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The Role of Calcium in Human Aging

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Calcium is an essential nutrient that is necessary for many functions in human health. Calcium is the most abundant mineral in the body with 99% found in teeth and bone. Only 1% is found in serum. The serum calcium level is tightly monitored to remain within normal range by a complex metabolic process. Calcium metabolism involves other nutrients including protein, vitamin D, and phosphorus. Bone formation and maintenance is a lifelong process. Early attention to strong bones in childhood and adulthood will provide more stable bone mass during the aging years. Research has shown that adequate calcium intake can reduce the risk of fractures, osteoporosis, and diabetes in some populations. The dietary requirements of calcium and other collaborative nutrients vary slightly around the world. Lactose intolerance due to lactase deficiency is a common cause of low calcium intake. Strategies will be discussed for addressing this potential barrier to adequate intake. The purpose of this narrative review is a) to examine the role of calcium in human health, b) to compare nutrient requirements for calcium across lifecycle groups and global populations, c) to review relationships between calcium intake, chronic disease risk, and fractures, and d) to discuss strategies to address diet deficiencies and lactose intolerance.

Key Words: Calcium intake, Nutrition, Growth, Bone formation

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Introduction

Calcium is a key nutrient in the human body. The primary emphasis on calcium consumption during its initial scientific discovery was focused on early human life primarily during growth periods of infancy and childhood. The interest on calcium requirements during the last decade has been expanded to apply to the entire life cycle from birth through elder years. Many commercial food and nutrition supplement products contain calcium fortification today in response to a wider audience.

The purpose of this narrative review is a) to examine the role of calcium in human health, b) to compare nutrient requirements for calcium across lifecycle groups and global populations, c) to review relationships between calcium intake, chronic disease risk, and fractures, and d) to discuss strategies to address diet deficiencies and lactose intolerance.

The role of calcium in human health

Calcium as a key nutrient

Calcium is the most abundant stored nutrient in the human body. More than 99% (1.2-1.4 kg) is stored in the bones and teeth. Less than 1% is found in extracellular serum calcium. When adults consume calcium as food or supplements, the average absorption rate is approximately 30%. The rate can vary widely due to multiple factors. For example, in pregnancy when more calcium is required for the growing fetus the calcium absorption rate increases [1-3].

Calcium distribution in the body

Calcium is distributed among various tissue compartments in the human body. The total serum pool of calcium, approximately 1,200-1,400 mg, is very small. This extracellular pool maintains the plasma calcium level in tight control at a constant serum level (typically 8.4-9.5 mg/dL) using a complex team of hormones and other substances. An example of another tight metabolic control mechanism system in the human body would be the maintenance of a normal serum glucose range in non-diabetics.

Serum calcium does not fluctuate with changes in dietary intake. The smallest drop in serum calcium below the normal level will trigger an immediate response. The body is ready to transfer calcium from other sources to maintain normal serum calcium levels and prevent hypocalcemia usually within minutes using one of three organ systems. Thus, serum calcium is not an accurate indicator of calcium stores in the body [1,3].

The three organ systems are the kidney, the intestines, and the bone. The kidney is the primary mechanism for rapid release or absorption of calcium through the filtration and urine excretion functions. Approximately 200 mg per day is typically excreted by adults through the kidneys via urine but varies by diet and serum parameters. The second organ system, the intestines, is slower in response. A daily dietary intake of 1,000 mg of calcium would potentially result in 800 mg available for tissue nutrient requirements and 200 mg to maintain serum calcium levels. Extra intestinal calcium can be processed through the kidneys and removed from the body through urinary excretion. In the third system, calcium can move both into and from bone matrix. The flexible bone pool, which varies by body size and bone density, typically has available calcium of approximately 150-200 mg. If more is required, actual bone calcium must be released ("borrowed") from the bone matrix and used to maintain serum calcium. Replacement of "borrowed" calcium does not always insure similar bone composition [1-3].

Function of calcium

Calcium is used throughout the body in small amounts. Research has confirmed that calcium is involved in vascular contraction, vasodilation, muscle functions, nerve transmission, intracellular signaling, and hormonal secretion. Each one of these functions could comprise a separate review in itself but as a group illustrate how essential calcium is in the human body. Any change in serum calcium affects one or more of these functions. For example, hypocalcemia has been linked to higher risk of seizures due to its relationship with nerve transmission and intracellular signaling [1,3].

