONICA N = 912	SBP/DBP	Dairy intake: ≤93 and >335 g/d	Total population, n = 912: Milk: inversely associated with SBP, P_{trend} 0.02 but not DBP All dairy + butter: NS trend for SBP and DBP Subjects untreated for HTN, n = 726: Milk: inversely associated with SBP, P_{trend} 0.006 but not DBP, P_{trend} 0.07 All dairy + butter: inversely associated with SBP, P_{trend} 0.004 but not DBP, P_{trend} 0.11	Age, BMI, exercise, dieting & energy intake, smoking, center, dyslipidemia drugs, diabetes, intake of Na, Mg, K, caffeine, alcohol
Snijder, 2007 [41]	50–75	M/F	Cross-Sectional Hoorn Study N = 1,896	SBP/DBP	Total dairy, median range intake of milk, cheese, yogurt, dairy desserts, 2.9–5.6 servings/d	Total dairy: inversely associated with DBP, (β −0.31 mmHg/serving, $P = 0.01$) but not SBP.	Age, sex, exercise, smoking, education level, antihypertensive drugs, intake of energy, fiber, alcohol
Snijder, 2008 [40]	50–75	M/F	Prospective Hoorn Study N = 1,124 (6.4 yrs)	SBP/DBP	Total dairy, median range intake of milk, cheese, yogurt dairy desserts, 2.9–5.6 servings/	Total dairy: was not associated with changes in SBP or DBP.	Age, sex, race, exercise, smoking, intake of energy, alcohol
Steffen, 2005 [35]	18–30	M/F	Prospective, CARDIA N = 4,304 (15 yrs)	Incidence of elevated BP (Hazard Ratio)	All dairy intake: <1.1 and ≥3.4 times/d Milk intake: <0.3 and >2.1 times/d	All dairy: NS association with elevated BP, HR = 0.85 (0.67–1.08, P_{trend} 0.06) Milk: inversely associated with elevated BP, HR = 0.87 (0.70–1.08, P_{trend} 0.03)	Age, sex, race, BMI, exercise, energy intake, smoking, center, intake of vitamins, alcohol, food groups

Table 1. Continued

Author, year [Ref.]	Age, mean or range (yr)	Gender	Design, Cohort Total/no. cases (follow-up, yrs)	Outcome (measure)	Dairy predictor, (range, or category or lowest and highest amount)	Results	Adjustments
Takashima, 1998 [36]	40–49	M	Cross-sectional, Japanese N = 473	SBP/DBP	Dairy intake: < 1.0 and >5.0 times/wk	Dairy: inversely associated with SBP (p = 0.003, P_{trend} 0.005) and DBP (P = <0.001, P_{trend} < 0.001)	Age, residence occupation, BMI, alcohol intake
Toledo, 2008 [37]	55–80 M 60–80 F	M/F	Longitudinal, PREDIMED N = 2,290 (1 yr)	SBP/DBP	Low-fat dairy intake: 3.1 and 631.6 g/d Whole-fat dairy intake: 34.9 and 261.1 g/d	Low-fat dairy: inversely associated with SBP −4.2 mm Hg (P_{trend} 0.01) but not DBP −1.8 (P_{trend} 0.09) Whole-fat dairy: no association with SBP, 0.0 mmHg (P_{trend} 0.84) or DBP, 0.3 mmHg (P_{trend} 0.61)	Age, BMI, exercise, smoking, center, diabetes, lipidemia, intake of energy, Na, Ca, Mg, K, protein, MUFA, fiber, fruits, vegetables, alcohol, NSAIDS, anti-hypertensive drugs
Wang, 2008 [38]	≥45 yrs	F	Prospective, Women's Health Study N = 28,886/8,710 (10 yrs)	HTN risk (Relative Risk)	Dairy intake (servings/d): Low-fat dairy: 0.13 and 2.71 High-fat dairy: 0.13 and 1.49 Total dairy: 0.56 and 3.69	Low-fat dairy: inversely associated with HTN risk, RR = 0.89 (0.82–0.96, P_{trend} 0.001) High-fat dairy: no association with HTN risk, RR = 0.97 (0.90–1.04, P_{trend} 0.17) Total dairy: inversely associated with HTN risk, RR = 0.86 (0.79–0.93, P_{trend} 0.003)	Age, race, smoking, exercise, postmenopausal, BMI, diabetes, hypercholesterolemia, intake of: energy, fruits, vegetables, whole grain, red meat

NR = Not reported, NS = non-significant, HTN = hypertension, M = male, F = female, BP = blood pressure, SBP = systolic blood pressure, DBP = diastolic blood pressure, OR = odds ratio, HR = hazard ratio, RR = relative risk, BMI = body mass index, CHD = coronary heart disease, Ca = calcium, Mg = magnesium, K = potassium, NA = sodium, MUFA = monounsaturated fatty acids, n−6 PUFA = linoleic acid, SAFA = saturated fatty acids, SUN = Seguimiento Universidad de Navarra, NHANES = National Health and Nutrition Examination Survey, CARDIA = Coronary Artery Risk Development in Young Adults, MONICA = MONItoring of trends and determinants of CArdiovascular disease, NSAIDS=non-steroidal anti-inflammatory drugs.

When only those men who were not being treated with antihypertensive drugs were considered, however, (n = 726, 76% of the cohort), the inverse associations with all dairy products, regardless of fat level, were strengthened and highly significant (milk, milk + fresh cheese, all dairy with or without butter: P_{trend} 0.006, 0.007, 0.002, 0.003, respectively) [34]. It was suggested that drug treatment may complicate the analysis because of varying degrees of control by antihypertensive drugs. Furthermore, hypertensive subjects may have improved their dietary behavior after being diagnosed. For example, subjects with controlled HTN have been shown to have significantly higher calcium intakes than un-controlled HTN; and in subjects treated with antihypertensive drugs, moderate sodium intakes in combination with calcium intakes >800 mg/d have reduced the risk of poor BP control by 52% [42].

