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The Risks and Benefits of Calcium Supplementation

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The association between calcium supplementation and adverse cardiovascular events has recently become a topic of debate due to the publication of two epidemiological studies and one meta-analysis of randomized controlled clinical trials. The reports indicate that there is a significant increase in adverse cardiovascular events following supplementation with calcium; however, a number of experts have raised several issues with these reports such as inconsistencies in attempts to reproduce the findings in other populations and questions concerning the validity of the data due to low compliance, biases in case ascertainment, and/or a lack of adjustment. Additionally, the Auckland Calcium Study, the Women's Health Initiative, and many other studies included in the meta-analysis obtained data from calcium-replete subjects and it is not clear whether the same risk profile would be observed in populations with low calcium intakes. Dietary calcium intake varies widely throughout the world and it is especially low in East Asia, although the risk of cardiovascular events is less prominent in this region. Therefore, clarification is necessary regarding the occurrence of adverse cardiovascular events following calcium supplementation and whether this relationship can be generalized to populations with low calcium intakes. Additionally, the skeletal benefits from calcium supplementation are greater in subjects with low calcium intakes and, therefore, the risk-benefit ratio of calcium supplementation is likely to differ based on the dietary calcium intake and risks of osteoporosis and cardiovascular diseases of various populations. Further studies investigating the risk-benefit profiles of calcium supplementation in various populations are required to develop population-specific guidelines for individuals of different genders, ages, ethnicities, and risk profiles around the world.

Keywords: Calcium; Supplement; Cardiovascular disease; Fracture

INTRODUCTION

Adequate calcium intake is essential for the maintenance of bone health during growing phases [1,2] and the preservation of bone mineral density in elderly individuals [3,4]. Therefore, calcium supplementation is generally recommended to individuals who might be at risk of inadequate dietary calcium intake or osteoporosis regardless of age in order to prevent the deterioration of bone strength. However, epidemiological studies have demonstrated that a significant proportion of people throughout the world fail to achieve the recommended daily calcium intake [5] and calcium and vitamin D are administered to both the control and drug groups in a majority of randomized trials investigating osteoporosis drugs [6-10]. In addition to its pivotal role in bone metabolism, the potential role of calcium in nonskeletal tissues has also been investigated, particularly in elderly people [11-13].

Although the issue remains controversial, an increasing

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amount of attention has been focused on the potentially harmful influence of excessive calcium supplementation on cardiovascular health. A secondary analysis of a large study evaluating the effects of calcium on bone fractures and loss in New Zealand found that a calcium-supplemented group exhibited an increase in the number of cardiovascular events [14]; however, these findings are contrary to those of previous observational studies [15,16]. As a result, this controversial report from New Zealand ignited a fierce, ongoing debate regarding the safety of calcium supplementation. Thus, the present review discusses the relevance of this controversy from a global health perspective.

THE ROLE OF CALCIUM IN SKELETAL HEALTH

Serum calcium levels are tightly regulated by various systemic hormones, including parathyroid hormone (PTH), vitamin D, and calcitonin. When serum calcium levels decrease, there is a rapid compensatory increase in PTH that stimulates osteoclast-mediated bone resorption, which is deleterious to the maintenance of bone mass [17,18]. Thus, calcium supplementation may inhibit the increase in PTH levels and prevent bone loss in individuals with a high bone turnover status, such as postmenopausal females and elderly individuals. The recommended daily allowance for calcium in the United States (US) is 1,200 mg for adult males and females and 1,500 mg for elderly individuals [2]. However, according to the 2003 National Health and Nutrition Examination Survey (NHANES), more than 80% of elderly people ingest less than an adequate amount of calcium from diet alone and approximately 43% of the general US population and almost 70% of older US females use supplemental calcium [19,20]. It is important to note that the average dietary calcium intake varies greatly around the world (Fig. 1) [21-24]. For example, the daily intake of calcium is very low in East Asian and some Central American countries where it may be only one-fifth to one-third of that in European and North American countries.

