Finding Consensus in the Dietary Calcium-Blood Pressure Debate

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No single study or avenue of investigation can resolve the scientific controversies that entangle efforts to determine the effects of specific nutrients on medical conditions. To reach consensus in this area requires a substantial body of plausible, reproducible and consistent data from various investigative approaches—such as the data that now exist regarding the relationship between dietary calcium and blood pressure. In this paper we describe the plethora of epidemiological and clinical studies and analyses that have been published in the last two years and which cumulatively reveal the consistency of the available data regarding the influence of dietary calcium on blood pressure regulation. Nearly 20 years of investigation in this area has culminated in remarkable and compelling agreement in the data, confirming the need for and benefit of regular consumption of the recommended daily levels of dietary calcium.

Key teaching points:

- After nearly 20 years of controversy, the relationship between dietary calcium and blood pressure is being confirmed by a large body of recently published data consistently reporting a blood pressure-lowering effect of adequate calcium intake.
- Meta-analyses of 23 observational studies and of 42 randomized controlled trials have identified statistically significant reductions in hypertension risk and in blood pressure levels.
- The impact of calcium on blood pressure appears to be greatest in persons consuming regularly low levels of dietary calcium, the primary source of which is dairy products.
- The health benefits of adequate calcium, including lower risk of osteoporosis and colon cancer as well as hypertension, can be realized by simply consuming the recommended dietary calcium levels for an individual's age and gender (1000 to 1500 mg/day).

INTRODUCTION

It's very simple: adequate dietary calcium intake is critical to optimal blood pressure regulation. Calcium is involved in normal muscle, including heart muscle, contraction and relaxation and, thus, in vascular tone and blood pressure control. Because of its role in muscle function and because it is not produced in the body, dietary calcium is required in sufficient daily quantities to achieve and maintain appropriate blood pressure levels through optimal regulation of vascular resistance. Physiologically, it just makes sense. What does not make sense is arguing against an effect of calcium intake on blood pressure; and yet that argument has been going on for nearly two decades. Over the past two years, however, a striking amount of data from a variety of investigative approaches has been published which, viewed collectively, should shed far more light, as well as reason, on the calcium-blood pressure debate.

The NHLBI-sponsored study "Dietary Approaches to Stop Hypertension," published in 1997, revealed that a diet high in fruits and vegetables significantly reduced blood pressure, but that the addition of about three daily servings of dairy products (predominately low-fat milk) doubled the blood pressure reductions observed with the fruits-and-vegetables diet [1]. In August of 1998, a corrected version of an earlier meta-analysis of the observational studies of dietary calcium and blood pressure revealed that the positive effects reported in the original study were actually 30 times greater than first reported [2]. In a commentary in the journal *Science*, also in August 1998, we noted a striking agreement between the blood pressure findings in DASH and a prediction of the relationship between dietary

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calcium and systolic blood pressure we originally published in *Science* in 1984 [3].

One month later the *American Journal of Clinical Nutrition* published a report of an intervention trial in African-American adolescents which suggested a dose response relationship between the blood pressure reduction observed with calcium supplementation and daily dietary calcium consumption [4]. Most recently, in January 1999, a meta-analysis of 42 randomized controlled trials of calcium supplementation trials confirmed a clear effect of calcium on blood pressure and determined that the heterogeneity in the blood pressure response to increasing calcium intake was significantly less when dietary calcium as compared to calcium supplements were used in the studies. Although not significantly different, the blood pressure reduction observed with dietary sources of calcium was almost twice that associated with supplementation [5].

Taken together these recent reports have demonstrated a remarkable consistency in the data from non-randomized observational studies as well as randomized controlled intervention studies. The additional findings of a dose-response relationship and a more predictable, greater effect from food sources of calcium provides a comprehensive consistency rarely observed in an exploration of diet's relationship to a common disorder such as hypertension. We intend to use this consistency of the data and the fact that the dose range of dietary calcium required to induce a beneficial blood pressure response falls readily within the current national guidelines for dietary calcium intake to validate the necessity of adequate calcium intake.

