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Vitamin E and Prostate Cancer: Is Vitamin E Succinate a Superior Chemopreventive Agent?

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There is convincing evidence that vitamin E succinate significantly reduces human prostate cancer growth in experimental models compared with α-tocopherol or tocopheryl acetate. Its intact delivery to cancer cells is questionable when administered orally; however, a study in transgenic mice showed a synergistic inhibitory effect of dietary vitamin E succinate, selenium, and lycopene on prostate cancer incidence. Clinical trials have yet to confirm this effect.

Key words: vitamin E succinate, selenium, synergy, apoptosis, prostate cancer

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INTRODUCTION

Prostate cancer is the most common non-cutaneous cancer and is the second leading cause of cancer death in American men, exceeded only by lung cancer. In 2004, the American Cancer Society estimated that over 230,000 new prostate cancer cases would be diagnosed and that 29,900 deaths would occur from this disease.[1] There is a close relationship between the occurrence of prostate cancer and the type of diet consumed by the population. Epidemiological studies have shown that in Asia, where the diet is low in animal fat and rich in soy protein, the incidence of prostate cancer is very low. Conversely, in industrialized western countries, where the diet is typically high in animal fat (30%–40% of calories from fat), the incidence of prostate cancer (and obesity) is concomitantly higher. Several studies have identified an association between various dietary substances with antioxidant properties and an inhibitory effect on the development and/or progression of prostate cancer.[2] Dietary micronutrients such as carotenoids, lycopenes, retinoids, and vitamin A, vitamin E, vitamin C, selenium, and phenol-containing dietary substances have been shown to have effects that extend beyond their antioxidant properties.[3]

Vitamin E is a general term used to refer to a group of naturally occurring compounds called tocopherols and tocotrienols, as well as vitamin E derivatives such as acetate, succinate, and nicotinate of both natural and synthetic α-tocopherol.[4] There have been relatively few in vivo studies on the effects of vitamin E on prostate cancer. This review summarizes the role of vitamin E in prostate cancer prevention and treatment and highlights the anti-neoplastic action of vitamin E succinate (VES).

VITAMIN E AND PROSTATE CANCER: ANIMAL STUDIES

Male *Lady* transgenic mice spontaneously develop localized prostate cancer and metastasis, which mimics the progression of human prostate cancer in many respects. In 2004, Venkateswaran et al.[5] showed a significant reduction in prostate cancer incidence in male *Lady* transgenic mice fed a standard-fat (25% kcal from fat) or a high-fat (40% kcal from fat) diet with antioxidant supplementation compared with the controls. The antioxidant supplement included a daily dietary dose of a combination of 800 IU of VES, 200 μg of seleno-dl-methionine, and 50 mg of lycopene. This was the first in vivo study showing the inhibitory effects of VES, in combination with selenium and lycopene, on the incidence of prostate cancer.

In this study,[5] transgenic animals were divided into four main groups: group 1 animals were fed a standard (25% kcal from fat) diet; group 2 animals were fed a standard diet with antioxidant supplementation; group 3 animals were fed a high-fat (40% kcal from fat) diet; and group 4 animals were fed a high-fat diet with antioxidant supplementation. At the end of 28 to 32 weeks, the prostate tumor incidence was approximately 11% in group 2 and approximately 16% in group 4. This was a striking reduction compared with the controls, which had

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a tumor incidence of about 74% in group 1 and 100% in group 3. These investigators also measured the protein expression of cytoplasmic p27 and proliferating cell nuclear antigen (PCNA) in prostate tissue sections using immunohistochemistry. The tumor suppressor gene p27 is an important regulator of cell cycle progression from the G_1 to the S phase, and works by binding and inhibiting the cyclin E-/cyclin-dependent kinase 2 complex. PCNA serves as a critical marker for increased proliferation of DNA polymerase-driven DNA synthesis.[5] Thus, both p27 and PCNA expression serve to elucidate possible mechanisms by which antioxidant supplementation could lead to a reduction in the incidence of prostate cancer. Venkateswaran et al.[5] reported that PCNA expression was markedly reduced in prostate sections from both of the antioxidant-supplemented groups (groups 2 and 4) compared with the untreated controls, while p27 scoring was increased in the antioxidant-treated animals, which is consistent with a reduction in the incidence of prostate tumors.