Metabolic aspects of calcium absorption

Calcium absorption occurs throughout the gastrointestinal tract but varies by region. The majority of the calcium, approximately 65%, is absorbed where the pH is 6.5-7.5. In the ileum, the primary mechanism is passive absorption as the food moves slowly through this area of the gastrointestinal tract. It is important to note that calcium is not absorbed in the stomach. The total amount of calcium that is absorbed compared to what is available is dependent on the quantity of calcium presented, the total and segmental transit time, and the amount of calcium that is present in each unique pH environment. The solubility of calcium supplements are directly affected by the pH level [4].

Identifying at-risk populations for calcium deficiency

There are three major population groups that are at highest risk for dietary calcium deficiency. These include women (amenorrheic, the female athlete triad, postmenopausal), individuals with milk allergy or lactose intolerance, and at-risk groups for dietary deficiency intake (adolescents and the elderly).

At particular risk are female adolescents when bone formation and growth is most crucial. Later in the life cycle, women continue to be at highest risk and this risk is elevated if early baseline bone is not strong during adolescence. Women who have diagnosed eating disorders or exhibit physical hyperactivity with female athlete triad syndrome have been shown to be at high risk for calcium deficiency. Postmenopausal women, due to hormonal changes that may affect bone mineralization processes, have also been widely studied for calcium deficiency risk [3,5].

Individuals with milk allergy or lactose intolerance often exhibit calcium deficiency due to the dietary restriction of

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calcium-containing foods. These individuals can be effectively treated with dietary modifications which will be discussed later in the manuscript [6].

Both adolescents and elderly populations often have high risk of calcium deficiency due to dietary habits. Adolescents throughout the world are growing in risk due to dietary pattern changes. Many adolescents decrease calcium intake by substituting dairy products particularly beverages or by decreasing total intake of calcium. Eating disorders in both male and female teens may result in nutrient deficiencies that include calcium. The elderly are at risk for multiple reasons including low calcium intake over time, medication interactions that may decrease dietary calcium absorption, and the underlying chronic disease osteoporosis which changes bone formation and strength [1,3,7,8].

Dietary recommendations for healthy and at-risk populations

Table 1 lists dietary recommendations for key nutrients in selected populations including healthy adults and at-risk populations. The minimum requirement is 700 mg per day for calcium. Dietary recommendations are established to prevent nutrient deficiencies [1,3,8-12].

However, many individuals both young and old are deficient. In the United States as in many countries, there are deficiencies in population groups. A subgroup of Chinese-American adolescents aged 11-15 were found to have low habitual mean calcium daily intakes of 648-666 mg/d [8]. In Korea, this pattern of risk has been shown using the Korean National Health and Nutrient Examination Survey (KNHANES) data. Females are at risk in many age categories but overall only 78% meet the dietary recommendation of 700 mg per day. Average intake was only about 517 mg/day [13-15].

Calcium food sources

In the United States, current predominant sources of calcium in the diet include dairy products (milk, yogurt, cheese) and commercially fortified foods (orange juice, cereals, breads) [1,3]. In Korea, the KNHANES data documented dietary calcium intake patterns. The most predominant food sources include dairy but also anchovy, soy, and kimchi [9-12].

A wide variety of foods is necessary to achieve dietary guidelines. This reinforces that eating one single food or food group will not achieve dietary balance.

Interaction of nutrients: calcium, phosphorus, vitamin D, and protein

It is important to remember that it is difficult if not impossible to discuss calcium alone. Calcium metabolism is a collaborative effort between calcium, phosphorus, vitamin D, and protein. Just like a musical orchestra, all of these nutrients are needed to create the end product whether it is a beautiful song or a perfect bone matrix.

