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Aging and Calcium as an Environmental Factor

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Introduction

Aging, by definition, is a genetically programmed process which is universal, progressive, irreversible and deleterious. Any environmental factor, therefore, cannot change the aging process fundamentally, but may influence it to various extents. Calcium, on the other hand, is essential to all forms of life. It is not only important as the constituent of a living organism, but is also vital as a messenger for intercellular control and transduction across the cell membrane, especially because of its specific distribution in the organism and across the cell membrane, creating a 10,000-fold concentration gradient. Because such a unique distribution of calcium is under the precise control of calcium regulating hormones, which in turn are markedly influenced by nutritional intake of calcium, calcium nutrition is in a position to control the function of individual cells, as well as the entire organism. Calcium in the environment has changed markedly when animals came out of seawater in the evolutional process. From seawater containing abundant calcium, land-abiding animals moved to a caclium-deficient environment, where calcium is supplied only through nutrients. Since calcium in the environment markedly influences the function of each cell and the entire organism, it could also influence the aging process. It is the purpose of the present study to assess the significance of calcium as an environmental factor and to define its influence on the aging process. Calcium intake from the environment in humans mainly depends on nutritional calcium intake and intestinal calcium absorption, under the control of vitamin D. Two communities in the Kii Peninsula, central Japan, were selected for an epidemiological study, to assess the influence of the difference in calcium as an environmental factor on the aging process in man.

Aging and calcium deficiency

A sharp difference is found in environmental calcium between fish living in seawater containing abundant calcium, and land-abiding animals (Fig. 1). Since calcium enters the body of fish with each breath of calcium-containing seawater, the main concern under such a calcium-excess environment is how to extrude the excessive calcium entering the body efficiently, to avoid hypercalcemia and resultant functional deterioration. The absence of parathyroid glands in the fish might be explained by the fact that the main function of the parathyroid glands is to conserve calcium and to raise plasma calcium by stimulating bone resorption and calcium removal from the bone. The absence of the bone marrow cavity with hematopoiesis in the fish is of profound interest, because it might suggest the role of the parathyroid glands in preserving the bone marrow cavity to ensure hematopoiesis there. In the fish, "extramedullary" hematopoiesis, located in such places as the spleen and other sites in the reticuloendothelial system, is the rule. In land-abiding animals, including humans, on the other hand, no calcium is naturally contained in the air they breathe, and the only calcium supply is *via* the gastrointestinal tract, as the nutrient. Consequently, calcium, as an environmental factor in land-abiding animals, is practically nothing but nutritional calcium intake and these animals, including humans, are always deficient in calcium, at least relatively, compared to the sea-abiding animals, such as the fish.

Thus, when we define ourselves to be in the state of calcium deficiency, it follows that the longer we live, the more calcium deficient we become (Fig. 2). Decrease of serum calcium is a direct stimulation to the parathyroid hormone (PTH), and calcium deficiency or negative calcium balance is also believed to stimulate PTH secretion,

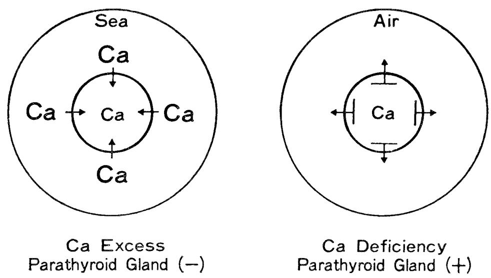

Fig. 1. Environment and calcium.

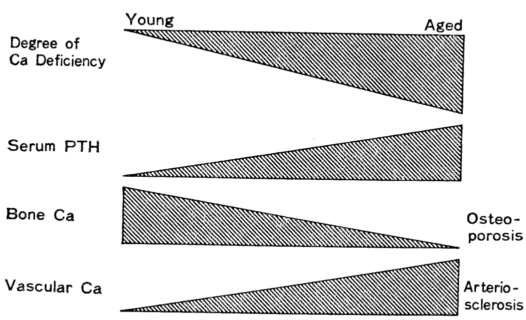

Fig. 2. Aging and calcium.