Fleshner et al.[6] previously reported an in vivo study using dietary supplementation of dl-α-tocopheryl acetate on the growth of human prostate LNCaP xenografts in nude mice. The human prostate LNCaP cell line (from lymph node metastasis) expresses androgen receptors and also produces prostate-specific antigen (PSA). Once implanted into nude mice, it undergoes local growth without metastases, making it well suited to studying tumor growth rates. In this study,[6] following subcutaneous inoculation of the LNCaP cells, animals were randomly assigned to four groups: group 1 animals were fed a diet with 40% kcal from fat; group 2 animals were fed a diet with 40% kcal from fat supplemented with dl-α-tocopheryl acetate; group 3 animals were fed a diet with 20% kcal from fat; and group 4 animals were fed a diet with 20% kcal from fat supplemented with dl-α-tocopheryl acetate. The level of dl-α-tocopheryl acetate included in the diets of groups 2 and 4 was 11.4 IU/kg/d. This 15-week study revealed a significant reduction in LNCaP tumor size in group 2 compared with group 1. However, there was no significant difference between group 3 and group 4. Animals in group 1 had the highest tumor growth, and 50% of the animals in this group attained the target tumor size (0.1 cm^3) in 6 weeks. Tumor growth was significantly slower in group 2 animals and in the animals fed low-fat diets (groups 3 and 4) with or without vitamin E supplementation.

Both Venkateswaran et al.[5] and Fleshner et al.[6] reported in vivo data emphasizing the fact that a high-fat diet promotes the incidence and growth of prostate cancer, and that vitamin E alone (as dl-α-tocopheryl acetate) or in combination with other antioxidants (as VES plus selenium plus lycopene) ameliorates this high-fat-associated prostate cancer effect. Interestingly, Venkateswaran et al.[5] reported a marked decrease in prostate cancer incidence even in the group fed the standard diet (25% kcal from fat) with antioxidant supplementation compared with the corresponding untreated controls, whereas Fleshner et al.[6] showed no difference between the groups fed 20% kcal from fat, with or without vitamin E supplementation. This difference could be attributed to a different vitamin E derivative, a higher amount of vitamin E, or the longer period of vitamin E supplementation in the study reported by Venkateswaran et al.[5] compared with Fleshner et al.[6] (800 IU of VES/d for 32 weeks versus 11.4 IU of dl-α-tocopheryl acetate/kg/d for 15 weeks, respectively).

VITAMIN E AND PROSTATE CANCER: IN VITRO STUDIES

According to Neuzil,[7] when VES reaches the circulation, it binds to circulating lipoproteins that carry it to the microvasculature, where it kills the cancer cells. Lipoproteins with bound VES are cleared in the liver, where the hepatic nonspecific esterase cleaves the succinate moiety and the newly generated α-tocopherol is inserted by the α-tocopheryl-transfer protein into nascent very low-density lipoproteins, which are then circulated in the biological system. While normal cells, including intestinal epithelial cells, are capable of hydrolyzing VES to α-tocopherol, cancer cells lack this ability. As a result, accumulation of the intact VES molecule in cancer cells causes their apoptosis. In vitro studies have provided evidence of the inhibitory effects of α-tocopheryl succinate or VES on the growth of human prostate cancer cells. Venkateswaran et al.[8] reported an overexpression of p27 and a dramatic reduction in the percentage of human prostate LNCaP and PC-3 (from bone metastasis) cancer cells in the S phase in response to VES treatment over a 72-hour period. Thus, VES at a 20 μg/mL (38 μmol/L) concentration (IC_{50} = 5 to 25 μg/mL) caused a maximum reduction of cells replicating DNA. This concentration of VES used in the cell culture study is comparable to the physiological concentrations of tocopherol in human serum (30–40 μmol/L). The results of this in vitro study on p27 induction by VES treatment[8] are consistent with the in vivo study by the same group using VES in combination with selenium and lycopene.[5] The mechanisms of VES action on human prostate cancer cells proposed by various investigators are numerous,[9-13] and include distinct mechanisms that are listed in Table 1 and summarized in Figure 1.