OBSERVATIONAL EVIDENCE

The association between higher dietary calcium intake and lower prevalence of high blood pressure in the U.S. population was first reported in 1984, based on analysis of the first National Health and Nutrition Examination Survey (NHANES I) database [6]. This investigation revealed that

• Deficiencies rather than excesses are the principal nutritional patterns that characterize the hypertensive person in America.
• Calcium was the nutrient for which lower intake was most consistent in hypertensive individuals, followed by potassium.

Since that seminal report, more than 30 well-designed epidemiological studies assessing the calcium-blood pressure relationship have been published. The majority of these surveys have identified an inverse association between dietary calcium and blood pressure levels or reduced risk of developing hypertension [2,7–10]. These observations have been consistent across both sexes and all age groups, geographical areas and ethnic and racial groups. Although not all surveys addressing this issue have reported a definitive calcium-blood pressure connection, recent meta-analysis of these reports has demonstrated that the link is indeed strong [2].

In their 1995 quantitative overview of the observational database, Cappuccio *et al.* [10] included 23 population studies deemed eligible for analysis from a total of 63 reported studies. These investigators stated that their meta-analysis demonstrated "a small, although statistically significant, inverse association between dietary calcium intake and blood pressure in men and in both sexes combined and a stronger relation in women." These generally positive findings have since been challenged by Birkett [2] who identified several methodological errors in the original analysis. In his re-analysis of these same studies with the appropriate corrections, Birkett found that the "small . . . inverse association" was actually nearly 30-fold greater than that reported in the original analysis. Pooled estimates for changes in systolic blood pressure in men increased from -0.01 to -0.34 mmHg/100 mg increase in dietary calcium, and from -0.009 to -0.22 mmHg/100 mg of dietary calcium for diastolic blood pressure.

The errors identified in the Cappuccio *et al.* [10] meta-analysis might simply be considered mistakes or oversights. However, in the editorial comment in the *American Journal of Epidemiology* accompanying the Birkett reanalysis of these data [2], Stoto raises the question of motivation [11]. The serious methodological flaws in the first analysis, combined with the striking errors of citation in the same paper, which were reported by Heaney in 1997 [12], would appear to reflect a bias against the dietary calcium-blood pressure hypothesis. This possibility is based on the unlikely chance that each of the multiple errors in the meta-analysis and its conclusions is in the direction that discounts the plausibility of the calcium-blood pressure connection by authors who have long been vocal opponents of it. As pointed out by both Stoto and Heaney, it is difficult to understand how such a large underestimate of the blood pressure effect or how the many misrepresented studies could have been simply oversights by these skilled and experienced investigators.

RANDOMIZED CONTROLLED TRIALS

Whatever the degree of uniformity observed among epidemiological surveys, the critical test of a viable relationship between dietary calcium and blood pressure regulation is whether changes in calcium intake levels produce changes in blood pressure in humans. The clinical relevance of observational data ultimately depends on the demonstration of an anti-hypertensive effect of calcium in controlled clinical studies. More than 60 calcium intervention trials in humans have been reported [5,13], and as with all nutrient modification trials [14,15], the results have been heterogeneous, including positive, negative and no effects. These variations parallel those of study design and quality and obviously complicate attempts to summarize the results of the studies. Thus, meta-analyses provide the most comprehensive means of reviewing the results of the numerous calcium-blood pressure intervention trials.

The most carefully conducted and recent meta-analyses of these studies are those of Bucher *et al.* [13] published in 1996 and an updated version of the analysis by these investigators published in 1999 [5]. They originally identified 56 randomized trials in nonpregnant populations of which 33 (n=2412) met the strict eligibility criteria for meta-analysis [13]. Eligible studies were those in which participants were randomized to receive either calcium supplementation or placebo and in which blood pressure was measured for at least two weeks. Their analysis revealed a distinct impact of sufficient intake of dietary calcium, with average blood pressure reductions of 1.3 mmHg systolic and 0.2 mmHg diastolic in the general population and 4.3 mmHg and 1.5 mmHg in hypertensive persons.