Other studies have found equivocal or no association between the consumption of dairy products and BP [39–41]. In a prospective study from the Nurses' Health cohort involving 41,541 middle-aged and older U.S. women followed for 4 years, after multivariate adjustments for factors related to BP, only fruits, vegetables, dietary magnesium and fiber intakes were inversely associated with SBP and DBP, whereas high-fat and low-fat dairy foods, calcium and potassium were not [39]. Similarly, in another prospective study of dairy consumption and 6.4-year change in BP from the Hoorn Study cohort involving 1,124 Dutch subjects, after multivariate adjustments, dairy consumption from the lowest (0–2.9 servings/d) to the highest (5.75–17.2 servings/d) was not associated with changes in SBP or DBP (P = 0.286 and 0.990, respectively) [40]. The results did not change after further adjustments for fiber intake, education and income level, or medication use, or exclusion of subjects using glucose-lowering, lipid-lowering or antihypertensive medications, or stratification by BMI or presence of hypertension. In contrast, a cross-sectional analysis of the same cohort involving 1,896 subjects, total dairy consumption was significantly associated with lower DBP (β −0.31 mmHg/serving, P = 0.01) but not with SBP [41]. High-fat and low-fat dairy products each showed non-significant inverse associations

with SBP and DBP, whereas when different dairy products were examined, significant or borderline inverse associations were found for milk and DBP ($P = 0.01$), dairy desserts and SBP ($P = 0.03$) and yogurt and SBP ($P = 0.08$), whereas no association was observed for cheese. In general, results from this study show that larger consumption of dairy products was associated with modest reductions in BP, whereas the discordant dairy-BP findings between these 2 studies from the same cohort are difficult to explain.

Dairy's Nutrients and BP. Dairy foods contain a number of nutrients that have been linked to reducing BP. Dairy foods contribute about 70% of the total calcium in U.S. diet and evidence suggests that the inverse association between dairy product intake and BP may be attributed to their high levels of calcium. Other minerals, particularly potassium and magnesium also have been linked to reducing BP [31,43–45]. Early cross-sectional studies suggested that the mix of nutrients in dairy may be a stronger predictor of reducing BP than individual nutrients based on findings showing that calcium and potassium from dairy foods were inversely associated with BP, whereas non-dairy calcium [30] or non-dairy calcium and potassium were not [33]. These results are supported by later findings from a cross-sectional analysis of the French MONICA cohort showing that the inverse association between dairy intake and SBP was stronger when the consumption of both dairy products and dietary calcium was high [34]. After multivariate adjustments, the changes in SBP between the highest and lowest levels of calcium intake and milk intake were −5.4 mmHg ($P = 0.008$, P_{trend} 0.006) and −3.6 mmHg ($P = 0.09$, P_{trend} 0.02), respectively, whereas the combination of milk and non-dairy calcium intake resulted in a statistically stronger inverse relationship −5.5 mm Hg ($P = 0.0006$). Other factors also may be involved since the highest quintile of dairy products and calcium intake was related to healthier diet and lifestyle behaviors including higher consumption of fruits and vegetables (70%), lower sodium intakes (20%), higher levels of physical activity and lower degrees of smoking and alcohol consumption. Using data from the cross-sectional NHANES 1999–2004 study, multivariate logistic regression models suggested that fluid milk, yogurt, magnesium and phosphorus intakes were inversely associated with SBP, whereas no association was found with calcium intake from other foods [27].

What Is the Association between the Intake of Dairy Foods and Risk of HTN?

Substantial evidence exists from epidemiologic and randomized clinical trials showing that dietary patterns containing high amounts of fruits and vegetables, foods that are major components of the DASH diet, are inversely and independently associated with BP [46–48]. Dairy products also are key components to the DASH diet but the independent role of dairy and dairy components on BP and HTN risk are not as well understood. The association between dairy product intake and HTN risk or changes in BP has been assessed mainly in cross-sectional studies (Table 1). On the other hand, only a limited number of studies have been conducted examining prospectively the association between the intake of dairy products and the incidence of HTN development in large cohorts with a range of follow-up periods [25,32,35,38] (Table 1).

In the Coronary Artery Risk Development In young Adults (CARDIA) study, a prospective study of 3,157 U.S. young adults 18–30 yrs followed for 10 yrs, the incidence of elevated BP (130/85) was inversely associated with total dairy food intake in subjects with a BMI ≥ 25 ($P_{trend} < 0.001$) but not in normal weight subjects, albeit this trend was marginally significant ($P_{trend} < 0.06$) [32]. The inverse relationship was observed for both reduced and high fat dairy products and the odds of elevated BP was lowered by about 20% for each daily eating occasion of dairy products. In a subsequent follow-up study in this same cohort involving 4,304 participants followed for 15 yrs, total dairy food intake (i.e. milk, cheese, yogurt, and dairy desserts) was unrelated to the incidence of elevated BP ($P_{trend} < 0.06$). However, in an analysis of dairy products subgroups, inverse associations with elevated BP were found for milk intake ($P_{trend} < 0.03$) and dairy desserts ($P_{trend} < 0.01$) but not for cheese ($P_{trend} < 0.57$) or yogurt ($P_{trend} < 0.14$) [35]. Thus, findings from this young adult cohort suggest some level of consistency of an inverse relationship between the intake of fluid milk and dairy desserts and elevated BP. In contrast, another prospective study examined the relationship between total, low-fat and whole-fat dairy intake and risk of HTN in 5,880 middle aged adults (mean age: 37 yrs) over a follow-up period of 2.25 years [25]. After multivariate adjustments, a significant reduction in the risk of HTN in the highest vs. lowest intake of low-fat dairy products was reported [Hazard ratio (HR): 0.46; 95% CI: 0.26–0.84; $P_{trend} < 0.02$], whereas no association was found with total dairy, whole-fat dairy or total calcium [25]. Likewise, calcium intake from low-fat dairy products was significantly associated with reduced risk of HTN, but not for whole-fat dairy products. It was noted, however, that calcium per se has only a small effect on BP and cannot fully explain the degree of reduction observed in this study [25].