Zu and Ip[14] compared the anti-neoplastic action of α-tocopherol and its two ester derivatives, vitamin E acetate and VES, on the growth of human prostate PC-3 cells in culture. Interestingly, a concentration of 20 μM VES was sufficient to achieve a 40% growth inhibition

Table 1. Summary of Proposed Mechanisms of Vitamin E Succinate Action on Human Prostate Cancer

- Chemotherapeutic effects of adriamycin on human prostate cancer cells[9]
- Inducing apoptosis by causing depletion of cytosolic Fas and enhancing the membrane levels of Fas in human prostate cancer cells[10]
- Decreasing the production of vascular endothelial growth factor by prostate cancer cells[11]
- Inhibiting the expression of prostate-specific antigen and androgen receptor mRNA expression and translation to proteins in human prostate cancer cells and a synergistic effect of a combination of vitamin E succinate and hydroxyflutamide on growth inhibition of prostate cancer[12]
- Inhibiting human prostate cancer cell invasiveness by inhibiting the activity of matrix metalloproteinases[13]

of PC-3 cells after 72 hours of treatment, whereas neither α-tocopherol nor α-tocopheryl acetate was able to achieve the same after the same length of exposure and with a dose 10 times higher. Thus establishing the possible superiority of VES as a chemopreventive agent in prostate cancer prevention, Zu and Ip[14] further investigated the effects of a combination of VES and selenium on PC-3 cells. Selenium exhibited anti-neoplastic effects similar to VES, resulting in cell cycle block, DNA synthesis suppression, and apoptosis induction. A combination of 2.5 μM methylseleninic acid and 20 μM VES produced a more effective apoptotic response than either agent alone after 72 hours of treatment.

Although in vivo studies with VES alone are lacking in the field of prostate cancer research, VES has shown dramatic results in the reduction of breast cancer xenografts in nude mice compared with controls. Malafa and Neitzel[15] demonstrated that mice injected intraperitoneally with VES had significantly lower final tumor weights (0.043 g) compared with the control vehicle-treated group (0.116 g), whereas no difference was noted between mice treated subcutaneously with VES (0.090 g) and the control subcutaneously treated group (0.071 g). Thus, the route of VES administration has a profound effect on its antitumor activity in vivo. This effect remains to be established in prostate cancer growth in vivo, and may produce a similar or even greater inhibitory effect than that reported with oral ingestion of VES by Venkateswaran et al.[5]

VITAMIN E AND PROSTATE CANCER: HUMAN STUDIES

Possible synergy between vitamin E and selenium was the basis for the initiation of a large clinical trial on prostate cancer prevention by the National Cancer Institute. The Selenium and Vitamin E Cancer Prevention Trial (SELECT) was designed to test the hypothesis that selenium and vitamin E alone or in combination can reduce the clinical incidence of prostate cancer in a population-based cohort of men at risk. This clinical trial, started in 2001, randomized 32,400 healthy men with normal digital rectal examination and serum PSA to one of four study arms: selenium (as 200 μg of L-selenomethionine) plus placebo; vitamin E (400 mg of racemic α-tocopheryl acetate, d- and l- isomers) plus placebo; selenium plus vitamin E; or placebo plus placebo. Study agents will be taken orally for a minimum of 7 and a maximum of 12 years, with assessment of general health, incident prostate cancer, and toxicity performed at 12-month intervals.