Based on findings such as these, calcium supplementation has become an integral aspect of standard care during the management of osteoporosis, even though its role in the prevention of osteoporotic fractures has yet to be convincingly demonstrated. Although monotherapy with 1,000 mg of calcium for 5 years prevented forearm and vertebral fractures over the 10-year duration of the Auckland study, this supplementation did not prevent hip fractures [25]. Additionally, other studies have failed to demonstrate the effects of calcium alone [26] or in combination with vitamin D [27] for the prevention of fractures.

Although the evidence demonstrating the benefits of calcium for fracture prevention is not convincing, calcium supplementation has been shown to have variable effects on bone mineral density depending on the study population. Daily supplementation with as little as 500 mg of calcium slows lumbar spine bone loss in perimenopausal Japanese females with low calcium intake [28] and similar effects have been observed in post-

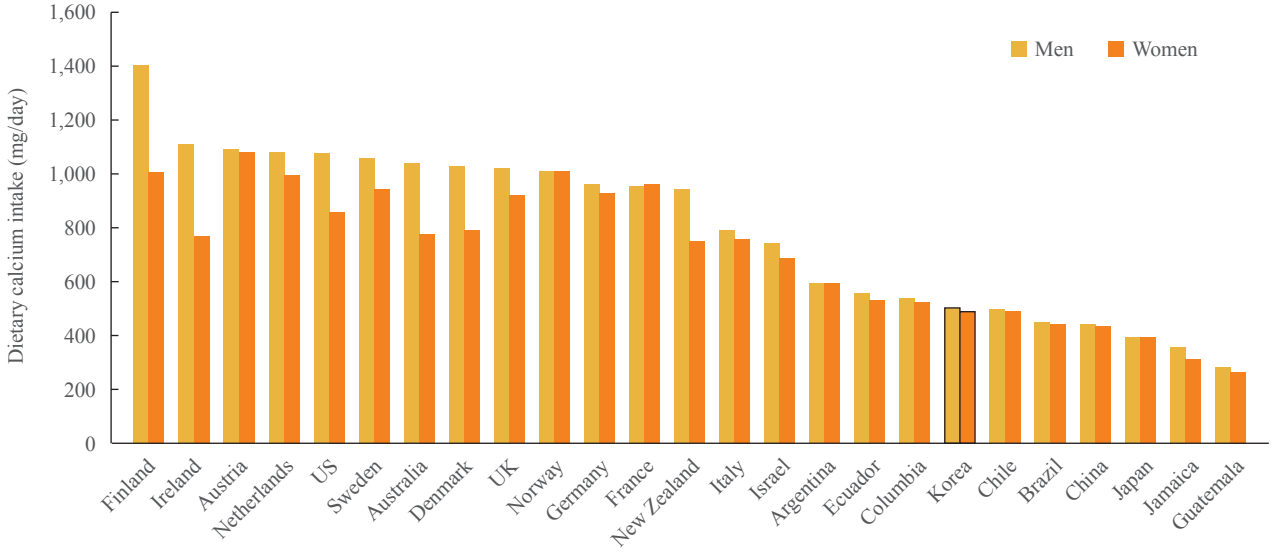

Fig. 1. Worldwide distribution of dietary calcium intake. Data obtained from the EFSA Panel on Dietetic Products [21], Weaver and Heaney [22], Wang and Li [23], and Pinheiro et al. [24].

menopausal females from Hong Kong [29-33], China [34], Chile [35], Argentina [36], and Nigeria [37]. In contrast, calcium supplementation had no consistent effects on bone mineral density in studies of calcium-sufficient populations [38-40]. These differential effects were clearly demonstrated in a study by Dawson-Hughes et al. [41] in which low-dose calcium supplementation (500 mg of elementary calcium/day) positively influenced bone in subjects with low calcium intake but not in subjects with higher calcium intake. Likewise, the daily administration of calcium (850 mg) to prepubertal females in Switzerland revealed that the greatest benefits were observed in girls with dietary calcium intakes below a median of 880 mg/day [42].