causing parathyroid hyperplasia, possibly through repeated incipient hypocalcemia. Increased parathyroid hormone secretion results in a decrease of bone mass through an increased resorption. This is at least one of the causes of age-bound bone loss or osteoporosis. By some unknown mechanism, the decrease of bone mass is associated with an increase of calcium content in soft tissues, such as the blood vessel. This apparent "calcium shift" from the bone to soft tissue, or the blunting of bone/soft tissue calcium gradient, apparently represents one of the characteristic changes associated with aging. Since another effect of PTH consists of an increase in calcium uptake by the cell, calcium deficiency resulting in secondary hyperparathyroidism tends to decrease the extracellular/intracellular calcium gradient. In addition to the simple persistence of a calcium deficient state, several factors might accelerate the calcium deficiency associated with aging. Intestinal calcium absorption progressively decreases along with aging, probably because of the aging changes of the intestine itself. Because elderly people generally eat less, and dislike fatty meals, vitamin D intake is decreased. Shorter solar exposure in elderly people will cause a decreased vitamin D biosynthesis in the skin. Finally the progressive decrease of renal function with aging is associated with decreased 1,25$(OH)_2$ vitamin D synthesis. Patients with chronic renal failure exhibit marked secondary hyperparathyroidism with a decrease of bone mass, and increased calcium deposition in the soft tissue, such as vascular calcification increases the calcium content in the brain and the nerve. Such a "calcium shift" from the bone to soft tissue in chronic renal failure is similar in direction to the phenomenon seen in aging, but much more severe. Chronic renal failure might therefore be regarded as a model of aging, as far as calcium deficiency, secondary hyperparathyroidism, and "calcium shift" from the bone to soft tissue is concerned.

Epidemiological studies

1. Background of the communities. Oshima Island, with a population of 2,184 at the tip of the Kii Peninsula on the Pacific side of the central part of the Japanese Mainland, is a seacoast village enjoying abundant sunshine all the year round. Shichikawa Island is 30 miles upstream from the Kozagawa River in the mountains, 1,000–2,000 feet above sea level, with a population of 1,667. Surrounded by mountain peaks, the hours of sunshine are much shorter than in Oshima. Fishery is the main occupation in Oshima village and the favorite food is fish cooked with bones and internal organs, no doubt with high calcium, protein and vitamin D content. In addition, sightseers have brought in western food, including milk and dairy products. Traditional Japanese food mainly consists of rice gruel with tea leaf and vegetables, which has governed the eating habit in typically agricultural Shichikawa village, where the majority of the population have been engaged in forestry for many years. Although the recent motorization and industrialization of Japan has modernized the mode of living, including eating habits in Shichikawa, like everywhere else, the difference in nutritional intake between these two communities has probably persisted, at least until 30 years ago.

In the present epidemiological study, 23% of the adults above the age of 30 years in Shichikawa and 29% of those in Oshima participated (*1*, *2*).

2. Causes of death. The causes of death in these two communities during the past decade, adjusted per 100,000 population, are shown in Table

Table 1. Causes of death in mountain and seacoast districts 1966–1975. (per 100,000)

	Mountain	Seacoast
Malignancy	243	182
Cerebrovascular disease	215	143
Cardiovascular disease	154	78
Pneumonia	83	34
Suicide	44	0
Senescence	88	304

Table 2. Prevalance of lumbago (%).

Sex	Age (yrs)	Shichikawa	Oshima
Males	40 and below	50	64
	41–50	28	50
	51–60	48	19
	61–70	63*	21*
	71 and above	60	40
Females	40 and below	38	18
	41–50	34	23
	51–60	33	18
	61–70	34	30
	71 and above	43	32

* Significant by χ^2 test, $p<0.05$.

1. The mountain village of Shichikawa showed a death rate, due to cardiovascular disease, of almost twice as high as that in the seacoast village of Oshima. Death due to cerebrovascular disease or malignancy was also definitely higher in the mountain than in the seacoast. Death due to pneumonia was also higher in the mountain community. The most remarkable difference was 44 suicides in the mountain and none in the seacoast, which might suggest the severe condition of living in the mountain community, contrasted to the comfortable mode of living in the seacoast community. Death due to senescence, with no remarkable illness, was more frequent in the seacoast than in the mountain.

3. *Lumbago*. Lumbago was a more prominent complaint in the mountain than in the seacoast, especially in females, as shown in Table 2. Seacoast people worked as hard as the mountain people, though the kind of work was somewhat different. No ready explanation was offered from the kind of work for the higher incidence of lumbago.