The primary end point for SELECT is the clinical incidence of prostate cancer as determined by a recommended routine clinical diagnostic workup, including yearly digital rectal examination and serum PSA level. Prostate biopsy will be performed at the discretion of study physicians according to local community standards. Secondary end points will include prostate cancer-free survival, all-cause mortality, and the incidence and mortality of other cancers (e.g., lung and colorectal cancers) and diseases (cardiovascular events) potentially impacted by the chronic use of selenium and/or vitamin E. Other trial objectives will include periodic quality-of-life assessments, assessment of serum micronutrient levels and prostate cancer risk, and evaluation of biological and genetic markers associated with the risk of prostate cancer. The enrollment for SELECT began in 2001 and the final results are anticipated by 2013.[16] The results may confirm the synergy between vitamin E and selenium that has already been established in animal studies[5,14] and has been shown to lower prostate cancer incidence in humans. The study should also determine whether there is an independent effect of dl-α-tocopheryl acetate as a chemopreventive agent.

The same ester derivative of vitamin E (50 IU of dl-α-tocopheryl acetate) was administered by the well-known Alpha-Tocopherol, Beta-Carotene (ATBC) cancer study, which resulted in a one-third reduction in prostate cancer incidence and a 41% reduction in prostate cancer mortality among Finnish male smokers.[17] While the ATBC study showed a protective effect of vitamin E supplementation on prostate cancer entirely among smokers, the US Health Professional Study (USHPS) revealed a slightly reduced risk among smokers but none among non-smokers taking regular vitamin E supplements (50, 200, 400, or 800 IU).[18] Thus, studies in human subjects have been inconsistent in establishing the chemopreventive action of vitamin E, either alone or in combination with other antioxidants, on prostate can-

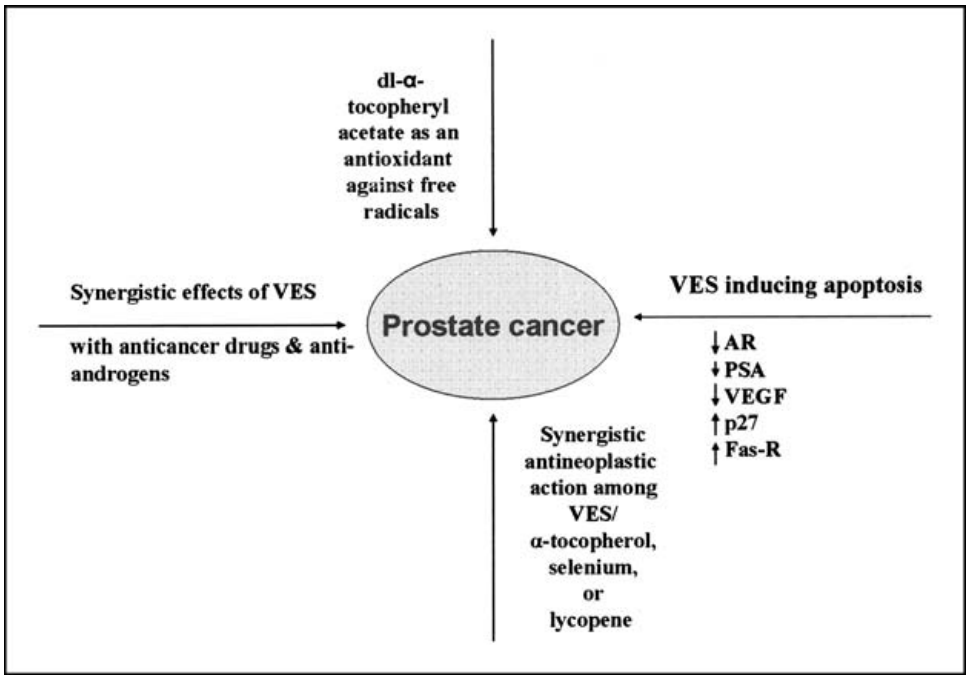

Figure 1. Schematic diagram of the relationship between vitamin E and prostate cancer. AR, androgen receptor; Fas-R, Fas receptor; PSA, prostate-specific antigen; VEGF, vascular endothelial growth factor; VES, vitamin E succinate.

cer incidence in the non-smoking, healthy male population. The choice of the form of vitamin E, its dose, and duration may be determining factors in relation to its chemopreventive action.