Similar to intervention studies using calcium supplementation, cross-sectional studies have also shown that the association between bone mineral density and dietary calcium intake varies based on the study population. In China [43], Japan [44], and Thailand [45,46], where the average dietary calcium intake is <500 mg/day, there are positive associations between bone mineral density and calcium intake. Likewise, calcium has a positive association with bone mineral density in Koreans whose average daily calcium intake is approximately 470 mg, particularly in those with very low serum 25(OH) vitamin D_3 levels [47]. However, this positive association is not observed in studies using calcium-replete populations. The 2005 to 2006 NHANES found that calcium intake exceeding the Recommended Dietary Allowance did not provide any benefits for hip or lumbar bone mineral density in cohorts of US males and females ≥50 years of age whose daily calcium intake ranged between 890 and 975 mg and 1,003 and 1,009 mg, respectively [48]. In a study of European females between 11 and 15 years of age, although dietary calcium intake was not a determinant of peak bone mineral density, there was a nonsignificant association in the low calcium intake group (<600 mg) [49]. These findings suggest that the skeletal benefits of calcium supplementation vary across the world and are dependent, at least to some degree, on the dietary calcium intake of the subjects; in other words, calcium supplementation has greater benefits for people in regions with low dietary calcium intake while the benefits may be marginal or absent for people with enough calcium in their diet. This is especially important in Asian countries because the number of hip fractures is rapidly rising due to a rapid increase in the aging populations within this region. It has been estimated that in 2050 more than half of all hip fractures worldwide will occur in Asia [50].

CALCIUM SUPPLEMENTATION AND CARDIOVASCULAR EVENTS

Beyond the established roles of calcium in the prevention and treatment of osteoporosis, its effects on nonskeletal outcomes, especially the risk of cardiovascular disease, have become increasingly contentious. Several observational studies have identified an association between calcium supplementation and a reduction in cardiovascular mortality. For example, in the Iowa Women's Health Study, which was a prospective cohort study of more than 30,000 postmenopausal females, both high dietary and supplemental calcium intake were associated with lower ischemic heart disease mortality [15]. It appears that the mechanisms by which calcium influences the occurrence of cardiovascular diseases operate via improvements in lipid profiles and glucose metabolism and reductions in blood pressure [51,52].

However, a secondary analysis of the Auckland Calcium Study, which was originally designed to study the effects of calcium on fractures and bone loss, revealed that calcium supplementation is associated with an increased incidence of cardiovascular events [14]. This report elicited much criticism for several reasons: the findings could not be reproduced in other cohorts [53], the design was not balanced and ignored the possible effects of confounders [54,55], and the data may have been misinterpreted [56]. The same research group published the results of a *post hoc* analysis of the Women's Health Initiative (WHI) and a meta-analysis of calcium (with or without vitamin D) supplementation studies. These analyses showed an increase in the number of cardiovascular events in people who received calcium supplementation [57,58] but these reports were also criticized due to their heavy reliance on unpublished data from the RECORD trial, because the rate of myocardial infarctions was not an endpoint, low compliance with supplementation [59], and the lack of a physiological pathway that could explain the observed relationship [60]. Additionally, Prentice et al. [61] found that the ingestion of supplements containing 1,000 mg of calcium and 400 international units of vitamin D was not associated with an increased risk of cardiovascular diseases after 7 years of follow-up in the same WHI subjects, which is contrary to Bolland et al. [58] Likewise, a meta-analysis of randomized controlled trials also failed to identify any significant increases in the risk of cardiovascular diseases such as myocardial infarction, angina pectoris, and acute coronary syndrome following the use of calcium supplements [62]. In support of the lack of adverse cardiovascular effects follow-

ing calcium supplementation, Lewis and colleagues [63] observed that daily supplementation with 1.2 g of calcium for 3 years did not increase carotid atherosclerosis in 1,500 older females who had a mean baseline calcium intake of 970 mg/day in both intention-to-treat and per-protocol analyses.