4. *Body height*. People in the mountain community were generally shorter than those in the seacoast community. Such a difference was not confined to females after middle age, with the loss of body height due to osteoporosis and vertebral deformity.

5. *Age-bound bone loss*. Age-bound loss was apparently more pronounced in the mountain community than in the seacoast community, based on several methods of assessment. Firstly, the thoracic spine deformity on the lateral spine X-ray film was more frequent (Fig. 3). Secondary, clavicular cortical thickness measured in the postero-anterior chest X-ray film was smaller. These changes were most pronounced in women after menopause. Thirdly, bone resonant frequency (*3*), reflecting bone density, and shown to be significantly correlated with bone mineral content, was lower in the mountain community at each age group (Fig. 4).

6. *Biochemical studies*. Serum calcium values showed no difference between the two communities. Serum inorganic phosphorus, however, was lower in the mountain community than in the seacoast community at each age group. Serum alkaline phosphatase, on the other hand, was higher in the mountain community than in the seacoast community, suggesting a tendency to osteomalacia, due to hypophosphatemia in the mountain com-

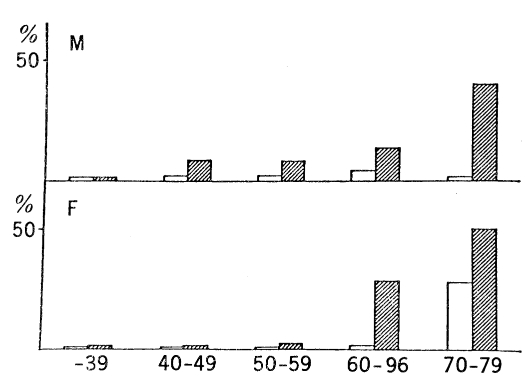

Fig. 3. Prevalence of thoracic spine deformity in Shichikawa (mountain), shown in shadowed bar, and Oshima (seacoast), shown in open bar. Mountain community showed a higher prevalence at each age group.

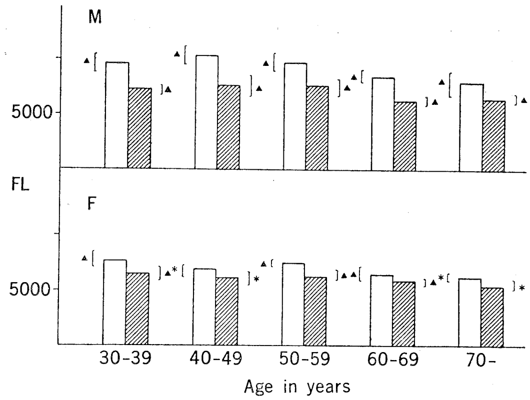

Fig. 4. Bone resonant frequency (FL) indicating bone mass in the mountain community (shadowed bar) and seacoast community (open bar). Mountain community showed lower values.

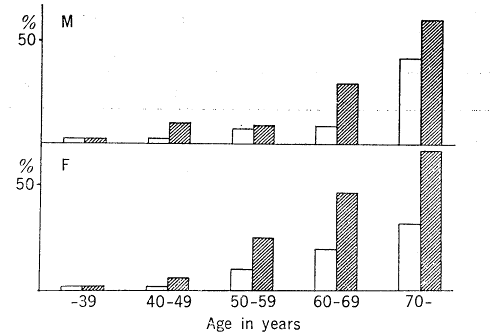

Fig. 5. Aortic calcification in the mountain community (shadowed bar) and seacoast community (open bar). In each age group of both sexes, the mountain community gave higher rates.

Table 3. Difference between mountain and seacoast villages.

	Mountain	Seacoast
Ca intake	Low	Moderate
VD intake	Low	Normal
Sunshine	Poor	Good
Lumbago	Frequent	Normal
Body height	Short	Normal
Vertebral deformity	Frequent	Normal
Clavicular cortex	Narrow	Normal
Aortic calcification	Frequent	Normal
Serum P	Low	Normal
Serum ALP	Hight	Normal
Serum protein	Low	Normal
Serum cholesterol	Low	Normal

munity. Lower serum total protein and cholesterol in the mountain community also suggests a factor of relative malnutrition in this area (Table 3).