The novel aspect of the study reported by Venkateswaran et al.[5] is the combination of VES with selenium and lycopene as an effective antioxidant combination causing inhibition of prostate cancer when consumed daily in mice. Thus, VES, independently or in combination with other antioxidants, has been reported to be an effective chemopreventive agent.[5, 9-15] By itself, when administered through routes that bypass its hydrolysis to α-tocopherol, VES exerts a dramatic anti-neoplastic action through its accumulation in cancer cells.[15,19] Considering the rising incidence of morbidity and mortality due to prostate cancer malignancy among US men, further research is warranted into the effects of the various forms and doses of vitamin E, alone and in combination with other antioxidants, as a potential chemopreventive agent.

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Calcium Supplementation during Childhood: Long-term Effects on Bone Mineralization

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Calcium supplementation has been shown to increase bone mineralization in children and adolescents. However, catch-up mineralization later in puberty appears likely if intake is consistent with usual average intakes in the United States. Ultimately, individualized risk assessment will be developed based on genetic and lifestyle factors that can be used to guide optimal calcium intake during childhood.

Key words: calcium absorption, dietary requirements, puberty, bone mass

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INTRODUCTION: OSTEOPOROSIS AS A PEDIATRIC DISEASE

During the past 20 years, a tremendous amount of research has demonstrated the crucial nature of the pubertal growth spurt in determining overall bone mass of adults.[1,2] It is estimated that 25% of adult bone mass is accrued during just 2 years of peak skeletal growth.[3] Similarly, in girls ages 12 to 16 years, 850 g of bone mineral or 37% of the adult bone mass is accumulated.[4] This rapid mineralization is accomplished by a marked increase in the fractional absorption of dietary calcium.[5,6] Numerous studies have clearly documented pediatric disease processes such as anorexia nervosa and juvenile arthritis, in which bone mineralization is not adequate during puberty, as leading to increased risks of fractures.[7]

This understanding has led to the concept that osteoporosis in the elderly is a disease with strong roots in childhood and adolescence. Resulting dietary guidelines and position papers[1,2,8] strongly support maximizing peak bone mass during early adolescence through either increased dietary calcium intake (naturally occurring or in fortified foods) or supplementation if optimal intake cannot be achieved through diet alone. Other benefits of increased calcium intake, including lower blood pressure, weight loss, and a decreased risk of cancer have been reported in adults.[9] However, the magnitude and calcium intake level needed for these benefits in children and adolescents remain poorly understood at present and require critical long-term appraisal.[1,2]

The driving force for increasing calcium intake in older children and adolescents has been the implicit understanding that optimizing calcium intake during puberty will provide lifelong bone health benefits that otherwise would be lost. Therefore, the questions are, what are the recent data to support or reject this understanding and how can such data be used to guide both public policy and individual medical and nutritional counseling? Designing studies to answer these questions is difficult because lifetime prospective studies are nearly impossible, as is the ability to make individual assessments of the consequences of not reaching peak bone mass. Furthermore, the ideal methods to measure bone status (size, mineral content, geometry, and strength)

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during growth remain incompletely defined. In recent years, most researchers have measured regional or whole-body bone mineral content (BMC) or bone mineral density (BMD) by dual energy X-ray absorptiometry, but considerable limitations to this approach and uncertainties about its functional meaning during growth remain.

PROBLEM: OPTIMAL CALCIUM INTAKE IS NOT ACHIEVED BY MOST CHILDREN DURING PUBERTY

A large series of research studies has demonstrated that optimal calcium intake—that needed to maximize calcium retention by the skeleton and presumably bone mineralization during puberty—is between 1200 and 1500 mg/d. A level of 1300 mg/d was set in 1997 by the Dietary Reference Intake (DRI) panel as the "Adequate Intake" (AI) of calcium for males and females 9 through 18 years of age.[1] However, some evidence shows that even 1500 mg/d might not be a true maximal "threshold" (i.e., the skeleton might use even more calcium).[10] In the case of extremely low intakes (<300–500 mg/d) during puberty, a very large gap between maximal retention and actual retention can exist.[11] Although low calcium intakes may lead to immediate problems such as increased fracture risk, the intake level needed to substantially decrease this risk is unknown. Calcium-deficient rickets in childhood and adolescents has been reported, principally outside the United States (and is usually associated with calcium intakes under 300 mg/d and other lifestyle risk factors). However, the frequency of these problems as directly related to dietary calcium deficiency in childhood is unclear.[2,12]