In their updated investigation of calcium intervention trials [5], ten new studies were included as well an analysis of the effect of the form of calcium supplementation, dietary (foods) *versus* non-dietary (tablets). Pooled estimates across all studies showed decreases in both systolic blood pressure, 1.44 mmHg and diastolic pressure, 0.84 mmHg with increased calcium. In the comparison analysis of studies using foods *versus* non-food calcium sources, systolic blood pressure decreased by 2.10 mmHg and by 1.09 mmHg (p=0.14) and diastolic pressure by 1.09 mmHg and 0.87 mmHg respectively (p=0.67). Although the blood pressure decreases between the two forms of supplemented calcium were not significantly different, the analysis did reveal significantly less heterogeneity in the results of the dietary calcium studies as compared to those that employed non-food sources of calcium.

In their original meta-analysis, Bucher and colleagues noted, as have others [7,16,17] that there was marked heterogeneity in the blood pressure response to increasing calcium intake [10]. They hypothesized that several factors might account for this, including baseline calcium intake; that is, persons consuming inadequate levels of dietary calcium may exhibit a stronger blood pressure effect from increased calcium than those whose intake is sufficient. Second, they speculated that nutrient interactions in trials that increased calcium intake from food sources, which would concurrently increase intake of other minerals, could have a greater effect than those that used calcium supplements. Third, they noted that groups at high risk of hypertension, such as African-Americans, salt-sensitive persons, and pregnant women may be particularly sensitive to the effect of increased mineral intake and would therefore experience stronger beneficial effects of increasing calcium intake to currently recommended levels.

The updated analysis addressed the possibility that the calcium source may influence the marked variations in blood pressure responses, and, as noted above, it revealed that there was indeed significantly greater heterogeneity when non-dietary compared to dietary calcium was used [5]. This and the other postulated contributors to inconsistent blood pressure responses were more fully dealt with in the carefully designed and executed NIH Dietary Approaches to Stop Hypertension (DASH) Study published in the *New England Journal of Medicine* in 1997 [1]. This study, which is described in more detail below, included a greater proportion of minority subjects, particularly African-Americans, and individuals with high normal blood pressure, used only commonly available foods rich in calcium to increase the mineral content of the diet and used a control diet with levels of mineral content that reflect the 25th percentile of the current U.S. population and thus reflect diets of individuals regularly underconsuming the nutrients of interest.

Dietary Approaches to Stop Hypertension Study

In the published rationale of that study [18], the DASH investigators proposed that a number of factors may contribute to the commonly observed discrepancies in the results of dietary nutrient studies. “First, the blood pressure-lowering effect of single nutrients may be too small to detect in small-scale clinical trials. Second, when several nutrients . . . are consumed together as in observational studies . . . their additive effect may be sufficiently large to be detectable. Third, interactions could exist among nutrients to amplify the effect of combinations. Fourth, untested or unknown nutrients in plant food may lower blood pressure. Fifth, nutrient supplements may not affect blood pressure to the same extent as do the same nutrients occurring naturally in foods.” The DASH study, therefore, was designed to assess the effects of *dietary patterns* rather than isolated nutrients on blood pressure.

Concluding that a diet low in essential minerals and fiber and high in fat was associated with increased blood pressure, the DASH Steering Committee identified the “ideal diet” for reducing blood pressure as one that is high in fruits, vegetables and low-fat dairy products. DASH was a multicenter ten-week dietary intervention study comparing the typical American diet—low in fruits, vegetables and dairy products and, thus, low in essential minerals and fiber and high in fat—to a diet that was high in fruit and vegetable content and to a diet high in fruits, vegetables and low-fat dairy products. This latter diet, the “DASH diet,” was distinguished by its higher contents of potassium, magnesium, calcium and fiber, lower fat and minimally increased protein.

