Review Article

Role of Calcium in Human Body – A Review

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ABSTRACT:

An adequate calcium intake throughout the life is essential for the maintenance of skeleton, by far the largest body reservoir of calcium. It is the fifth most abundunt element on earth and a major mineral required by body. A healthy human adult contains about 1250 gms of calcium. Calcium has an important role in suppressing the formation of atheromatous plaque .Calcium is an important constituent of G.C.F, saliva calculus and also bone. Calcium ions regulate cells of bone marrow. Imbalance between bone formation and resorption,favouring resorption results in demineralization leading to osteoporosis. In periodontitis also bisphosphonates are effective in slowing down bone loss caused by periodontal disease. The amount of calcium needed for signaling and maintaining the extracellular calcium content is relatively small, however skeletal turnover is enhanced in calcium deficiency, the increased turnover representing the body attempt to preserve skeleton.

Keywords: Calcium, Bone, Periodontitis, Osteoporosis, Atherosclerosis

Calcium is essential for life and is the fifth most abundant element on earth.The body of healthy adult human body contains about 1250 gms of calcium.Calcium exist in three domains in vertebrate body :as a solid in the form of calcium phosphate which is the extracellular mineral component of the skeleton;in ionic and protein bound formin the blood and extracellular fluids;and intracellularly,inside the cell it is found in variety of fixed binding sites.About 99%is present in the skeleton as hydroxyappatite and the rest 1%inin the soft tissues and extracellular fluids.Normal plasma calcium level is about 10 mg%1.The amount of calcium bound to proteins varies with the total protein concentration as well as ph of the plasma.

Functions of Calcium ions

1. Calcium ions decreases capillary and cell membrane permeability.
2. decreases neuromuscular excitability
3. necessary for muscular contraction
4. for normal transmission of nerve impulses.
5. blood coagulation.
6. also activates certain enzymes, including lipase,adenosine triphosphatase and some proteases.

The normal adult requires1 a minimum daily intake of 0.45 to 0.55 gm(7 to 8.5 mg per kg) for maintenance of equilibrium;for purpose of safety it is advisable to provide an excess of about 50% above the figure.

The requirement and retention of calcium is considerably increased during pregnancy.The Food And Agricultural organization of the United Nations has stated that high intakes of calcium are unnecessary and that requirements can be met with one half of the customary intakes or 400-500mg for adults.other requirements are 360-540 mg/day for infants,800 mg/day for children and 1200 mg/day for teenage pubertal growth2 .

Dietary calcium comes mainly from milk and milk products excluding butter.Human milk contain less calcium than cows milk.Green vegetables are a poor second as a sorce of calcium.oral calcium supplements comes in the form of chloride ,lactate and gluconate.Calcium is absorbed from all parts of the small bowel especially the upper region.

Calcium homeostasis

Of the calcium is blood ,nearly all is in the plasma,where its concentration is 2.5 mmol/l,10 mg/100 ml ,almost half of which is bound to process3.The ionized calcium cone is about 1.2 mmol/l with some plasma calcium in the form of citrates ,phosphates and other complexes.Plasma calcium is in very rapid dynamic equilibrium with the calcium in extracellular fluid of which the plasma volumes makes up 17%.When calcium is injected intravenously ,it expands into the extracellular fluid with a half time of less than one minute.From there calcium is lost exponentially to the bone compartment ,excreted into the urine and lost in stool.Few factors which ,help in regulation and preservation of normal plasma calcium levelare parathyroid hormone4,calcitonin,vitamin D ,plasma phosphate and plasma protein.

Calcium Antagonists and Artherosclerosis :

Calcium antagonists suppresses the formation of calcific fibrous artheromatous plaques by cellular and extracellular mechanisms. These Ca antagonists include Ca'-entry blockers lanthanum, nifedipine, verapamil and nicaradipine as well as the hormone thyrocalcitonin. Studies indicate that the f ocal increase in arterial calcium may facilitate (a) excessive activation of cellular functions in response to artherogenic stimuli leading to lesion formation. (b) development of extracellular artherosclerotic abnormalities of connective tissue. Maintainence ofCa homeostasis may play a key role in prevention of artherosclerosis5.

Calcium – Its presumptive role in Hypertension.

High B.P is the consequence of a number of alterations and derangements which involve a large sequence of events including haemodynamic, endocrine and neural systems- important hypothesis are those that see connections with intracellular Ca , where it is argued that any transport abnormality that leads to increased intracellular Na would predispose to high BP by leading

to reduced extrusion of Ca by the Na-Ca exchange system thus increasing the intracellular Ca concentration and causing increased shortening and tension in vascular smooth muscle fibers.