Despite considerable and widespread public health campaigns, calcium intake in adolescents, especially girls, remains far below the target AI. Recent data, consistent with large amounts of previous data over the past 20 years, suggest that mean calcium intakes are about 800 to 900 mg/d in girls and 950 to 1050 mg/d in boys during puberty, with median intakes as much as 100 mg lower than the means, and as many as 20% to 30% of girls having extremely low intakes (<500 mg/d).[1,13]

The reasons for this discrepancy between actual diets and the recommendations are numerous and are the subject of recent behavioral and public policy research and interventions. Despite such efforts, very little, if any, increased calcium intake has occurred in adolescents. It is very likely that in the near future, achieving calcium intakes for most adolescents of at least 1300 mg/d will require either aggressive food fortification, such as by mandatory fortification of grains,[14] or much more widespread use of calcium supplements (generally pills). Although supplements may not be the ideal vehicle to increase calcium intake, it would be foolish to look at the experiences of the last 20 years and expect educational efforts currently under way to lead to near doubling of the typical dietary calcium intake via food consumption in the near future. Nor is it appropriate, if this is truly a significant health issue, for pediatric and other caregivers to respond to inadequate calcium intakes with simplified advice to "eat more calcium-containing foods." Rather, if the health care consequences of calcium deficiency during pubertal growth are significant, careful dietary history taking, laboratory (or bone mineralization) studies, follow-up visits, and consideration of supplementation would be appropriate, an approach analogous to that used by pediatricians to respond to iron-deficiency anemia.

SOLUTION: INCREASING INTAKE VIA SUPPLEMENTS OR FORTIFICATION

It is not surprising then that over the last 20 years, a large number of controlled trials have evaluated the effects of 1 to 4 years of calcium supplementation on bone mineralization in children and adolescents. To discuss them in detail is beyond the scope of this review, but they have been uniformly positive, often suggesting a relative benefit to BMC or BMD at various anatomical sites of about 1% each year for the group receiving supplements relative to a placebo control group.[1,2] That is, they have demonstrated that giving additional calcium in the form of a supplement pill, a dairy supplement, or fortified foods leads to increases in BMC (or, in some cases, total calcium absorbed). Some studies have found greater effects at different levels of pubertal development, and some reports suggest a greater benefit for calcium given with dairy products.[15] In general, however, benefits have been shown in pre-, mid-, and post-pubertal children and have occurred with all forms of calcium provided. No reports have suggested any harmful effects; some have found greater benefits in children with naturally low calcium intakes, but others have not made this distinction.[1,2,15]

QUESTIONABLE LONG-TERM BENEFIT

Early on, a rather surprising finding was reported: when subjects were reevaluated after stopping calcium supplementation, the benefit relative to placebo did not persist.[16,17] This gave rise to some skepticism over whether calcium supplementation was of any use at all to increase bone mineralization beyond an initial brief period when it suppresses bone resorption and remodeling. Other researchers suggested that a lack of benefit might have been related to sample-size issues and a failure to completely account for the bone-remodeling transient.[18] However, in the last few years, several reports have provided substantial new information related to long-

term studies that may help guide our understanding of the fundamental role of calcium supplementation during childhood.

The first study to consider is that of Bonjour et al.[15] In 2001, they reported that 3.5 years after stopping a milk-based supplement they had received for 1 year, a group of girls maintained the benefit in bone mineralization they had received. The supplement provided about 850 mg of calcium, and the baseline intakes were about 900 mg/d. At the end of the follow-up period, most of the girls were still pubertal, averaging about 12.5 years. In 2005, additional follow-up at a mean age of 16.4 years was reported.[19] For the entire group, a persistent significant benefit to supplementation was no longer seen. Of interest is that for some but not all bone sites, the girls whose age of menarche was earlier than the median age showed a benefit, whereas those whose menarche was later did not.