The DASH study population comprised 459 adults with an average age of about 44 years and blood pressures of 132 mmHg systolic and 85 mmHg diastolic. Approximately 50% were women and 65% were members of racial minorities. The three diet groups included 154 participants in the control group, 154 in the fruits-and-vegetables group and 151 in the DASH diet group. Table 1 lists the targeted and achieved intake levels of the major nutrients and food group servings in each of the diets. Participants ate lunch and dinner on-site and were provided meals to be consumed off-site on weekends. Both sodium intake and weight were kept stable in all subjects throughout the study. Excellent adherence was achieved in the study, with attendance at on-site meals by 95.8, 95.4, and 96.1% and study

Table 1. DASH Nutrient Targets, Menu Analyses, and Average Daily Servings of Foods* [1]

Item	Control Diet		Fruits-and-Vegetables Diet		Combination Diet	
	Nutrient Target	Menu Analysis†	Nutrient Target	Menu Analysis†	Nutrient Target	Menu Analysis†
Nutrients						
Fat (% of total kcal)	37	35.7	37	35.7	27	25.6
Saturated	16	14.1	16	12.7	6	7.0
Monounsaturated	13	12.4	13	13.9	13	9.9
Polyunsaturated	8	6.2	8	7.3	8	6.8
Carbohydrates (% of total kcal)	48	50.5	48	49.2	55	56.5
Protein (% of total kcal)	15	13.8	15	15.1	18	17.9
Cholesterol (mg/day)	300	233	300	184	150	151
Fiber (g/day)	9	NA	31	NA	31	NA
Potassium (mg/day)	1700	1752	4700	4101	4700	4415
Magnesium (mg/day)	165	176	500	423	500	480
Calcium (mg/day)	450	443	450	534	1240	1265
Sodium (mg/day)	3000	3028	3000	2816	3000	2859
Food groups (no. of servings/day)						
Fruits and juices	1.6		5.2		5.2	
Vegetables	2.0		3.3		4.4	
Grains	8.2		6.9		7.5	
Low-fat dairy	0.1		0.0		2.0	
Regular-fat dairy	0.4		0.3		0.7	
Nuts, seeds, and legumes	0.0		0.6		0.7	
Beef, pork, and ham	1.5		1.8		0.5	
Poultry	0.8		0.4		0.6	
Fish	0.2		0.3		0.5	
Fat, oils, and salad dressing	5.8		5.3		2.5	
Snacks and sweets	4.1		1.4		0.7	

* Values are for diets designed to provide an energy level of 2100 kcal.

† Values are the results of chemical analyses of the menus prepared during the validation phase and during the trial. NA denotes not available.

completion by 95.5, 97.4, and 98.7% of the control, fruits-and-vegetables, and DASH diet groups respectively.

Highly significant blood pressure reductions were achieved with the DASH diet compared to the control diet (Fig. 1). With the DASH diet systolic pressure was reduced by 5.5 mmHg more and diastolic pressure by 3.0 mmHg more than with the control diet. Blood pressure reductions with the fruits-and-vegetables diet compared to those of the control were also highly significant, but were only about half (2.8 mmHg systolic and 1.1 mmHg diastolic) of those achieved with the DASH diet. The reductions with both intervention diets were observed within the first two weeks of study and were sustained for the remaining six weeks of the intervention.

Blood pressure reductions observed in the hypertensive participants receiving the DASH diet compared to those receiving the control diet were 11.4 mmHg systolic and 5.5 mmHg diastolic blood pressure. Comparison of the DASH diet to the fruits-and-vegetables diet in hypertensive persons also showed significant differences, with reductions of 4.1 mmHg systolic and 2.6 mmHg diastolic more with the DASH diet than with the fruits-and-vegetables diet. It was noted by the DASH investigators that the observed blood pressure reductions with the DASH diet in the hypertensive subgroup were similar in magnitude to those reported in pharmacological trials of antihypertensive treatment of mild hypertension [19].