.Ca 2+ Regulation Of Cells Form Bone Marrow :

Blood diseases like polycythemia vera and various other leukemias reveal disturbances of balance b/w proliferation and differation of the bone marrow cells. This balance seem to get affected by specific regulatory factors, among which are Ca 2+ and 1 a, 25-dihydroxyvitamin D3.

Calcium in bone

Almost all calcium in vertebrate bone is in the form of one of several calcium phosphates with at least 90% of the crystalline solid in the form of calcium hydroxyappatite3.Calcium is deposited in the form of brushite,on collagen fibrils that have been synthesized inand extruded by osteoblasts.Additional phosphate is deposited by accretion.With time the bone crystal matures probably passing through some or all the form of phosphates.The final stage is hydroxyappatite the form that get stabilized by osteoclasts.When osteoclasts resorb bone their podosomesseals off a regioninto which the cell extrudesprotons and lysosomes.This causes the bone salt to become solublized and destroy the matrix.The resulting increase is in. the calcium concentration of the fluid surrounded by osteoclastic podosomes seems ultimately to stall the metabolism of the cell,loosening the podosome attachment and causing the fluid with the resorbed calcium to diffuse.The cell itself also seem to move to another location where it resumes it actively.The minute to minute regulation of plasma calcium must be by an exchange process between the plasma calcium on the various bone salts with their different calcium binding affinities..Newly deposited bone salts with relatively with low calcium binding affinity are found in association with osteoblasts,whereas mature bone salts with high binding affinity are associated with osteoclasts.Parathyroid hormone causes osteoblasts, only bone cells with (PH) receptors to contract and to lease their metabolic activity temporarily.When osteoblasts6 contract more low affinity calcium binding sites are exposed and the plasma concentration goes up.only osteoclasts possess calcitonin receptors.When calcitonin interacts with osteoclasts these cells in turn contract and diminish their metabolic activity.More sites of calcium phosphate with high calcium binding affinity are exposedand the plasma calcium level will go down.Cross talk between osteoblasts and osteoclasts will also be affected so that osteoclasts become more active,covering up additional high affinity siteswhen osteoblasts contract as in response to parathyroid hormone stimulation.This process would add to calcium that enters plasma.Contrariwise,when osteoclasts in response to calcitonin ,osteoblasts may spread out.,covering up more low affinity sites and less calcium would be available to enter plasma.Osteoblasts are also equipped with Vit D receptors and respond to 1.25(OH)2D3 in a manner similar to their resonse to parathyroid hormone,but the resulting rise in plasma calcium is slower.

Third type of cell are osteocytes which are found deep inside the lacunae of the bone. They are equipped with the long slender processes by means of which they communicate with one another and with bone cells on the surface.They may be involved in sensing and responding to strain in bone tissues and thereby contributing to adaptive modeling and remodeling of bone.Intermittent but not continous treatment with parathyroid hormone has been shown to stimulate bone formation and may be due to the reconversion of the metabolically inactive bone liningcells to the active bone lining cells

Calcium In Teeth :

Teeth are the most dense structures in the body, having the highest calcium content , per unit volume . Here the calcium does not get resorbed and does not participate in the body's calcium turnover. Reports also indicate a correlation between bone health and periodontal disease . In a study conducted by Klemetti and collaborators7 , in which they used 227 healthy postmenopausal women , between the age of 48 to 57 yrs . They concluded that the individuals with high mineral content of their bones , seem to retain teeth with deep periodontal pockets more easily than those who had osteoporosis .

Nishida 8 colleagues studied the role of dietary Ca intake as a contributing risk factor for periodontal disease , measured by attachement loss . Their subjects were in The Third National Health and Nutrition Survey.

Several studies relate the lower level of calcium intake with increased level of periodontal disease . Wical and Brussel9 found that Ca supplementation reduced the rate of residual ridge resorption in the first year after extraction of tooth .

Kribbs et al10,11 , in his study have reported that mandibular bone mass was not related to age but was related to skeletal bone mass .

Daniel showed that severely osteoporotic females are three times as likely as controls , to experience edentulism .

Calcium in GCF, Saliva and Calculus :

GCF – Calcium is one of the component of GCF. The calcium concentration in sulcular fluid is higher than serum but does not appear to increase significantly when correlated with increase in gingival inflammation. Osteocalcin is the calcium binding pRotein of bone and most abandunt non collagenous protein of the mineralized tissuesElevated level of osteocalcin are found in blood during the process of rapid turn over as resorption.SO it is imp component of G.C.F and acts as ammarker for bone resorption inGCF12. Calcium is also among one of the organic constituents of saliva.13,14

Studies have shown that decrease in caries activity in children with high conc entration of calcium in saliva is because of remineralization of incipient caries lesion.the saliva supersaturated with calcium acts as a reservoir for these ions15

Calculus – Calcium is the principal inorganic component of calculus (39%)13,14.