Calcium metabolism is collaborative

Calcium comprises a complex interactive dependency on the actions of other nutrients. Dietary calcium must move across the intestinal lumen during normal digestion to provide a calcium pool to maintain serum levels. However, dietary protein is required to provide serum IGF-1 which in turns interacts with the renal system to transform vitamin D to an active form. The resulting vitamin D receptor transcription provides the necessary substrates to move the calcium across luminal, basolateral, or intercellular compartments as needed to maintain

Table 1. Nutrient recommendations for healthy adults for calcium, phosphorus, vitamin D, and protein by country

Country	Nutrient/Nutrient unit			
	Calcium, mg/d	Phosphorus, mg/d	Vitamin D, IU/d	Protein, g/kg/d
France	1,200	750	200	1.0
			400-600*	
Korea	700	700	100	0.8-1.0
			600*	
United Kingdom	700	550	400*	0.8
United States	1,000	700	600	0.8
	1,200*		800*	

Sources: [1,3,8-12,15].
*Elderly (50 years of age or older).

serum levels. Without these interval steps, calcium would not be available to replace and maintain serum pools. Each step requires an interaction with another nutrient [16,17].

Calcium metabolism interacts with phosphorus in healthy adults

A recent meta-analysis by Fenton and colleagues illustrated the dependent relationship between phosphate and changes in calcium balance that occur primarily in the kidney. This research showed an inverse correlation between decreases in urinary calcium with increasing phosphate doses while demonstrating that calcium balance increases proportionately with phosphate. Particularly during periods of growth, foods that contain both calcium and phosphorus can lead to positive effects on bone health [18].

Relationship between fractional calcium absorption and serum vitamin D

Cumulative research by Heaney and colleagues help understand the strong correlation between vitamin D level and calcium absorption. The work has reinforced the concept that teams of nutrients collaborate to control and maintain serum levels within the human body. The absorption fraction dramatically climbs until an upper limit of 80 nmol/L of serum vitamin D is reached and then levels off. This compensatory mechanism shows the unique communication system which directly affects how much of an available nutrient is absorbed and the signaling mechanism to change metabolic pathways to adjust transport. These mechanisms help changes in dietary intake and available nutrients to undergo adaptation at the system level to assure consistent nutrients for metabolic functions [16,19].

Effects of nutrient deficiencies of vitamin D and calcium

There are tissue-specific effects of inadequate calcium and vitamin D on both plasma serum calcium and vitamin D. The role of calcium-sensing receptors that direct metabolic changes to maintain normal extracellular calcium levels is only beginning to be understood. Calcium-sensing receptor cells are found primarily on the parathyroid glands but are also located in other areas of the body. They have been shown through research to detect even the smallest changes in serum calcium and look for immediate sources of cellular calcium to restore plasma levels to the normal range. Low plasma vitamin D will also decrease enzymatic 25-OHD-one-alpha-hydroxylase activity. This in turn may change the normal differentiation and proliferation of bone and intestinal cells. Deficiencies in both dietary calcium and vitamin D will impair the function of these mechanisms and others to restore serum calcium. Long term deficiencies set the stage for chronic disease risk [2,15,17,20].

Importance of dietary protein

Skeleton and muscle comprise approximately 50% of body protein stores. Saropenia is a term used to describe loss of muscle strength and mass. Some degree of saropenia is found in more than 50% of adults 80 years of age and older. It is a leading cause of fall risk. Adequate dietary protein is needed to provide the amino acids required for muscle protein synthesis. The quality of the protein is also important. Dairy products are good sources of these nutrients because they contain the amino acid leucine as well as calcium to support both muscle and bone maintenance. Fall risk can be reduced by consuming adequate protein that also contains calcium [21-24].

Bone formation and maintenance: changes throughout the lifecycle

Bone is comprised of 60% mineral, 30% matrix, and 10% water. A very simplified explanation of bone formation will be used to help understand the true complexity of this ongoing lifecycle process. To create new bone or maintain bone composition, bone-forming cells (osteoblasts) migrate into the non-mineralized matrix vesicles (structure). This is followed by attraction of phosphorus and then calcium ions to create the mineralization (density) of the bone. On the cellular level, sodium phosphorus transporter protein molecules create the hydroxyapatite crystals as the precursor of the actual bone mineralization. Both phosphorus and calcium play essential interdependent roles in the formation of both new bone and repair of existing bone [15,17,25].