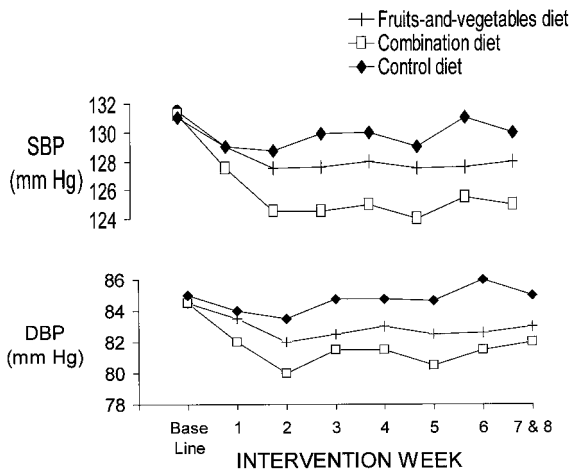

Fig. 1. Mean systolic and diastolic blood pressures at baseline and during each intervention week of the DASH Study, according to diet, for 379 subjects with complete sets of weekly blood pressure measurements [1].

CONCORDANCE OF THE PUBLISHED DATA

The blood pressure reductions observed in the DASH diet, with the addition of 2.7 servings per day of dairy products,

correspond remarkably with those revealed by meta-analyses of both the epidemiological and clinical intervention studies. Furthermore, they parallel the reductions that could be predicted from the analysis of the NHANES I nutrient intake database, published in *Science* in 1984 [6], which illustrated the inverse relationship between dietary calcium intake and blood pressures across the population (Fig. 2). The DASH findings show that increasing the mineral profile provided by increased dairy product intake from a level matching the lowest 25th percentile of consumption in the U.S. population to recommended levels can produce blood pressure reductions consistent with those reported in observational as well as randomized controlled trials assessing the calcium-blood pressure relationship. The consistency of DASH with the surrounding body of evidence provides compelling evidence of the connection between dairy product consumption and reduced hypertension risk.

Detractors of the calcium-blood pressure connection have focused not on the dramatically increased calcium content of the DASH diet, but on the lower level of fats, attributing to the latter the striking blood pressure reductions achieved in this study. However, as described above, the preponderance of prior data regarding the effect of dietary calcium on blood pressure regulation establishes a clear relationship, whereas this is not the case for dietary fats. While the detrimental influence of high levels of dietary fat, particularly saturated fat and cholesterol, on coronary artery disease risk is well established, the bulk of the published dietary fat-blood pressure data argue against a specific effect of fat intake on blood pressure control [20–24].

Omega-3 fatty acids administered in large quantities (>3 g fish oil/day) were shown to have a beneficial effect on blood pressure in a 1993 meta-analysis of 17 trials [25], but these high intake levels were associated with the negative effects of gastrointestinal symptoms and high caloric content. A second meta-analysis published the same year which included 31 studies [26] reported a significant effect on blood pressure in studies in hypertensive persons consuming a mean fish oil dose of 5.6 g/day, but in studies with non-hypertensive participants, there was no effect of fish oil on blood pressure. On the basis of available information, the NIH Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure concluded in their most recent report that "... diets varying in total fat and proportions of saturated to unsaturated fats have had little, if any, effect on blood pressure" [17].