RISK AND BENEFIT PROFILE OF CALCIUM SUPPLEMENTATION FROM A GLOBAL HEALTH PERSPECTIVE

The evidence indicating whether calcium supplementation is causally related to the risk of cardiovascular events is inconsistent and inconclusive. Moreover, whether or not such a risk exists in regions with low calcium intakes, such as East Asia, has yet to be determined. The average dietary calcium intakes in South Korea, Japan, China, Thailand, and other East Asian countries range between 300 and 500 mg/day [47] while, according to the Auckland and WHI studies, the average daily calcium intakes in New Zealand and the US are 800 and 850 mg, respectively (Fig. 1). Furthermore, none of the nine studies included in the meta-analysis conducted by Bolland et al. [58] and only one (Thailand) of the 18 studies included in the meta-analysis conducted by Lewis et al. [62] utilized data from Asian countries or from individuals of other ethnicities. The majority of these studies evaluated in these meta-analyses involved Caucasians from the US, the United Kingdom, France, Denmark, Australia, and New Zealand—the average dietary calcium intake in these countries ranges between 800 and 1,200 mg/day. This average is almost twice the calcium intake in East Asian or Central and South American countries (Fig. 1). Therefore, whether or not approximately 1,000 mg/day of supplemental calcium would result in a similar risk of cardiovascular events