Finally, in the Women's Health Study, a prospective study of 28,886 U.S. older women ages ≥ 45 yrs (mean age: 53.8 yrs) followed for 10 yrs, after adjustment for HTN risk factors, the relative risk (RR) of incident HTN was inversely associated with total dairy product and low-fat dairy product intakes: RR: 0.86; 95% CI: 0.79–0.83; P_{trend} 0.0003 and RR: 0.89; 95% CI: 0.82–0.96; P_{trend} 0.001, respectively, but not for high-fat dairy products [38]. When additional adjustments were made for dietary calcium, the inverse association of total dairy and low-fat dairy products intake with HTN risk was attenuated and no longer significant, suggesting a strong role for dietary calcium. Of the four categories of low-fat dairy products (skim milk, sherbet, yogurt, cottage cheese) only skim milk intake was inversely associated with HTN risk. Both dietary calcium

and dietary vitamin D were inversely associated with HTN risk, whereas non-dairy supplemental calcium and vitamin D were not, suggesting the possible synergistic interaction of dairy calcium with other potential antihypertensive nutrients in dairy foods.

Taking the cross-sectional and prospective studies together (Table 1), results from most [24–38,41,49] but not all [39–41] observational studies have demonstrated that increased intakes of at least one category of dairy products (e.g. total, high-fat, low-fat) are inversely associated with changes in at least one parameter of BP (i.e. SBP, DBP) and the risk of HTN. When only considering those studies that have examined the dairy-BP-HTN relationship in prospective trials, most [25,29,32,35,38] but not all [39,40] have observed an inverse association between dairy product consumption and changes in BP or development of HTN.

EVIDENCE FROM RANDOMIZED CLINICAL TRIALS

Effects of Calcium, Potassium and Magnesium

Randomized clinical trials (RCTs) provide stronger evidence for causality; clinical studies have been conducted to examine the effect of calcium [10,12,14,17,50] and mixtures of calcium, potassium and magnesium [44,51–53] supplementation on BP, but reductions are generally modest. In a meta-analysis of 40 RCTs, Van Mierlo (2006) reported that calcium supplementation (mean 1,200 mg/d) reduced SBP by −1.86 mmHg (95% CI: −2.91 to −0.81) and DBP by −0.99 mmHg (95% CI: −1.61 to −0.37) [17]. The differences in BP response did not change significantly based on stratification for age (<45 vs. ≥45 years), initial BP (<140/90 vs. ≥140/90 mmHg) and gender, but there was a tendency toward greater BP response to calcium in groups with habitually low baseline calcium intake i.e. ≤800 mg/d (−2.6 SBP/−1.3 DBP mmHg) compared to those with higher intake (−0.9 SBP/−0.6 DBP mmHg). Additionally, in further subgroup analysis, studies that increased calcium intake from conventional foods (primarily dairy) tended to have a larger effect on SBP than calcium supplements (−2.56 mmHg; 95% CI: − 4.98 to −0.13) vs. −1.70 mmHg; 95% CI: −2.85 to −0.55), but this was not consistent for DBP (−0.51 mmHg; 95% CI: −1.96 to 0.95) vs. −1.10 mmHg; 95% CI: −1.78 to −0.41). This observation is consistent with an earlier meta-analysis which compared dietary and non-dietary trials resulting in an estimated reduction in SBP and DBP of −2.10 and −1.09 mmHg in the dietary studies vs. − 1.09 and 0.087 mmHg for the non-dietary studies [14]. Although the results from both meta-analyses found that the inverse effects on SBP and DBP were 50–100% greater for the dietary vs. non-dietary studies, the differences were not statistically different.

In a meta-analysis of randomized clinical trials, potassium supplementation reduced both SBP (−5.9 mmHg) and DBP (−3.4 mmHg) [54]; and in another meta-analysis of 33 randomized controlled trials in which potassium was the only variation between intervention and control groups, a significant but less decrease in SBP (−3.11 mmHg) and DBP (−1.97 mmHg) was reported [45]. The effect of potassium was enhanced in those with a high intake of sodium; and the blood pressure lowering effect was greater in trials in which the majority were black. In a large clinical trial of 300 normotensive women with low habitual intakes of potassium, calcium, and magnesium, supplemental potassium (40 mmol), calcium (1200 mg), magnesium (336 mg), a combination of all nutrients, or placebo, was consumed for 16 weeks [44]. The change in 24-hour ambulatory blood pressure only was lower following the potassium supplement (−2.0 mmHg, 95% confidence interval, −3.7 to −0.3) vs. placebo, and the combined effect of calcium and magnesium with potassium did not improve the effect of potassium alone [44]. This suggests that potassium may have a stronger influence on blood pressure compared with calcium and magnesium.

Overall, the results of calcium supplementation on SBP and DBP have been modest ranging from −2.6 to −1.27 mmHg for SBP and −0.84 to −0.24 for DBP [12,14,17,50]. Meta-analysis of potassium and magnesium combinations showed statistically non-significant reductions in both SBP and DBP (−4.6 and −3.8 mmHg, respectively) [51], however potassium supplementation alone has improved BP [44,54]. Nevertheless, despite the relatively small reductions in BP resulting from calcium, potassium and magnesium supplementation, even small changes in BP in large proportions of the population for a condition such as HTN could have important public health implications for reducing adverse cardiovascular outcomes.

Dairy Product RCTs and BP

There are five published intervention studies that have examined the independent effect of dairy products on BP [55–59] and 2 that have assessed the effect of dietary patterns that contained dairy products in conjunction with other food groups [60,61] (Table 2).