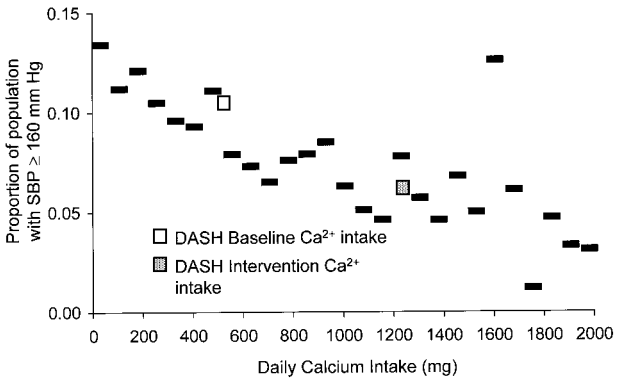

Fig. 2. National Health and Nutrition Examination Survey I data portraying the relationship between dietary calcium and systolic blood pressure [6], in relation to values (boxes) at baseline and end of the DASH combination diet intervention for dietary calcium intake and systolic blood pressure [1].

MINERAL METABOLISM AND THE DASH DIET

Studies have suggested that a renal calcium "leak" resulting in elevated excretion of calcium in the urine paradoxically develops when calcium is deficient in the diet [27,28], which may create disturbances in mineral metabolism, including calcium, potassium and other minerals involved in blood pressure regulation. In this regard, it is noteworthy that a detailed analysis of the relationships among blood pressure, mineral excretion and mineral hormones in the DASH study demonstrated that the observed fall in blood pressure with both the fruits-and-vegetables and the DASH diet interventions were statistically associated with improvements in mineral balance and normalization of urinary calcium excretion. In an abstract presented at the 1998 American Society of Nephrology Annual Meeting [29], the authors of this analysis concluded that their findings indicate "that the DASH diets result in mineral conservation, particularly Ca^{2+}."

This conclusion is supported by the fact that at baseline, higher levels of urinary calcium, urinary phosphorus, vitamin D and parathyroid hormone (PTH) predicted higher baseline systolic and diastolic blood pressures. Subjects consuming the fruits-and-vegetables diet exhibited reductions in urinary calcium and PTH; those receiving the DASH diet experienced reductions in urinary vitamin D levels in conjunction with normalization of urinary calcium and urinary phosphorus excretion, as would be expected with increased dairy product intake, given the substantial calcium and vitamin D contributed by these foods. This updated analysis from DASH documents that abnormal mineral metabolism was predictive of baseline blood pressure in the DASH study population. The subsequent blood pressure reductions with both the fruits-and-vegetables and DASH diet interventions were significantly linked to improvements in mineral balance. It is noteworthy that even in the fruits-and-vegetables diet, a reduction of urinary calcium losses (i.e., a reduction in the renal calcium leak) correlated with reductions in both systolic ($p<0.01$) and diastolic blood pressure ($p<0.05$). In contrast, changes in urinary potassium excretion as a marker of dietary potassium intake, to which some attribute the DASH diet blood pressure effect, did not correlate with the beneficial blood pressure changes observed [29].

It had been assumed by some experts that improvements in

potassium balance produced the blood pressure reductions observed with the fruits-and-vegetables diet, but this detailed analysis of hormone data revealed that was not the case. The physiologic relevance of the decrease in urinary calcium with the fruits-and-vegetables diet was supported by its correlation with a decrease in parathyroid hormone values ($p<0.005$), suggesting that blood pressure reductions in this group were largely mediated through a calcium-sparing mechanism, and points to a possible role of calcium in reducing blood pressure in this group. This may also help explain why the blood pressure reductions in the fruits-and-vegetables group were substantially smaller than those reported for the DASH diet, which was rich in potassium as well as calcium. These data support the role of the combination of nutrients in dairy products as an independent factor that contributes significantly to reducing blood pressure and, thus, hypertension risk. The debate regarding what constituent or constituents in the DASH diet were linked to the dramatic improvements in blood pressure could be greatly attenuated with multivariate analysis of the food items, food groups and nutrient clusters that best predicted the observed blood pressure responses.

