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Calcium, Parathyroids and Aging

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Since life was probably created in seawater with abundant calcium content on earth which might be called a planet of calcium, calcium is indispensable in all the functions of each cell. When some form of life decided to come out of the abundance of calcium to live on land, inevitable calcium deficiency occurred, with aggravation in aging. Parthyroid glands secrete PTH which mobilizes calcium from bone to restore serum calcium which may decrease mildly and transiently in calcium deficiency. PTH may therefore be called a hormone for calcium deficiency. It may not be a coincidence that no parathyroid glands are found in fish, which are living in an environment with abundant calcium. Calcium, parathyroids and aging thus appear to be three imporant factors interrelated to each other to control the body and cell function.

Role of Calcium in Physiology and Nutrition

Calcium is the 5th most abundant element in the human body and is unique in its distribution. While 99% of calcium in the body is distributed in the skeleton to provide the hardness it requires to support the body, a small amount circulating in the blood serves to maintain a constant serum calcium level, which is the most strictly regulated biological constant [1]. Serum calcium should be maintained constant because it is vital for the cells to maintain a constant level of intracellular free cytosolic calcium, which is only 1/10,000 that of extracellular calcium level. Such a vast intra-extracellular concentration gradient is unique for calcium and essential for the maintenance of cell membrane integrity and all cell functions including secretion, excitation, locomotion differentation, and proliferation. Signal transduction heavily depends on this vast extra- and intracellular calcium concentration gradient. Whenever such a concentration gradient is

blunted between the extra- and intracellular compartment, serious disturbances occur in the signal transduction.

Parathyroid hormone is known to increase intracellular calcium in at least 8 kinds of cells, osteoblasts, renal tubular cells, lymphocytes, neutrophilic leucocytes, red blood cells, myocardial cells, vascular smooth muscle cells and pancreatic β-cells [2, 3]. Since calcium deficiency stimulates PTH secretion, calcium deficiency tends to increase intracellular calcium, blunting the extra- and intracellular calcium concentration gradient. A shift of calcium from the skeleton to the soft tissue like blood vessel and from the extracellular to the intracellular compartment thus takes place on calcium deficiency through the action of PTH. Since aging is characterized by calcium deficiency, such progressive increase of soft tissue and intracellular calcium leading to a blunting of calcium concentration gradients between compartments invariably occurs in aging. Aging is also associated with decreasing appetite and decrease of gastrointestinal absorptive function leading to less calcium intake and absorption. Age-bound decrease of renal function with a fall of 1,25(OH) vitamin D synthesis also decreases intestinal calcium absorption. All these factors contribute to calcium deficiency in aging. Aging may also be regarded as a slowly progressive renal insufficiency.

Consequences of the Rise of Intracellular Calcium Concentration and Blunting of Intra- and Extracellular Calcium Concentration

All cell death is characterized by an increase of intracellular calcium as exemplified by hepatic cell necrosis on exposure to carbon tetrachloride, progressive muscular dystrophy due to hereditary membrane abnormality, myocardial and nerve cells on ischemia and cells infected by viruses or bacteria [4]. Increase of cytoplasmic free calcium may therefore be called 'the final common path' of cell disease and cell death. Aging as a background of diseases is also characterized by an increase of intracellular calcium. Diseases typically associated with aging include hypertension, arteriosclerosis, diabetes mellitus and dementia.

Hypertension is caused by contraction of the vascular smooth muscle induced by the increase of intracellular calcium. Although the acute action of PTH is hypotensive, mediated by relaxation of the smooth muscle, chronic parathyroid hyperfunction in response to calcium deficiency invariably causes an increase in intracellular calcium in vascular smooth muscle and hypertension in humans and animals with experimental hypertension, including spontaneously hypertensive rats [5]. Disturbance of calcium transport due to generalized membrane abnormalities manifested

by increased urinary calcium secretion and decreased intestinal calcium absorption leads to calcium deficiency which is aggravated by decreased calcium intake. Oral calcium supplement understandably had a favorable influence on hypertension. Hypertension is thus an example of calcium deficiency.

Diabetes mellitus is another example of calcium deficiency. Calcium deficiency leads to PTH hypersection and increase of the intracellular calcium of pancreatic β-cells. Ensuing blunting of intra- extracellular calcium concentration gradient interferes with the signal transduction mechanism of insulin secretion by β-cells causing a derangement of timely insulin secretion in response to glucose load. Calcium supplement would cause recovery from such a disturbance of insulin secretion. In many diabetics, the calcium intake is not sufficient to meet the requirement of the body, because adequate calcium intake has not been one of the goals in the dietary therapy of diabetes mellitus. Such persistent calcium deficiency may not only produce osteopenia, but also blunting of the intra- extracellular compartment to aggravate cell injury in diabetic complications such as nephropathy, neuropathy and retinopathy.

Calcium Preparation in Intervention Studies of Calcium Supplementation

Calcium supplement has so far been given mainly as calcium carbonate. Oyster shell electrolysate (OSE) was recently developed through subjecting powdered oyster shell to electrolysis at a high temperature. This preparation has a characteristic lamellar appearance under the scanning electron microscope which is to be distinguished from oyster shell powder, calcium carbonate and calcium oxide [6]. This material is also called active absorbable calcium (AACa) because of its high efficiency in intestinal absorption even in the absence of vitamin D. Complete balance studies in 4 healthy elderly human subjects indicated a much better bioavailability of AACa than that of calcium carbonate calcium lactate.