In an 8 week free-living crossover study of 50 normal adult subjects with low baseline calcium intakes of 500 mg/d, supplementation with 1,150 mg calcium/d from dairy products resulted in a 5 mmHg reduction in SBP ($P < 0.02$) and a 1 mmHg non-significant reduction in DBP, whereas supplementation with 1 L/d of orange juice did not significantly alter SBP or DBP [62]. In this study, however, no comparison of BP changes between the dairy and control (orange juice) groups were provided. In another study involving 53 free-living, normotensive young adult female subjects with a mean baseline calcium intake of 930 mg/d, who then adopted a low calcium diet of <500 mg/d during the experimental period, supplementation of their typical diet for 6 weeks with 1 L/d of conventional dairy products (milk and yogurt) that provided 1,180 mg

Table 2. Intervention Trials of Dairy Product Intake on Blood Pressure

Author, year [Ref.]	Age, mean or range (yr)	Gender, (Race)	Design, No. subjects	Duration (wks)	Intervention, amount	Baseline, SBP/DBP (mm Hg)	Δ SBP (mm Hg)	Δ DBP (mm Hg)
Dairy studies								
Barr, 2000 [55]	65.2	M/F, (white)	Free living, randomized, controlled, parallel N = 204	12	Milk: 1% or skim 3 cups/d	126 ± 12/ 76 ± 8	− 2.0, P = 0.57	− 1.0, P = 0.44
Bierenbaum, 1988 [56]	21–65	M/F (NR)	Free living crossover N = 50	8	Dairy intake: 1% Milk, 1 pint/d + 1% cottage cheese, 4 oz/d + Yogurt, 1 cup/d	120 ± 1.5/ 79 ± 0.85	− 5.0, P < 0.02[a]	− 1.0, NS[a]
Hilary Green, 2000 [57]	> 40 yrs	M/F (white)	Free living, randomized, double-blind, crossover N = 38	4	SM, 480 ml/d SM + Ca, 480 ml/d SM + Ca + K, 480 ml/d	121 ± 14/ 77 ± 9	SM: − 3.0, P < 0.05[a] SM + Ca: − 4.0, P < 0.005[a] SM+Ca+K: − 8.0, P < 0.001[a]	SM: − 2.0, NS[a] SM + Ca: − 2.0, NS[a] SM+Ca+K: − 2.0, NS[a]
Kynast-Gales, 1992 [58]	46–75 yrs	M (white)	Free living, randomized, controlled, crossover N = 13	4	Dairy foods: 7 exchanges/d @ 100 mg Ca/exchange	136/83	+ 4.0, P = NS	+ 1.0, NS
Van Beresteijn, 1990 [59]	19–23 yrs	F (white)	Free living, randomized, double-blind, controlled, parallel N = 53	6	Regular vs. mineral poor dairy: Milk and yogurt: 1 L/d	114.0 ± 10.1/ 63.2 ± 8.2	− 2.9, P = 0.03	est. + 0.2, NS
Dietary pattern studies								
Appel, 1997 [60]	44.5 yrs	M/F (white/ black)	Randomized, controlled, parallel N = 459	8	Fruits + vegetables, 5.2 + 3.3 servings/d Fruits + vegetables + low-fat diary, 5.2 + 4.4 + 2.7 servings/d	131 ± 10 85 ± 13	Fruits + Vegetables: −2.9, *P* < 0.001 Fruits + Vegetables + low-fat dairy: −5.5, *P* < 0.002	Fruits + Vegetables: −1.1, *P* < 0.07 Fruits + Vegetables + dairy: −3.3, *P* < 0.001
Sacks, 2001 [61]	48 yrs	M/F (white/ black)	Randomized, controlled parallel N = 412	4.3	DASH high Na DASH intermediate Na DASH low Na	134.5 ± 10 86.0 ± 5	DASH high Na: −5.9, P < 0.001 DASH intermediate Na: −5.0, P < 0.001 DASH low Na: −2.2, P < 0.05	DASH high Na: −2.9, P < 0.001 DASH intermediate Na: −2.5, P < 0.01 DASH low Na: −1.0, N.S.
Nowson, 2004 [67]	55.6 yrs	M/F (NR)	Free living, randomized, controlled, crossover N = 94	4	LNAHK: Low Na, very high K, high F&V, low dairy HC: Very high Ca, mod K, high dairy ≥4 servings/d OD: DASH, High Ca, High K, ≥8 servings/d F&V, ≥3 servings/d dairy	129.4 ± 11.3 80.6 ± 8.6	LNAHK −OD: −3.5, P < 0.001 HC −OD: +3.3, P < 0.01	LNAHK − OD: −1.9, P < 0.05 HC −OD: +0.8, NS

NR = Not reported, NS = non-significant, M = male, F = female, SBP = systolic blood pressure, DBP = diastolic blood pressure, SM = skim milk, F&V = fruits and vegetables, Ca = calcium, K = potassium, Na = sodium,

[a] compared to baseline.

calcium, 1,650 mg potassium and 110 mg magnesium/d resulted in a 5.1 mmHg reduction in SBP ($P = 0.03$) compared to a 2.2 mmHg reduction in subjects consuming equivalent amounts of 'mineral poor' dairy products (95 mg calcium, 580 mg potassium and 10 mg magnesium/d). No effect on DBP was observed with either treatment [59]. In a short term 4-week crossover study that examined BP responses to dairy products enriched with calcium and potassium in 38 normotensive and hypertensive subjects (37% of group) with baseline calcium and potassium intakes of 1,120 mg and 4,009 mg/d, respectively, replacing their usual milk intake with 2 servings/d of conventional skim milk (control: 1,480 mg calcium and 1,700 mg potassium/d), high-calcium skim milk (2,150 mg calcium and 1,710 mg potassium/d) or potassium enriched high-calcium skim milk (2,080 mg calcium and 3,170 mg potassium/d) resulted is SBP changes of −3.0 mmHg ($P = 0.05$), −4.0 mmHg ($P = 0.05$) and −8.0 mmHg ($P = 0.001$), respectively [57]. No effect on DBP was observed with the control or high-calcium treatments; whereas the potassium enriched high-calcium treatment resulted in 2.0 mmHg reduction in DBP. In contrast, other studies have found no effect of dairy supplementation on BP. In a small short term 4-week crossover study involving 13 hypertensive middle-older aged Caucasian men not taking hypertensive medications with baseline calcium and potassium intakes of 964 mg and 3,085 mg/d, respectively, consumption of a low-calcium (406 mg/d) or high-calcium (1,515 mg/d) diet through manipulation of dairy product intake did not result in any significant changes in SBP or DBP [58]. Similarly, in a relatively large multi-center parallel study involving 204 older Caucasian normotensive men and postmenopausal women (mean age: 65.2 yrs; SBP/DBP: 127/76.5) with baseline calcium and potassium intakes ranging from 649–801 mg and 2,564–3,295 mg/d, respectively, and intakes of ≤1.5 servings/d of dairy products, consumption of a diet containing 3 cups/d of low-fat or fat-free milk that increased calcium and potassium intakes to 1,404–1,556 mg and 3,444–4,059 mg/d, respectively, compared to subjects that maintained their usual intake of dairy, decreased SBP and DBP similarly over time in both groups ($P = 0.005$) but no differences were observed between groups. In a *post-hoc* analysis of 32 subjects with high SBP (>140 mmHg), DBP decreased 3.8 mmHg in subjects in the milk group compared with a non significant 0.8 mmHg reduction in the control group. The authors noted that unlike the subjects in this study who had normal baseline BP and good nutrient intake profiles, individual's showing BP reductions from the DASH diet that included, among other components, increased intakes of calcium, potassium and magnesium, tended to have higher initial BP's, have poorer diets and typically were African American [60,63]. Additionally, it was noted that the final blood pressures measured after interventions in the Dietary Approaches to Stop Hypertension (DASH) trial [60] and in the current study were very similar, suggesting that there may be a threshold of BP below which any additional intakes of calcium (and other minerals) have no additional beneficial effect.