THE BOTTOM LINE

There is no question that the calcium available to the organs that participate in cardiovascular control is integral to blood pressure regulation. Furthermore, it is becoming increasingly clear that dietary calcium is a key factor in this process. However, it has been argued by some that the antihypertensive effect of calcium has not been shown to be large enough to justify recommending calcium supplementation to treat hypertension [10,30]. It is particularly noteworthy that 1) they do not deny that there is a statistically significant effect of dietary calcium and in some cases have actually demonstrated this in their own studies [10,30] and 2) they conclude their arguments by opposing something that even the strongest calcium-blood pressure advocates have never advocated.

Unlike on-going arguments surrounding changes in the intake guidelines of some nutrients, among investigators who agree with the extensive body of data supporting the calcium-blood pressure connection, the bottom line for optimal blood pressure management is simply that people consume the currently recommended daily level of dietary calcium [3,7,14,16,17]. No one is insisting that these levels be increased beyond the current guidelines or that government regulations be passed to mandate changes in food manufacturing to meet intake recommendations or that the public be advised to consume an arbitrary intake level of a nutrient impossible to measure in the diet. Bringing dietary calcium to optimal levels in the diet requires simply drinking three glasses of milk (or consuming their easily-determined dairy equivalents) each day. The dietary maneuvers necessary to realize the health benefits of adequate calcium—including bone health, reduced risk of osteoporosis and colon cancer [16], as well as normal blood pressure—do not require that people give up foods they like or be compelled to forego flavors they enjoy or compromise their overall nutrient profile [31]—in fact, it requires and accomplishes exactly the opposite.

The blood pressure benefit of a diet that provides the extensive constellation of minerals found in dairy products, fruits and vegetables may be the greatest for individuals whose dietary patterns are deficient in these foods (Fig. 3 [1,4,7]). While most Americans fall into this category, meeting the recommended daily intakes of calcium, potassium, magnesium and other essential minerals is particularly critical for subgroups in the U.S. population known to consume inadequate levels of dietary calcium, including African-Americans, the elderly, and pregnant women [16,32]. Despite widespread emphasis on optimal dietary practices and evidence of improved diets in the general population in recent years [33], neither calcium intake nor hypertension prevalence has improved in these groups, particularly in the African-American population [34].

The scientific plausibility of the calcium-blood pressure hypothesis, first postulated almost two decades ago [35,36], has been largely validated in the most compelling fashion possible, that of consistency of the data from peer-reviewed scientific publications. The past two years have seen a coalescence of the data establishing reproducibility and plausibility. The latter is supported by 1) a dose response relationship, 2) a stronger effect with foods than with supplements, 3) a greater impact in populations at higher risk of the disorder, 4) although not addressed in this paper, parallel observations in laboratory experiments [7,37] and 5) a response range well within the currently recommended levels of dietary calcium intake.

The findings from the DASH study [1] and the summary reports of Birkett [2] and Bucher *et al.* [13], covering in excess of 75 well designed trials, leave little doubt that adults would be prudent to consume adequate dietary calcium to reduce their risk of developing hypertension, the most common cardiovascular disorder in adults. Future investigations will refine our

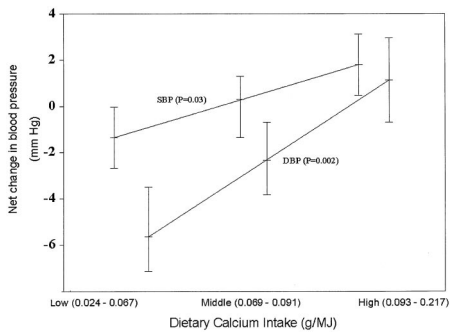

Fig. 3. Net effect of calcium supplementation at 1.5 g/day on systolic (SBP) and diastolic (DBP) blood pressure over eight weeks of intervention by tertile of dietary calcium intake [4].

understanding of the mechanisms and more fully explore potential clinical benefits that accrue to individuals who meet this widely accepted nutritional goal, but additional clinical research will not likely change what we now know. Adults who consume 1000 to 1500 mg/day of calcium through their diets reduce their risk of hypertension. We need now only to achieve the same level of agreement among the "experts" as there is among the data.

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