7. *Calcium shift from the bone to the soft tissue.* It is noteworthy that aortic calcification in the chest X-ray film was definitely more frequent in the mountain community than in the seacoast community, in parallel with the bone loss as reflected by the vertebral deformity and shortening of the stature (Fig. 5). Taken together with the higher mortality rate due to cardiovascular disease, and higher incidence of ECG abnormality, 53 *versus* 42%, in the mountain community, such parallelism between bone loss and cardiovascular abnormality might suggest a calcium shift from the bone to the soft tissue (*4–7*), in response to calcium deficiency and secondary hyperparathyroidism. Such a calcium shift typically occurs in chronic renal failure (*8*).

Discussion

Epidemiological studies are becoming increasingly more difficult, because of the rapid shift of the population between various districts. The two communities in the Kii Peninsula provided an ideal site to evaluate the role of calcium as an environmental factor on aging and many associating changes on the human body, because of an exceptional stability of the population over a period of 10 years, this excellent cooperation making it possible to survey as many as 26% of the adult population and showing a marked contrast in the calcium and vitamin D intake, as well as the solar exposure between the two communities. The mountain community of Shichikawa probably represents an ideal model for long-term calcium and vitamin D deficiency, with the seacoast community playing the role of a control. It is noteworthy that amyotrophic lateral sclerosis has been exceptionally prevalent in this mountain area, along with Guam and Papua New Guinea. Such a high prevalence of amyotrophic lateral sclerosis has been ascribed to low contents of calcium in the drinking water, leading to calcium deficiency, secondary hyperparathyroidism and calcium de-

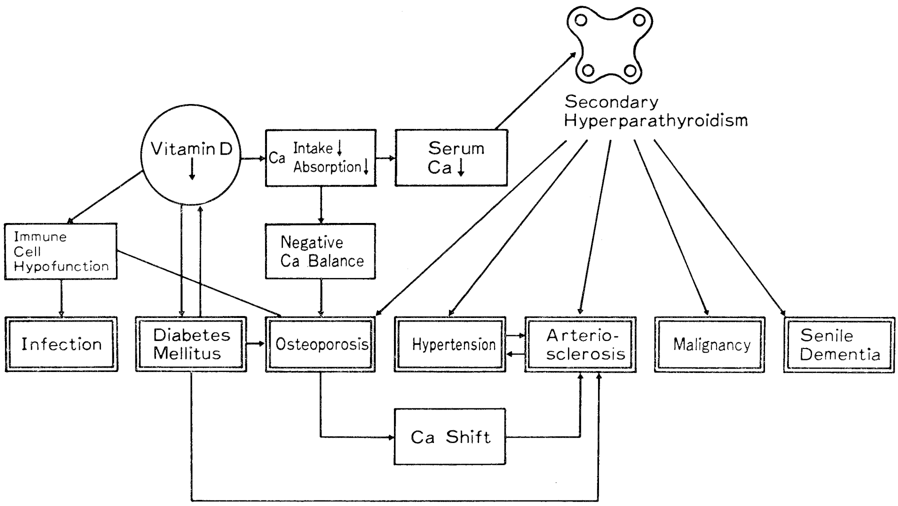

Fig. 6. Ca deficiency and diseases of old age.

position to the brain and spinal cord (*9*). This exceptional community thus provides a warning to the consequences of long-term calcium and vitamin D deficiency. Fortunately, the situation has improved remarkably during the last decade, with improvements in communications and food supply, so that the young population in this community would no longer be exposed to the calcium deficiency of 3 years ago.

Summary and conclusion

Calcium deficiency is a constant menace to land-abiding animals, including mammals. Humans enjoying exceptional longevity on earth are especially susceptible to calcium deficiency in old age. Low calcium and vitamin D intake, short solar exposure, decreased intestinal absorption, and falling renal function with insufficient 1,25$(OH)_2$ vitamin D biosynthesis all contribute to calcium deficiency, secondary hyperparathyroidism, bone loss and possibly calcium shift from the bone to soft tissue, and from the extracellular to the intracellular compartment, blunting the sharp concentration gap between these compartments. The consequences of calcium deficiency might thus include not only osteoporosis, but also arteriosclerosis and hypertension due to the increase of calcium in the vascular wall, amyotrophic lateral sclerosis and senile dementia due to calcium deposition in the central nervous system, and a decrease in cellular function, because of blunting of the difference in extracellular-intracellular calcium, leading to diabetes mellitus, immune deficiency and others (Fig. 6).

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