DASH and the Role of Dairy

The DASH multi-center controlled-feeding trial involved 459 subjects with high-normal blood pressures (SBP/DBP = 131/84.7 mmHg), not taking hypertensive medications, and low baseline intakes of calcium, potassium and magnesium intakes (25th percentile of U.S. consumption) [60]. Subjects consumed one of three diets for 8 weeks: 1) a control "typical American" diet low in fruits, vegetables and dairy products, 2) a diet high in fruits and vegetables (8.5 servings/d), high in dietary fiber (31 g) and low in dairy products, or 3) a "combination diet" similarly high in fruits, vegetables and fiber, and that also contained 2.7 servings of dairy products/d and was lower in total fat and saturated fat (DASH diet). The DASH diet lowered SBP and DBP by 5.5 and 3.0 mmHg greater than the control diet, whereas the fruits-and-vegetables diet (i.e. without dairy foods) produced BP reductions of roughly half that of the DASH diet (SBP −2.8 mmHg; DBP −1.1 mmHg). Blood pressure changes with the DASH diet were greatest in subjects with established hypertension (SBP ≥140 mmHg or DBP ≥ 90 mmHg; 29% of subjects). In a subgroup analysis of hypertensive subjects, the high fruits-and-vegetables diet reduced SBP and DBP by 7.2 and 2.8 mmHg more than the control diet, whereas the DASH diet, with its inclusion of dairy foods, resulted in decreases of 11.4 and 5.5 mmHg, respectively. It was noted that, in hypertensives, the BP improvements produced with DASH rival those observed in trials with antihypertensive medications [64]. At study completion, 70% of the DASH diet cohort had normal BP (SBP <140 mmHg, DBP <90 mmHg), compared with 23% of the control group and 45% of the fruits and vegetables diet group [65]. Among African Americans, the DASH diet resulted in BP reductions of 6.9 mmHg SBP and 3.7 mmHg DBP greater than the control diet [66]. These reductions were approximately double those achieved with the fruits and vegetables diet that did not include dairy foods. Particularly noteworthy in the African American cohort, in which lactose maldigestion is presumed to occur more commonly than in other racial groups, was the lack of adverse gastrointestinal effects that might be expected with the addition of 3 dairy servings to the daily diet [60]. The greater reductions in BP seen with the DASH diet compared to the high fruits and vegetable diet cannot be ascribed to dairy products *per se* because the study was not designed to identify the independent BP effects of the dietary components and because other dietary alterations besides the addition of dairy products were incorporated including a reduction in total fat and saturated fat. Nonetheless, since changes in diet related factors known to effect BP such as sodium, body weight, and alcohol consumption were small and consistent across the diets, it is highly suggestive that some aspects of the DASH diet including

increased calcium, potassium and magnesium or other components provided by the addition of dairy products and/or the lower level of saturated fat may play significant and possibly synergistic roles in reducing BP. The BP effects of the DASH diet were further examined in a second study: the DASH-Sodium Trial, in which the diet was tested with various levels of sodium (high: 140 mmol/d; intermediate: 100 mmol/d; low: 65 mmol/d [61]. Consistent with the first DASH trial, BP was significantly reduced in persons consuming the DASH diet compared to the control diet, and this occurred across all levels of sodium intake and in a dose-response manner with sodium reductions. This study confirmed that for most adults, with the exception of older persons with established HTN, regular consumption of a high quality diet, rich in fruits, vegetables, and dairy products, which also is reduced in sodium, is the optimal dietary means of controlling BP. Following this, Nowson et al. [67] examined the effects on BP of two different self-selected diets under free-living conditions in which a low-sodium, very high-potassium diet, rich in fruits and vegetables (≥9 servings/d) (LNAHK) and a very high-calcium diet rich in low-fat dairy foods (≥4 servings/d) (HC) were compared to a DASH-type diet high in potassium and calcium (≥3 servings of low-fat dairy and ≥8 servings of fruits and vegetables) (OD). Compared with OD, both SBP and DBP fell during the LNAHK diet period (−3.5 mmHg, $P < 0.001$ and −1.9 mmHg, respectively, $P < 0.05$), whereas they increased during the HC diet period (+3.1 mmHg, $P < 0.01$ and +0.8 mmHg, $P = 0.15$, respectively). Furthermore, when compared to a low calcium, low potassium, low magnesium diet, the OD (DASH) and LNAHK (high potassium) diet resulted in significant reductions in SBP (−1.8 and 4.4 mmHg, respectively), whereas no significant BP changes were observed with the HC (high calcium) diet. These results suggest that foods high in potassium effectively reduce BP whereas this study did not observe additional BP lowering benefits from other components of the DASH type diet (e.g. increased calcium and reduced saturated fat).