This lack of a substantial persistent benefit in the overall original cohort studied was similar to the earlier results of Slemenda et al.[20] That study reported that the benefits of calcium supplementation, which had been seen only in children supplemented beginning in the prepubertal period, did not persist 3 years after the supplementation was stopped.

Further questions about the benefits of high calcium intakes during adolescence have come from a longitudinal study of calcium intake, exercise, and bone mass (and strength) from Pennsylvania State University.[4,21] This study involved both a 4-year calcium supplementation phase beginning at about age 12 in females and a post-supplementation analysis of calcium intakes and bone growth. Overall, the gains in BMC associated with supplementation during early puberty were not maintained after supplementation was stopped. Furthermore, overall variations of calcium intakes between about 600 and 1400 mg/d from the age of 12 years to 20–22 years led to little variation in total body bone mass increment. There were very few subjects with intakes under 600 mg/d, making it impossible to determine a lower level of intake that provided adequate bone outcomes. Exercise appeared to be a more important determinant of bone outcome than calcium in this cohort.

Matkovic et al.[22] provided 7 years of calcium supplementation to early pubertal Caucasian girls in Ohio. The data were reported in two phases: phase 1 represents the first 4 years of the trial (mean age of 11 years at onset), and phase 2 represents years 4 to 7 of the trial. The first phase showed a small but relatively consistent benefit of supplementation for total body and proximal radial BMD. However, the adjusted difference between supplemented and unsupplemented groups (averaging about 1500 and 800 mg/d calcium intakes, respectively, during the trial) in proximal radial BMD gain was not significant despite nearly doubling calcium intake. Furthermore, group differences were even smaller by the year 7 follow-up, with no statistical effect of the supplement on most outcome measures, such as total body BMD. There appeared to be some catch-up in BMD between years 4 and 7 in the unsupplemented group despite much lower calcium intakes. Overall, little if any long-term benefit to a very high level of calcium supplementation was demonstrated in this study, which provided the longest time period of supplementation of any pediatric trial.

A secondary post hoc analysis indicated that supplementation was beneficial throughout the course of the study for "tall" girls (those whose height at the end of the study was greater than the median) but not for "short" girls. As with the post hoc findings of the Bonjour study regarding a benefit to those with earlier menarche,[19] this finding suggests genetic regulation of calcium utilization. It is difficult to see, however, from a nutritional guidelines perspective, how this type of analysis can be used in formulating policy.

Taken together, the data from six controlled trials with follow-up studies[4,16,17,19,20,22] provide strong evidence that the modest benefits of calcium supplementation on bone mineralization seen in prepubertal or early pubertal children are subject to partial, if not nearly complete, catch-up later, even if a high calcium intake is not maintained. Randomized, controlled trials showing any substantial long-term benefit to bone mass of calcium supplementation to levels at or above the current AI have not been reported. Although some,[23] but not all, epidemiological research studies suggest a long-term benefit to high calcium intake during childhood, the lack of effects in these six controlled trials must be considered as the primary evidence. It should be noted that there are some gaps in our knowledge, especially regarding populations other than healthy Caucasian females, who were the most frequently studied group, excepting the early studies in Asians by Lee et al.[16,17]

This catch-up in late adolescence is consistent with similar data regarding the possibility of catch-up bone mineralization in infants,[24] during pregnancy and lactation, and even in lactating adolescents.[25] It is not entirely clear if catch-up is complete in these situations, but a significant catch-up of lost bone mineral is possible, even if mineral intake was not maximized during a time of high calcium requirement (such as preterm infant growth or adolescent lactation). Animal studies also are consistent with this perspective, including one study demonstrating that severe inhibition of bone growth by dexamethasone in early life did not affect adult bone mass.[26] Remarkably, recent long-term data in some chronic illnesses find the same catch-up opportunity. One recent study found that adolescents with anorexia nervosa

whose disease resolved did not have long-term deficits in BMD 11 years later.[27]

IMPLICATIONS OF THESE NEW FINDINGS

As we conclude nearly two decades of clinical studies into calcium supplementation in pubertal children, beginning with the original "twin" study reported by Johnston et al. in 1992,[28] it is reasonable to question the implications of the long-term data for public policy and for guiding nutritionists, pediatricians, and other health care providers who care for individual children and adolescents.