The priorities of bone formation differ by population group. In children and young adults, emphasis is placed on strong baseline bone growth and structure as a foundation. By ages 25-30, the majority of new bone formation is completed. After this growth period, emphasis is placed on maintaining bone density and preventing loss. After the age of 50, research has shown bone density often decreases substantially so the goal at this life cycle phase is to sustain bone mineral density and minimize bone loss. Progressive bone mineralization loss over time increases the risk of bone fracture and falling [1,23,26].

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Intake of adequate dietary calcium and vitamin D reduces risk of hip fracture

In the United States, more than 1.5 million fractures are reported each year in individuals over the age of 60. Several recent meta-analyses have correlated a higher calcium dietary intake to reduced fracture risk. A meta-analysis by Boonen and colleagues compared randomized clinical trials in the published literature between vitamin D alone versus vitamin D and calcium. All trials had a placebo group. Results confirmed the use of vitamin D with calcium resulted in a statistically significant reduction in hip fracture compared to the placebo group [21].

Reid and colleagues updated a prior meta-analysis to include randomized controlled studies from more than 30,000 total patients. Two other large randomized trials, the 2010 OSTPRE and the 2013 WHI (Womens' Health Initiative), provided even more evidence of use of calcium with vitamin D was the most effective preventative intervention to reduce hip fracture risk compared to control/no treatment [27].

Undernutrition and pathogenesis of hip fracture

Adequate nutrition is an underlying principle to bone maintenance. All calories are not the same. Foods must be chosen wisely to provide nutrient density of key nutrients of calcium, phosphorus, vitamin D, and protein. The required dietary intake of all four of these nutrients is necessary to support the overall goal of reducing fracture risk through partnerships with bone formation, bone mineralization, muscle mass and strength. Chronic deficiency of these interactive nutrients will result in an increased in fall risk particularly in the elderly. It is logical that adequate nutrition in adolescent and adults years helps create stronger bones with age [1,11,24].

A study of 502 adults over the age of 50 found the highest risk in those consuming less than 1,200 mg of dietary calcium per day assessed by food frequency questionnaire. More than 43% of the adults had a deficiency of both nutrients. This study infers that it is important to evaluate the nutrition status of all adults since many of these individuals had normal bone mineral density using standardized methodology. This study also supported an individualized calcium intake based on fracture risk [28].

Calcium and osteoporosis

Yang and Kim [15] recently published an analysis of bone mineral density in Korean middle-aged and older men using data from the 2008-2010 KNHANES. The population group at lowest risk for osteoporosis consumed a high quality diet that included adequate amounts of fruits, vegetables, and calcium. These individuals also had a higher serum vitamin D which is consistent with the findings linking low serum vitamin D with higher fracture risk. Moderate physical activity in conjunction with healthy body weight may contribute to the muscle mass and strength as well as bone density reducing osteoporosis risk.

A comparative effectiveness review report was recently updated in March 2012 from the Agency for Healthcare Research and Quality, United States Department of Health and Human Services. This evidence-based consensus report recommended adequate dietary calcium as an effective treatment option in both men and women who already had bone density and osteoporosis. The education message is that dietary adequacy through food or supplementation may help sustain or improve bone composition even when overt bone changes are already present [26].

Calcium and cardiovascular disease

The research literature continues to discuss multiple viewpoints on the relationship between calcium and cardiovascular disease. A major controversy lies in understanding where the calcium deposits in the soft tissue originated and what metabolic process is responsible for their formation. Many of the published analyses are retrospective using large databases which may have poor long term dietary information. It is important also to argue that the investigation of single nutrients rather than complex dietary patterns is difficult to assess. Many confounding variables are present such as physical activity and genetic predisposition that are difficult to control for in the statistical methods. The risk information is evolving and professionals need to keep updated on the emerging data [29-31].

A recent published analysis compared five similar trials of calcium supplementation including the Womens' Health Initiative cohort. All of these trials used calcium supplementation rather than increase in dietary intake to achieve intervention levels. The higher risk with calcium supplementation alone compared to dietary intervention alone appears to support adequate intake by food as a more effective strategy [27].

Positive associations with adequate calcium intake

Several reviews and individual studies have provided support that consuming a diet adequate in calcium may help in maintaining normal body weight and decreasing the risk of obesity.

This is consistent with both Korean and global recommendations to include dietary sources of calcium to decrease chronic disease risk and promote preventive health [15,20,32-34].