In summary, numerous observational [24,27–31,33,34,36,37] and some clinical [56,57,59] studies have demonstrated a relationship between the intake of dairy products with modest but significant reductions in SBP and in some cases DBP. In some studies, these effects have been shown to be highly correlated with the intake of dairy calcium and potassium; and greater BP lowering effects were sometimes reported in African American populations. Some observational studies also have shown inverse associations between dairy product consumption and reduced prevalence of HTN, mainly among individuals consuming less saturated fat [28], while others have shown an inverse association between BP or HTN risk and the intake of low-fat but not whole-fat dairy products [25,37,38]. Although no definitive explanation can account for these observations, the evidence is consistent with a mitigating effect of dairy product consumption on high BP, and prevalent HTN in amounts that are consistent with the DASH diet and current U.S. Dietary Guidelines of 3 servings of milk or milk equivalents/d. The published results of the PREMIER Trial, an RCT assessing effects of simultaneous lifestyle modifications to improve BP including the DASH diet, demonstrated the feasibility of increasing dairy intake in the population [68]. Nearly 60% of the study participants on the DASH diet met their dairy intake goal, whereas only one-third achieved the fruits and vegetables intake goal.

MECHANISMS OF ACTION

Hypertension results from the imbalance between a number of mechanisms that contribute to pressure regulation, such as hyperactivity of the sympathetic system, or an altered renin-angiotensin system.

Sodium is the major nutrient involved eliciting a hypertensive effect. Sodium balance is almost entirely controlled by the kidney's ability to regulate urinary sodium excretion. Acute intakes of dietary sodium have been reported to increase plasma Na^+ and extracellular fluid volume [69–71], increase Na^+ excretion [70,72], decrease plasma renin and aldosterone activity [70] and increase BP [69,73]. Some studies however have reported that following a high salt intake, small increases in blood volume were not always followed by increases in pressure [74–76]. In addition, two studies in conscious dogs showed that the natriuretic responses to salt loading which increased BP were almost completely abolished following administration of angiotensin II (a vasoconstricting agent) [77,78]. It was concluded that neuro-humoral signaling to the kidney can be initiated before changes in pressure occur, and the corrective natriuresis after intake of excess sodium can be mediated solely via these pathways, activated by volume receptors [78]. Therefore, blood pressure and renal excretory function are related such that a modest elevation in salt intake may be corrected by natriureses. However, following a prolonged high salt intake, the pressure natriuresis relationship may be shifted to higher arterial pressures whereby higher pressures are necessary to maintain sodium balance. This persistent increase in pressure would subsequently lead to increased BP and therefore HTN.

Mechanisms relating to the proposed antihypertensive effects of dairy products are largely centered on the key nutrients: potassium, calcium and magnesium. Dietary potassium restriction leads to potassium (K^+) deficiency as the kidneys cannot conserve potassium [79] thereby increasing renal Na^+ and chloride (Cl^-) retention [80,81]. In rats, potassium deficiency has been shown to increase the sodium-hydrogen (Na^+-H^+) exchange system by inducing acidosis and by stimulating the sympathetic nervous system and the renin-angiotensin system [82]. Although unclear, such an increase in Na^+-H^+ activity in vascular smooth muscle cells may elevate cellular Na^+ concentration, thereby reducing calcium (Ca^{2+}) efflux through Na^+/Ca^{2+} exchange. This would lead to increases in cytosolic

Ca^{2+} concentration and vasoconstriction [83]. Low concentrations of K^+ also have been shown to limit the Na, K-ATPase activity, resulting in increased intracellular Na^+ [84]. The Na, K-ATPase pump distributes ions between the intracellular and extracellular space and is responsible for total-body sodium homeostasis. Again, elevated Na^+ in the cytosol would slow the Na-Ca exchange thus decreasing urinary Ca^{2+} excretion and increasing intracellular Ca^{2+} concentrations. Potassium supplementation has opposite effects promoting K^+ retention and Na^+ loss [85,86], and lowering daily sodium intake has been shown to prevent the increased BP effect of a low potassium intake [81]. Other mechanisms for the anti-hypertensive effect of potassium are unclear but also may be mediated by atrial natriuretic peptide and eicosanoids [87].

Dietary salt intake is the initiating and ongoing extracellular stimulus to Ca^{2+} entry into the cell. As dietary sodium intake increases, urinary Ca^{2+} excretion increases, and as dietary calcium intake increases, Na^+ excretion increases [88–90]. The mechanism by which increased intracellular Ca^{2+} concentrations occur (from a high dietary sodium, low calcium intake) is partly explained through the stimulation of the calcium regulatory hormones: 1,25-dihydroxyvitamin D_3 and parathyroid hormone (PTH). 1,25-dihydroxyvitamin D_3 acts as a steroid hormone and via the vitamin D receptor, plays a role in bone remodeling by changes in gene expression [91] and numerous other physiologic cell functions [92]. Beyond its steroid hormone effects, 1,25-dihydroxyvitamin D3 also can trigger rapid effects including Ca^{2+} influx, the release of calcium from intracellular stores, activation of protein kinase C, the opening of voltage-gated Ca^{2+} and Cl^- channels, and the regulation of adenylyl cyclase [93]. In models of rat artery-derived smooth muscle cells, 1,25-dihydroxyvitamin D_3 increased Ca^{2+} channel current resulting in changes in cytosolic Ca^{2+} [94,95]. In this way, elevated levels of circulating 1,25-dihydroxyvitamin D_3 have been independently associated with increased peripheral vascular resistance [96,97] and therefore BP. In contrast, it has been demonstrated that increasing intakes of dietary calcium have prevented the increases in 1,25-dihydroxyvitamin D3, and BP [88–90,98].