Formation :

Soft plaque is hardened by precipitation of mineral salts, which starts b/w 1st and 14th day of plaque formation. However calcification occurs in little as 4 to 8 hrs. Calcifying plaques may become 50% mineralized in 2 days and 60-90 % mineralized in 12 days. Plaque has the ability to concentrate calcium .Calcification entails the binding of calcium ions to the carbohydrate protein complexes of the organic nature and the precipitation of crystalline

calcium phosphate salts . Calcification begins along the inner surface of supragingival plaque adjacent to tooth in a separate foci that increase in size and coalesce to form solid masses of calcium.

With the occurrence of calcification, filamentous bacteria increase in number. In calcification foci there is a change from basophillia to eosinophillia.

Calculus is formed in layers which are often separated by a thin article that becomes embedded in the calculus as calcification progresses.

Mineralization of Hard Tissues

The inorganic component of mineralized tissue consists of a biological appatite which is essentially a calcium phosphate salt approximately in composition to calcium hydroxyappatite.Any local increase in the concentration of inorganic ions permits a sufficient number of ionic clusters and crystallites to form.This is called homogenous nucleation. The presence of a nucleating substance also allows crystal formation to occur,in the absence of a locally increase ionic concentration.This is called hetrogenous nucleation.16,17

Mechanism

The mechanism which involves the mineralization of hard tissues involve a structure called matrix vesicle.Within it first form of crystallite is seen.Matrix Vesicle provides a mechanism by which all the proposed mechanism for initial mineralization exists.Althogh it is possible that membrane control might increase the local concentrations of ions to permit homogenous nucleation,it is likely that heterogenos nucleation takes place within the vesicle.In Heterogenous nucleation apatite crystals are deposite in relation to collagen fibrils ,although collagen does not have any role in their initiation.The noncollagenous proteins fulfil this function.In the gap zones at the end of collagen molecules the mineral first appears .Initially these gaps are filled with proteoglycaNS which binds to calcium.these proteoglycans are removed enzymatically leaving behind calcium.As they are removed phosphoproteins bind to s to this collagen

Neither of these mechanisms are involved in the mineralization of enamel.Matrix vesicles are absent and enamel mineralization is thought to be achieved by the crystal growth from the already mineralized dentin with the subsequent size and shape of the crystals determined by the enamel proteins of the matrix.

How mineral reaches the mineralization site

There are two ways ,either through or between cells

1. Tissue fluid is supersaturated ,at least with respect to octacalcium phosphate and it could therefore be supposed that fluid simply needs to percolate between cells to reach organic matrix,where local factors would then be permit mineralization,
2. Transcellular transport;The cytosolic free calcium ion concentration cannot exceed 10-6 M because a greater concentration would cause calcium to inhibit critical cellular function leading to cell death.Two mechanisms have been proposed that permit transcellular movement of calcium without exceeding the threshold concentration.

A) First suggests that calcium enters the cell through specific calcium channels,it is sequestrated by calcium binding protein, that in turn is transported through the cell to the site of release

B) Second suggests that a continu ous . and constant flow of calcium ions over exceeding 10-6M.

Degradation16,17

Bone is constantly remodeled by an orchestrated interplay between the removal of new bone and replacement of new bone. The remaining hard tissues do not remodel but are degraded and removed during the normal physiologic process involving in the shedding of the deciduous teeth.The degradation and removal of hard tissues are cellular events brought about by osteoclasts.Sequence of reorptive events are

1. attachment os osteoclasts to the surface of bone.
2. creation of an acidic environment through action of proton pump,which demineralizes bone and exposes the organic matrix.
3. Degradation of the exposed organic matrix to its constituents amino acids by the action of released enzymes such as acid phosphatase and cathepsin B.
4. Uptake of mineral ions and amino acids by the cells.