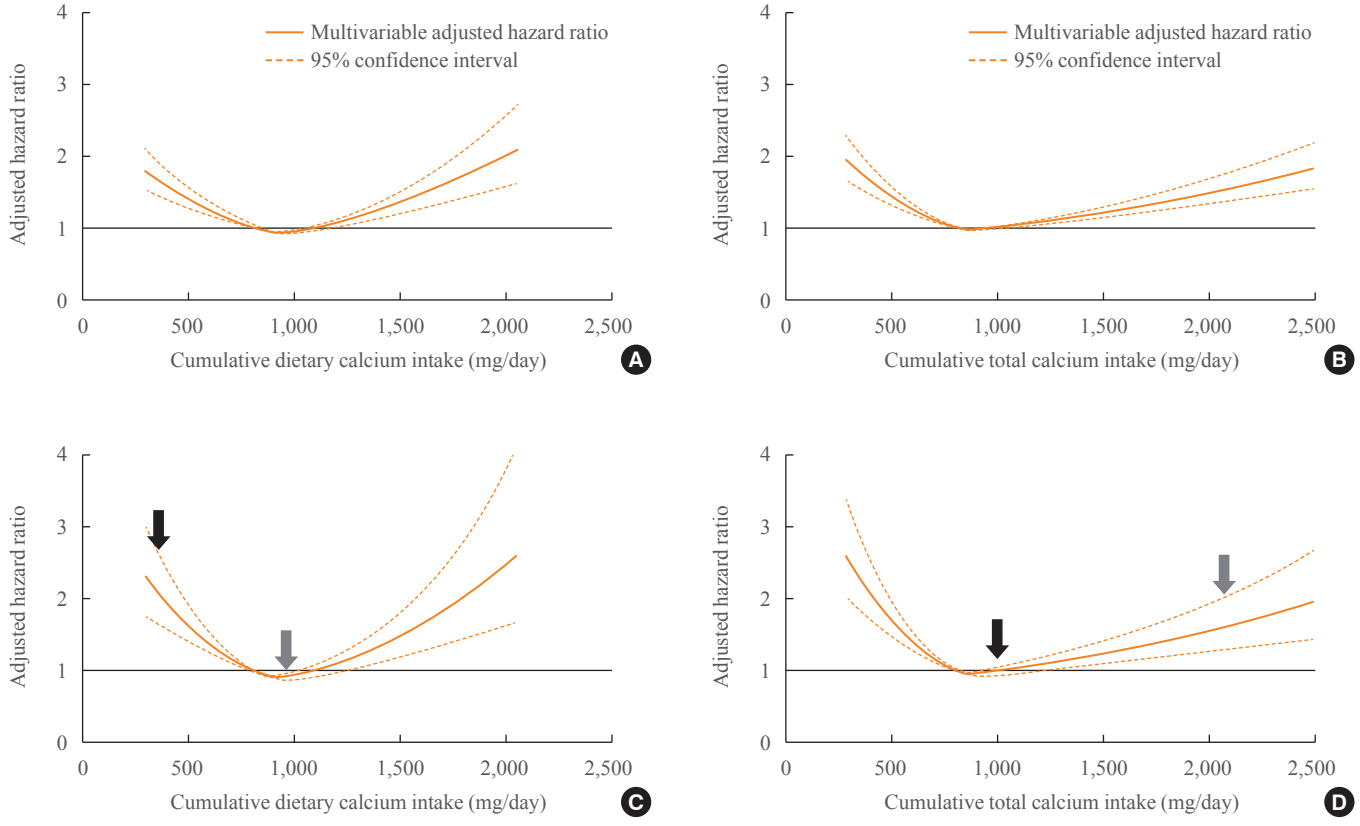

Fig. 2. Multivariable adjusted spline curves displaying the relationships among cumulative average dietary intake (A and C) and total calcium intake (B and D) with the time to death from all causes (A and B) and cardiovascular disease (C and D). Adjusted for age, total energy, and vitamin D intake, healthy dietary patterns, body mass index, height, living alone, educational level, physical activity level, smoking status, use of calcium-containing supplements, and score on the Charlson Comorbidity index. The reference value for estimation was set at 800 mg, which corresponds to the Swedish recommended calcium intake for females older than 50 years of age. Adapted from Michaelsson et al., with permission from BMJ Publishing Group Ltd. [65].

in people with insufficient dietary calcium intakes remains unresolved. Additionally, the rates of consumption of antihypertensive and anticholesterol agents in Korea are among the lowest of the Organisation for Economic Cooperation and Development nations; for example, they are less than half and one-third, respectively, of the rates in Denmark [64]. The ischemic heart disease mortality rate is also lower in East Asian countries relative to the US, Oceania, and Eastern European countries [64].

A recent study from Sweden demonstrated that the use of calcium tablets is associated with all-cause mortality only in individuals with a dietary calcium intake of >1,400 mg/day but the mortality rates were higher among females with an intake of <600 mg/day, which resulted in a J-shaped relationship between calcium intake and mortality [65]. These findings strongly suggest that, if it in fact exists, the relationship between the risk of cardiovascular events and calcium supplementation is related to total calcium intake (dietary plus supplemental) rather than the use of calcium supplements *per se*. Based on this J-shaped curve, individuals already replete with a dietary calcium intake of up to 1,000 mg/day, such as in the US, New Zealand, and other Western countries, may have an increased cardiovascular mortality following supplementation with 1,000 mg of elemental calcium because their total calcium intake would have been approximately 2,000 mg per day [65] (gray arrow in Fig. 2). However, it could also be argued that in individuals with a dietary calcium intake <500 mg/day, such as in East Asian countries, the risk of cardiovascular mortality would be decreased by increasing calcium intake via supplementation (black arrow in Fig. 2). Prospective studies investigating the discrete effects of supplemental calcium on cardiovascular events according to varied levels of dietary calcium intake are needed.

CONCLUSIONS

The effects of calcium supplementation on the risk of cardiovascular disease have yet to be adequately investigated and, at present, there is not enough evidence to support the potential adverse cardiovascular outcomes that have been described by some studies. In fact, a majority of the adverse events that have been reported originated from studies conducted in calcium-replete countries and, therefore, the issue may be limited to whether supplementation with 1,000 mg of elemental calcium in people with a dietary calcium intake of approximately 1,000 mg is safe. Because dietary calcium intakes vary widely around the world, the effects of calcium supplementation are likely to differ according to specific dietary intake levels. Therefore, it would be reasonable to take dietary calcium intake into account when analyzing the risk-benefit profiles of calcium supplementation in different populations.

In their Auckland Calcium Study, Reid and colleagues [66] reported the presence of statistical interactions between dietary calcium intake and adverse cardiovascular effects such that individuals with calcium intakes above median values exhibited a majority of the adverse effects. Moreover, the skeletal benefits and cardiovascular disease risk factors and outcomes tended to be better following calcium supplementation in regions with low calcium intakes. In the Auckland Calcium Study [58], the number needed to treat one fracture with calcium supplements was 302, whereas the number needed to produce a cardiovascular event was 178. Although the present review was unable to calculate these values in other regions due to insufficient data, it is possible that the number needed to harm (cardiovascular disease) versus the number needed to treat (osteoporotic fracture) by calcium supplementation may differ according to the dietary calcium intake and cardiovascular disease risk profiles in different parts of the world. For individuals living in countries or regions with low calcium intakes, an appropriate regimen of calcium supplementation might be beneficial in terms of fracture prevention and the reduction of all-cause mortality. In the future, the collection of population-specific data using subjects of different genders, ages, ethnicities, and risk profiles from different parts of the world is warranted prior to the extrapolation of the results obtained from a few studies.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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