A recent randomized, cross-over, clinical trial in 23 stage 1 hypertensive Caucasian adults evaluated the hypotensive effects of a dairy-rich diet and whether the effects differed according to changes in intracellular Ca^{2+} [99]. The experimental diets lasted 5 wks and included a high dairy, high fruits and vegetables diet (D-F&V; 30% fat, 7% saturated fat (SFA), 3.4 servings/d dairy), a low dairy, high fruits and vegetables diet (F&V; 30% fat, 7% SFA, 0.4 servings/d dairy), and an average Western diet as a control (AWD; 36% fat, 15% SFA, 0.4 servings/d dairy). Sodium content was matched across diets (3500 mg/d) and body weight was maintained. While all three diets significantly lowered BP from study entry, the reductions in SBP and DBP following the D-F&V diet (-12.0 ± 1.5 mmHg and -7.0 ± 1.2 mmHg) and F&V diet (-12.3 ± 1.5 mmHg and -7.2 ± 1.2 mmHg) were significantly greater compared with AWD (-9.9 ± 1.5 mmHg and -5.3 ± 1.2 mmHg, $P < 0.05$). Following consumption of a high dairy diet, 1,25-dihydroxyvitamin D_3 concentrations also decreased compared with the other two low calcium diets. In addition, the high dairy diet significantly increased intracellular Mg^{2+} levels and significantly reduced intracellular Ca^{2+} levels, which were correlated with improved DBP. Importantly, only subjects who responded to the high dairy diet by significantly reducing intracellular Ca^{2+} levels (Subjects who responded to the D-F&V diet by decreasing (Ca)i $\geq$ 3.4 mmol/L were defined as the *$(Ca)_i$ Change Group,* n = 8; others were labeled the *$(Ca)_i$ Stable Group,* n = 10) exhibited significantly greater drops in DBP (Fig. 1B) on the high dairy diet vs. the other two diets (Fig. 1). It is important to note however that the sample size used in these analyses was small and compared with previous studies that often reported a significant SBP lowering response to dairy foods, we found only a reduction in DBP. Moreover, while we focused on calcium and its role in decreasing BP in

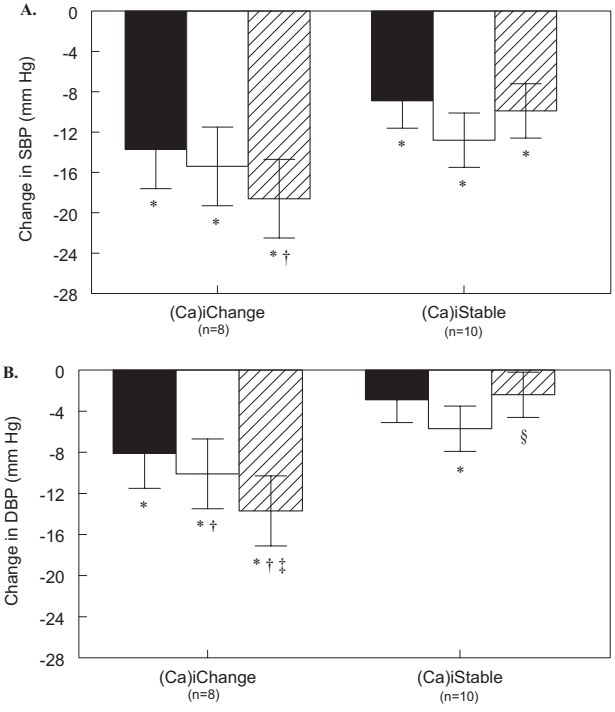

Fig. 1. Diet-related changes in systolic blood pressure (SBP: Fig. 1A) and diastolic blood pressure (DBP: Fig. 1B) from study entry, according to intracellular calcium status. The $(Ca)_i$ Change Group exhibited a decrease in erythrocyte calcium by 3.4 μM or more, whereas the $(Ca)_i$ Stable Group exhibited a decrease of less than 3.3μM. A) SBP, diet by group interaction, $P \leq 0.05$. B) DBP, diet by group interaction, $P < 0.001$. Black bars control, white bars fruit and vegetable diet, and striped bars high dairy, fruit and vegetable diet. * Different from Screening, $P < 0.05$; † Different from control diet within $(Ca)_i$ Change group, Tukey $P < 0.02$; ‡ Different from fruit and vegetable diet within $(Ca)_i$ Change group, Tukey $P < 0.02$; § Different from high dairy diet of $(Ca)_i$ Change group, Tukey $P < 0.04$.

the current study, it is possible that changes in other micronutrients contributed to the response as the D-F&V diet was higher in calcium, potassium, magnesium, and phosphorous, and RBC levels of calcium were lower and magnesium was higher. Thus, it may be that the BP response noted was the result of changes in micronutrients beyond calcium or due to other components of dairy products. Nevertheless, the results suggest that intracellular ion levels are responsive to diet and that a dairy-rich diet promotes a favorable intracellular environment, which results in an improved BP in some hypertensive populations.

Parathryroid hormone (PTH) is involved in the regulation of intracellular Ca^{2+}. PTH increases intracellular ionic calcium by enhancing Ca^{2+} influx in erythrocytes [100] and vascular smooth muscle cells [101]. PTH also may inhibit the Na, K-ATPase. Inhibition of this pump results in an accumulation of intracellular Na^{+}, therefore slowing Na-Ca exchange and increasing intracellular Ca^{2+} concentrations. It also has been hypothesized that PTH may increase intracellular ionic Ca^{2+} by depleting intracellular Mg^{2+}. Intracellular Mg^{2+} is tightly controlled and because it is a vital component in many biochemical reactions, small changes in its ionic concentration may lead to significant effects on signaling pathways that regulate vascular function. In experimental animals, increased levels of extracellular Mg^{2+} cause vasorelaxation, decreased vascular resistance and attenuated agonist-induced vasoconstriction [102–104], whereas decreased concentrations cause contraction, potentiate agonist-induced vasoreactivity, and increase vascular tone and BP [105,106]. Some of these actions may be mediated via effects on intracellular Na^{+}, K^{+} and Ca^{2+}, which also are involved in regulating vascular function.