Calcium and Osteoporosis

Osteopenia is a reduction in bone mass due to an imbalance between bone formation and resorption ,favouring resorption resulting in demineralization and leading to osteoporosis. Osteoporosis18 is a disease characterized by low bone mass and fragility and consequent increase in fracture risk.Periodontitis is characterzed by inflammation of the supporting tissues of the teeth, resulting in resorption of the alveolar bone as well as loss of soft tissue attachement to the tooth . and this is a major cause of tooth loss and edentulousness in adults . one hypothesis is that osteoporosis results in less crestal alveolar bone per unit volume . the bone of lesser density may be more readily absorbed. Recently from an accessement of osteoporosis in the jaws by dual photon absortiometry, it was found that deduction in total skeletal mass is directly related to deduction in mandibular bone density in women with osteoporosis .studies by Kribbs n Chesnut19 and Hernikson and Walenius20 showed that the mandibular measurements did correlate with skeletal measures of bone mass however, Mehajery n Brukks21 found that there was no correlations b/w skeletal n mandibular bone measurements. A study Humphries n coworkers22 showed that the loss of bone mineral density with age in edentulous adult mandibles was significant in females but not in males. The effect of age was cumulative loss, whereas in famales a second factor may be involved, namely , the effect of bone loss associated with menopausal cessation of ovarian function. Recently, Hirai et al23 found that the presence of skeletal osteoporosis strongly affects the reduction of residual ridge in edentulous pts.

Hormone replacement therapy with estrogen n progesterone24,25 is still the gols standered for treating women , an alternative treatement omits progesterone with estrogen taken daily throughout the month. In females a decline of estrogen secretions is one of the main factors that affect systemic bone density after menopause. It is well known that estrogen26 depletion after menopause can increase the rate of skeletal bone loss. Krall et al

examined the efect of estrogen therapy on tooth retention and edentulism. They found that estrogen users add more teeth remaining, than non users after controlling age, smoking status and education.

Because of increase of breast cancer, two estrogen related molecules have been approved for treatment : raloxifene and tamoxifen. These selective estrogen receptor modulators compete with estrogen for high affinity binding to the same ligand binding domain of the estrogen receptor, this antagonizes estrogen actions in breast and uterus. As far as their actions on bone is concerned, these estrogen- receptor modulators have the same general effects as estrogen , although definitive clinical studies have not yet been completed.

Fluoride has been used in the treatment of osteoporosis27. According to Ring ether can be little doubt that pharmacologic doses of fluoride stimulate osteoblastogenesis and increase bone mass. The therapeutic window for fluoride treatment is quite narrow b/w 10 mg and 20mg daily of bioavailable fluoride ions.

Heaney has concluded that there is virtually no evidence that calcium supplementation alone, in any quantity will lead to substantial bone calcium gain in persons who already, have osteoporosis. However substantial calcium supplementation is combination with other regimens for e.g Hormone replacement or bisphosphonate treatment.

CALCIUM & PERIODONTITIS :

Increased level of serum calcium has been observed in patients with periodontitis28

There are possibilities for management of periodontitis by controlling systemic risk factors in conjunction with anti infective theraoy.For e.g Bisphosphonate29 one of the drugs known to slow bone loss in osteoporosis has been shown to be effective for oral bone loss caused by periodontal disease in an animal study as well as pilot human experimental study.Recent evidence shows that bisphosphonates like ,tetracycline have anticollagenolytic properties30.Some bisphosphonates appear to be less toxic and more efficacious than first generation drugs.31

According to Fleisch and collaborators3 there are two general classes of bisphosphonates :those are metabolized within the cell to form toxic analogs of adenosine triphosphatase and those that inhibit the enzyme farensyl diphosphate enzyme,with its effect on cholesterol synthesis inhibit osteoclast activity is still under study.Certain disorders are characterized by lowered level of calcium in blood and others involved elevated calcium level.Cause of hypocalcemia are hypoparathyroidism,Vit D deficiency, Malabsorption syndrome, renal failure with uremia and raised plasma phosphorous,new born infants,acute haeorrhagic pancreatitis,pseudohypoparathyroidism.Hypocalcemia can also occur by reduction of ionized fraction and reduction of protein bound fraction only.

Hypercalcemia occurs in hyperparathyroidism,multiple myeloma,skeletal neoplasm.sarcoidosis.milk alkali intoxication.

Conclusion

An adequate calcium intake throughout the life is essential for the maintenance of skeleton ,by far the largest body reservoir of calcium.Appropriately high calcium intake is particularly important in first two decades when the body calcium mass increase to near maximum.In subsequent decades because calcium absorption is relatively modest ,typically 25%or less calcium intake must be kept nearly 100 mg per day in order to minimize the possibility that the skeleton will be mined for its mineral content.The amount of calcium needed for signaling and to maintain the extracellular calcium content is relatively small,however skeletal turnover is enhanced in calcium deficiency,the increased turnover representing the bodyd attempt to preserve skeleton.