Short-term absorption studies in young normal subjects revealed no significant difference in the rise of serum calcium during the first 4 h after the oral administration of AACa and calcium carbonate, but serum phosphorus was significantly lower after administration of AACa than $CaCO_3$, indicating a higher phosphate-binding capacity of AACa, which would represent a promising agent as a phosphate binder in chronic renal failure [7].

Hypertension is in a group of hospitalized elderly patients with hypertension, blood pressure was constantly monitored and the effect of AACa

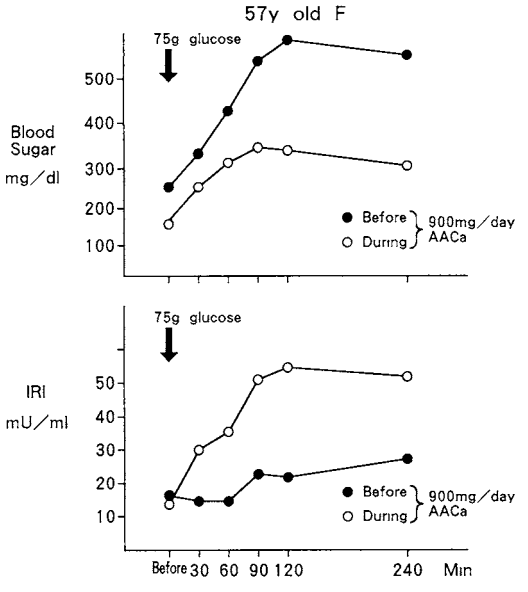

Fig. 1. Effect of oyster shell electrolysate (AACa) on oral glucose tolerance test in steroid-induced diabetes mellitus.

on blood pressure was tested against placebo and calcium carbonate in a crossover design.

Blood pressure fell significantly during the use of AACa compared to placebo or $CaCO_3$. Serum ionized calcium was also higher and PTH lower when using AACa than with placebo or calcium carbonate. AACa was more efficiently absorbed than $CaCO_3$ and apparently suppressed PTH better to normalize the blunted inter- extracellular calcium concentration gradient.

Similar results were obtained in diabetes mellitus. Oral administration of 3 g of calcium lactate was shown to have a favorable influence on insulin secretion in diabetes mellitus [8]. On the use of AACa supplying 900 mg elementary calcium, the results of 75 g glucose loading was definitely more favorable in a 57-year-old female diabetic (fig. 1). Blood sugar was lower, and blood insulin higher. In another 61-year-old female diabetic, the daily blood sugar profile definitely improved in response to 900 mg calcium supplement in the form of AACa (fig. 2). In a 65-year-old male diabetic, such an improvement in the control of diabetes mellitus in response to calcium supplement in the form of AACa was extended over a 24-hour period (fig. 3). Significantly more insulin was secreted and a lower blood sugar level was achieved in response to calcium supplement. Special care

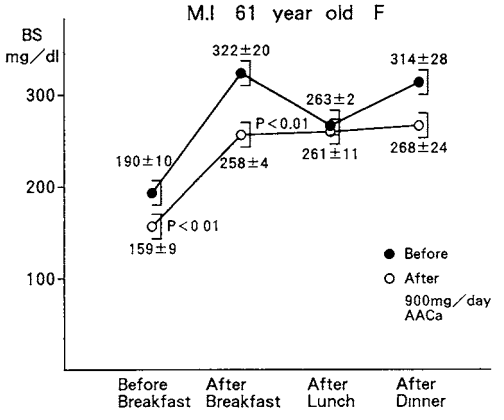

Fig. 2. Effect of oyster shell electrolysate (AACa) on blood sugar profile in diabetes mellitus.

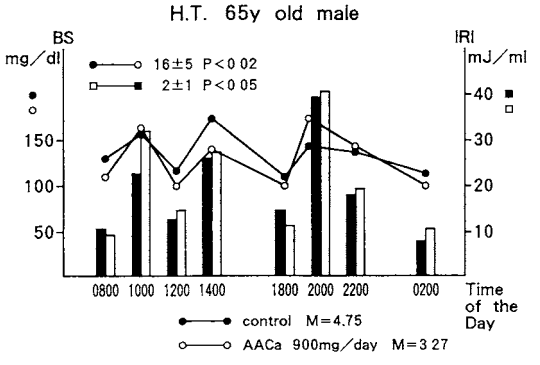

Fig. 3. Effect of oyster shell electrolysate (AACa) on blood sugar and insulin profile in diabetes mellitus.

should be taken to use the calcium source of high bioavailability for the assessment of the effect of calcium supplementation. Calcium carbonate is not necessarily the best agent available for this purpose.

Summary

Calcium is unique in its distribution in living organisms with an extremely high hard and soft tissue and extra- intracellular concentration gradient. Calcium deficiency through stimulating parathyroid hormone secretion tends to blunt such a difference by paradoxically increasing the calcium concentration in the soft tissue and intracellular compartment. Since

aging is associated with the progressive aggravation of calcium deficiency, such blunting also progresses with aging. The dysfunction, damage and death of cells occurring in all diseases is always associated with a blunting of the extra- and intracellular calcium components. Calcium supplement especially with highly biologically available active absorbable calcium, was associated with the suppression of parathyroid hormone secretion and the normalization of a such blunting of intercompartmental distribution of calcium examples in hypertension and diabetes mellitus with evident improvement of clinical manifestations and laboratory tests.

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