The AI of 1300 mg/d of calcium intake was based upon short-term supplementation studies and a now enhanced set of data indicating that this level of intake is needed to approximate maximal skeletal calcium accretion during the peak of pubertal growth.[1] None of the recent studies has clearly demonstrated that peak rates of calcium retention and bone mineral accrual are readily achieved during maximal pubertal growth with lower calcium intakes. Furthermore, this calcium intake level or higher is extremely safe and consistent with other potential, albeit not well-proven, health benefits to higher calcium intakes in adolescents.

To understand why different intake guidelines are identified based on the approach used in the study, one has to recognize that different approaches measure different end points. The calcium balance studies used to derive the AI demonstrated the capacity of an adolescent to absorb large amounts of calcium at a time of rapid growth. Given the variability in the availability of food in the natural world and in many diets, this is likely to be a powerful adaptation directed toward meeting skeletal needs. The supplementation studies suggest the presence of complementary means for achieving bone mineralization during growth. The skeleton, in targeting a genetically set bone mass (and height), when provided a moderate calcium intake maintained throughout adolescence, will adapt by gradually reaching approximately the same end point of mineralization.

Whether the lack of evidence of a long-term benefit of supplementation justifies changing the AI would depend on how future groups, such as those established by the Food and Nutrition Board to determine Dietary Reference Intakes, view the purpose of the dietary guidelines. These new data should at least be used to establish Estimated Average Requirements (EAR) and Recommended Dietary Allowances (RDA). The goal of optimizing calcium retention during a narrow time period of peak pubertal mineralization using high intakes may need to be considered in light of the apparent long-term adequacy of a more modest intake. The difficulties of targeting calcium intakes far above the current intake of most children and adolescents, including about 90% of US adolescent females, should be considered.

Now the question is, what do we advise those whose dietary intakes do not reach the AI, especially most US adolescents, whose calcium intake is between 700 and 1200 mg/d? It is extremely difficult to justify supplementation of calcium for this group based on current data. It is reasonable to ensure that pediatricians and other caregivers discuss and at least attempt to assess calcium intake in their pediatric patients.[8] Very low intakes (especially those under 500–600 mg/d), health issues that affect bone metabolism, a strong family history of osteoporosis, or a lack of adequate exercise should trigger a multifaceted response including dietary counseling and, if dietary approaches are unsuccessful, the use of supplements or other appropriate health interventions.

Osteoporosis, like many other chronic illnesses, can be seen as an often genetically determined disorder with higher frequencies in women, some racial groups, and those with a family history of osteoporosis. Specific genetic polymorphisms, such as those related to the vitamin D receptor, might also affect calcium absorption, bone mass, and risk of osteoporosis.[29] Further studies might best try to further understand genetic factors affecting bone status and how they interact with modifiable factors such as exercise, diet, and medications. In this way, risk profiles could be generated and specific individualized monitoring programs devised, possibly beginning in childhood and adolescence.

There is little doubt that a relatively high intake of calcium, exceeding that of most of the US pediatric population, is beneficial in the short term for pubertal children by optimizing calcium retention and bone mineralization. However, for those who are healthy, a lower calcium intake level in the range of the current US average, when maintained throughout adolescence and early adulthood (and combined with appropriate exercise), appears to support comparable long-term rates of bone mineralization. Little if any bone mineral deficit may occur from missing the peak calcium intake levels currently recommended. Evidence from controlled trials of calcium supplements in children and adolescents do not support their widespread use during puberty. Ideally, an individualized risk assessment will be developed based on genetic and lifestyle factors that can be used to guide families and caregivers.

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