References

1. Walter B. , Evan C. In : Garafield G. Duncan, Editors. Diseases of Metabolism ; 1961 : 4th Edition.
2. Thannhauser's Nepomuk Z, Editors ; textbook of Metabolic Disorders :1961:2nd edition.
3. Dental Clinics of North America 47 (april 2003) 209-224.
4. Kebin D Healey, Janeen L .Vanhooke, Jean M. Prahl . Parathyroid Hormone decreases renal vitamin D receptor expression in vivo. March 2005 ; vol 102 ; no 13: 4724- 4728
5. Bader H, geitzen K editors : intracellular calcium regulation 1984.
6. Mc Donald F, Ion Channels in osteoblasts : a story of two intracellular orgenelles. Surgeons 2004 Apr; 2 (2): 63-9.
7. Klemetti E, Collin HL, Foss H , et al . Mineral status of skeleton and advanced periodontal disease J Clin Periodontal 1994 : 21 : 184-8
8. Nishida M, Grossi SG , Dunford RG, et al . Calcium and risk for periodontal disease. J periodontal 2000; 71;1057- 66
9. Wical KE, Brussae P. Effects of calcium and vitamin D supplements on alveolar ridge resorption in immediate denture patients. J Prosthet Dent 1979 : 41:4-11.
10. Kribbs PJ, Chesnut CH. Relationship b/w mandibular and skeletal bone in a population of normal women. J prosthet Dent 1990:63:86-89
11. Kribbs PG. Comparison of mandibular bone in normal and osteoporotic women J prosthet 1990 :63 :218 – 222
12. Shivamanjunath .G.R .Role of G.C.F as a potential biomarker in periodontal disease.Jounal of Dental Science and Oral Rehabilitation 2013;July-September issue
13. Carranza , Newman , Takai – clinical periodontology- 9th edition
14. Jan Lindhe – clinical periodontology and implant dentistry. 4th edition
15. Preethi B.P, Dodawad R,Anand j. Estimation of flow rate, ph, buffering capcity total proteins and total antioxidant capacity levels of saliva in careies and cries active children:an in vivo study. International Journal of Clinical Biochemistry 2010;25(4);425-428
16. Orban's oral histology and embryology. 11th edition
17. Tencate AR. Oral histology :Development structure and function :fifth edition.
18. Jean Wactawski – Wende , Sara G, Grossi et al . the role of osteopenia in oral bone loss and periodontal disease . J Periodontal 1996:67;1076-1084.
19. Kribbs PJ, Chesnut CH : osteoporosis and dental osteopenia in the elderly. Gerodontology 1984 :3:101-106.

20. Henrikson PA , Wallenius K. The mandible and osteoporosis . a qualitative comparison between the mandible and the radius. J Oral Rehabil 1974:1;67-74.

21. Mohajery M, Brooks SL. Oral radiographs in the detection of early signs of osteoporosis.Oral surg oral med Oral Pathol 1992 :73 ;12- 117.

22. Humphries S.A radiographic investigation into bone resorption of mandibular alveolar bone in elderly edentulous adults .J Dent 1989;17:94-96.

23. Hirari J,Ishijima T.Osteoporosis and reduction of residual ridge in edentulous patients .J Prosthet Dent 1993;69:49-56

24. Charles F,Hildebolt,Thomas K.Pilgram estrogen and/or calcium plus vitamin D increase mandibular bone mass.J Periodontol 2004 ;75:811-816

25. Norderyd OM,Grasi SG .Periodontal status of women taking postmenopausal estrogen supplementation.J Periodontol 1993 ;64:957-962

26. Mine T,Sara G,Grossi.The relationship between bone mineral density and periodontitis in postmenopausal women,J periodontol2000;71:1492-1498

27. Von W ,Klausen B.Osteoporosis :A risk factor in periodontal disease J Periodontol 1994;65:1134-1138

28. Harsha.L,Vishnu.P,Bedra.A Estimation of serum calcium level in patients with chronic periodontitis in Kancheepuram district .Journal of Pharmaceutical Sciences and Research2015;7(6),334-335.

29. Brunsvold M,Chaves ES et,al.Effect of bisphosphonates on experimental periodontitis in monkeys.J Periodontol 1992;63:825-830

30. Deluisse JM,Eeckhout Y.Bisphosphonates and bone resorption:effects on collagenase and lysosomal enzyme secretion.Life Sci1985Dec 16;37(24):2291-2296

31. Golub LM,Ryan ME :Modulation of the host response in the treatment of periodontitis.Dentistry Today.Vol 17 No.10 Oct .1998.

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