In another recent systematic review and meta-analysis, 14 studies were analyzed to quantify the amount of dairy product consumption that was linked to lower incidence of type 2 diabetes. The authors concluded intake of as little as 200 g/day of total and non-fat dairy intake was protective [35]. Other studies have documented the role of calcium through dairy products consumption with diabetes risk reduction [36].

Practical ideas to overcome barriers to adequate calcium intake

Ideally, a varied and diverse diet should be able to provide adequate intake of the calcium and key supportive nutrients. However, the evidence of common dietary deficiencies in the NHANES and KNHANES data as well as other studies demonstrates that achieving intake can be challenging regardless of age.

Calcium supplementation

Diet and food are the preferred methods to achieve dietary goals. However, oral calcium supplementation may be required. In the United States more than 50% of women over the age of 50 years of age are taking calcium supplements. Different calcium compounds may have different absorption rates. Most are absorbed in the ileum where the pH level promotes degradation and transport. The use of vitamin D in conjunction with oral calcium supplements is more effective than calcium alone [1,27].

Lactase deficiency

Lactase is the enzyme specific to the breakdown of the sugar lactose found primarily in dairy products. The majority of individuals who are milk intolerant have lactase deficiency, not milk allergy. Milk allergy would require a diagnosis of an immunological response to milk protein. Lactase production decreases naturally with age and also declines when an individual stops consuming lactose in their diet. Asian populations as well as African Americans are often lactase deficient. Also, as people age lactase deficiency appears to be more common [1,6].

Most individuals manufacture some lactase but may be unable to produce sufficient quantities to handle a load of 200 mL of milk at one meal. Consuming lactose-containing foods in conjunction with a meal appear to decrease symptoms in many individuals. Therefore, it is recommended to gradually introduce small amounts of lactose-containing foods. This strategy may help to stimulate the gastrointestinal tract to increase production of lactase or determine the maximum quantity that can be consumed at a single meal or snack [6].

Another strategy is to start by introducing dairy foods with a higher fat content to delay gastrointestinal transit and potentially allow for a longer time for the lactase to be available during the digestion process. Higher fat dairy often contain amounts of calcium so habitual intake will not address dietary adequacy. However, this strategy may lower the fear of trying new dairy foods if they can successfully consume ice cream or add cream to their cereal.

Lactose content of foods

Different foods have different lactose content. Tables of lactose content of foods can be found from government sources [1]. Fermented foods such as kimchi and aged cheeses are lower in lactose content. Lowering the lactose content does not lower the calcium content.

Other strategies to address lactose intolerance or lactase deficiency include specialty products. Lactose-free or lactose-reduced commercial products are available in the United States, Korea, and other countries. Lactase tablets or drops can also be added to foods themselves [6].

In the United States, there are an increasing number of new dairy products for consumers to try than emphasize more natural taste and formulas. Greek-style yogurt has become very popular primarily because its consistency is thicker. There is also a new soft cheese in the French "crème fraiche" style that is sold in smaller four-ounce portions which is thicker, more tart, and less sweet. The trend in the United States is moving away from thinner, sweeter yogurt products that were thickened with gelatin and often tasted artificial.

Keifer is a type of drinkable yogurt product which is 98% lactose-free due to its fermentation. It provides a considerable amount of positive bio-bacteria to keep the gastrointestinal flora healthy. Consumption of keifer and other active fermented dairy products on a regular basis can help establish and maintain a healthy gut flora. This is particularly important after a course of oral antibiotics which may have reduced, changed, or destroyed gut microbial diversity.

Conclusion

In summary, this narrative review has emphasized the following key information regarding calcium through the lifecycle.

1. Calcium is an essential nutrient

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2. Dietary requirements vary slightly by population group, age, gender
3. Adequate calcium is needed throughout life cycle
4. Calcium consumed as food naturally contains many other nutrients and should be primary method of intake
5. Calcium supplements may be required to correct deficiencies particularly in at risk populations
6. Calcium is an essential component of bone health
7. Inadequate intake may change bone mineral density, particularly in the elderly
8. Barriers to adequate intake need to be addressed including lactase deficiency and innovative ways to increase intake with at risk populations

Conflict of Interests

No conflict interests were declared by the author.

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