Salt-sensitivity is defined by the difference in BP following a low and high sodium intake, such that a difference of 10% in BP considers one to be salt-sensitive [107]. Salt-sensitivity occurs in normotensive and hypertensive subjects [86], however is particularly prevalent in African American and elderly populations [108]. It has been reported that salt sensitive individuals exhibit a tight relationship between Ca^{2+} and Na^{+} excretion [88–90]. Increasing dietary salt increases urinary Ca^{2+} excretion, thus triggering the calcitropic hormone response, leading to increased PTH, 1, 25-dihydroxyvitamin D_3, intracellular Ca^{2+} [109], and therefore increased BP. As such, salt sensitive individuals are likely to be more responsive to low salt and increased dairy intakes. This was confirmed in the findings of the DASH study where a low/normal sodium intake, in addition to a high dairy, fruit and vegetable diet, had no added benefit in BP lowering, except in African American females, as well as overweight, older, and hypertensive participants [110]. In addition, following a low potassium, high salt loading diet in normotensive black men, salt sensitivity occurred when dietary potassium was marginally deficient but was dose-dependently suppressed when dietary potassium was increased within its normal range [86]. This indicates salt sensitivity suppression through increased dietary potassium may prevent or delay the occurrence of hypertension in black men.

Dietary salt intake is a major cause of elevated BP, affecting multiple mechanisms of action. Relationships also exist between sodium and some nutrients in dairy products (eg. potassium and calcium), and currently there is a growing database to suggest a greater role for increasing dietary potassium to reduce sodium retention and its effects on BP. Nevertheless, it is evident that minor changes in *in vivo* potassium and calcium concentrations can have major effects on cellular excitability and response. This ionic misbalance in vascular smooth muscle cells can lead to vasoconstriction, arterial stiffness and ultimately hypertension.

Dairy and Milk Peptides

Milk peptides are formed from milk proteins by enzymatic breakdown by digestive enzymes or by the proteinases formed by lactobacilli during the fermentation of milk. The two main milk proteins are casein and whey proteins, which are rich sources of bioactive peptides. Milk caseins comprise approximately 80% of the total protein content in bovine milk and consist of α-, β- and κ-caseins. These milk-binding peptides stabilize calcium and phosphate ions, and upon digestion, the casein proteins yield caseinophosphopeptides (CPPs) [111]. In rats, CPPs have been shown to increase passive calcium transport in the distal small intestine [112], and in humans, small casein phosphopeptides in the stomach, duodenum, and in the ileostomy fluid have been found following milk ingestion [113], indicating their ability to survive the passage down to the distal human ileum. Whey protein is composed of β-lactoglobulin, α-lactalbumin, immunoglobulins (IgGs), glycomacropeptides, bovine serum albumin, and minor proteins such as lactoperoxidase, lysozyme and lactoferrin. A number of whey peptides from β-CN terminal, including β-CN f193–206, f193–207, f193–208 and f195–206, f195–207, f195–208, f195–209 were identified from Mozerella cheese, and were found to have antiproliferative properties in human epithelial cells [114]. Novel angiotensin-I-converting enzyme (ACE) inhibitory activities were detected in synthetic peptides (α-la f(50–53) (IC_{50} = 733.3 μM) and the dipeptides (Tyr-Gly, IC_{50} = 1522.6 μM and Leu-Phe, IC_{50} = 349.1 μM), corresponding to sequences of β-lactoglobulin and α-lactalbumin [115]; and the tripeptide Tyr-Gly-Leu (α-la f50–52) also has demonstrated ACE-inhibitory activity at approximately the same concentration [116].

The most studied mechanism underlying the antihypertensive effects of milk peptides is inhibition of ACE. ACE is an enzyme that plays a crucial role in the function of the renin-angiotensin system (RAS), an important regulator of blood pressure [117]. Renin is a protease synthesized and secreted predominantly by the juxtaglomerular apparatus in the nephron in response to a decrease in circulating blood volume as well as sympathetic nervous stimulation. Renin cleaves angiotensin I

from liver-derived angiotensinogen, which is then converted to angiotensin II by ACE. After binding to its membrane receptors, angiotensin II activates protein kinase C and the production of inositol triphosphate. This causes the mobilization of stored Ca^{2+} into the cytoplasm and reciprocal sequestration of free Mg^{2+} into storage. As such, elevated levels of angiotensin II can lead to elevated intracellular Ca^{2+} ions and low Mg^{2+} concentrations, resulting in vasoconstriction. Inhibiting ACE therefore lowers the production of angiotensin II, which subsequently inhibits the release of aldosterone, a hormone which acts on the renal tubules to conserve sodium, secrete potassium, increase water retention, and increase BP. Inhibition of this pathway decreases sodium concentration and therefore BP.

A number of ACE inhibitory peptides have been found in various cheeses [118] and skim milk [119,120], however the best known ACE-inhibitory peptides are Val-Pro-Pro (VPP) and Ile-Pro-Pro (IPP) which have been identified from a Japanese sour milk drink [121]. Some studies have shown that consumption of 95–150mL/d sour milk which contained these two tripeptides has reduced systolic and diastolic blood pressure over 4–8 weeks in borderline/moderately hypertensive [122,123] or untreated hypertensive [124] patients. This ingested dose would be equivalent to an ACE inhibitory peptide amount of 2.6 mg/d, much lower than the typical 1500 mg/d found in BP lowering medications. Other studies however have found no decrease in BP in hypertensive subjects following daily consumption of 200 mL dairy drink with 14 mg lactotripeptide for eight weeks [125], or 125 mL of milk drink supplemented with whey peptides for 12 weeks [126].

Milk peptides also may act via other mechanisms to lower BP including binding to opioid receptors (which induces nitric oxide release, therefore improving flow mediated dilatation), inhibition of ACE, and modification of antithrombotic and immune responses [127]. However, the primary mechanisms of blood pressure regulation are thought to be explained by calcium, magnesium and potassium metabolism, as well as dairy and milk peptides, as discussed.

SUMMARY

The present review has summarized important epidemiologic and randomized controlled studies on the beneficial effects of dairy nutrients and dairy components on blood pressure. Although a spectrum of mechanisms contributes to the pathophysiology of hypertension, it is evident that increases in nutrients found in dairy products (eg. calcium, potassium and magnesium) along with a diet that is low in sodium is beneficial for BP lowering, with certain populations, such as African Americans, more responsive to this dietary pattern. There also is emerging evidence relating dairy peptides to reduced blood pressure via ACE inhibitory mechanisms. The efficacy of these bioactive components, however, needs to be investigated further in animal studies to better understand the underlying mechanisms of action by which dairy products lower BP.

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