INVITED ARTICLE

Vascular calcification and metabolic acidosis in end stage renal disease

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Abstract

Cardiovascular manifestations are very common in patients with end stage renal disease and those undergoing dialysis treatment. One of the factors, causing cardiovascular disorders due to mineral metabolism disturbances in uremia is the appearance of cardiovascular calcification. The precise mechanism of the mineral metabolism disturbances acting through the existing metabolic acidosis in chronic renal failure is not yet clarified. The influence of acidosis is a complex one, acting as a stimulator of the solubility of Ca-P deposits, a suppressor of parathyroid secretion, an inhibitor of some osteogenic enzymes, a blocker of formation of bone matrix, a modulator of the up-regulation of Pit-1 and finally as a blocker of phosphate uptake by the arterial smooth muscle cells. Hippokratia 2009; 13 (3): 139-140

Key words: cardiovascular disturbances, cardiovascular calcification, metabolic acidosis, parathyroid secretion, phosphate uptake, arterial smooth muscle cells

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Cardiovascular disease is the major cause of morbidity and mortality in end stage renal disease (ESRD) patients. Cardiovascular calcification is one of the main rsk factors responsible for cardiovascular disease in these patients, due to disturbed bone and mineral metabolism[1,2]. Uremic patients develop calcification of the intima in the process of atherosclerosis and calcification of the arterial media in the process of arteriosclerosis[1-3]. Because of renal failure, ESRD patients excibit usually metabolic acidosis due to abnormal protein metabolism and failure of the kidney to excrete the acid produets[4].

The influence of acidosis on the mineral and bone metabolism is not precisely known. Interestingly some authors had shown that acute decrease of pH in normal dogs causes an increase in parathyroid hormone (PTH) secretion, when the ionized calcium levels are clamped at normocalcemia, and potentiates hypocalcemia on PTH secretion. When ionized calcium spontaneously increases however, PTH levels decrease[1,5,6]. In nephrectomized rats metabolic acidosis has been found to play a beneficial role on the secondary hyperparathyroidism, frequently observed in ESRD patients. Metabolic acidosis may retard the development of chronic renal failure as well, as it might be related to prevention of nephrocalcinosis[6,7]. On the other hand, acid pH has a negative effect on bone as it promotes a physico-chemical bone dissolution, increases the osteoclast activity and suppresses the bone formation by osteoblasts[9-10]. The process of medial calcification is realized by transformation of vascular media to an osteoid-like tissue, so that metabolic acidosis might act in the same way on the arterial wall as on bone, preventing vascular calcification. This suggestion is supported by some studies that have shown that vascular smooth muscle cells in a medium of calcifying condition but low pH [7.2] have not been transformed to osteoid-like cells and have not calcified. Two direct mechanisms are proposed to be involved in the protective effect of acidosis on vascular calcification: a physico-chemical mechanism and a cellular mechanism. The physico-chemical mechanism is based in the fact that low pH decreases calcium and phosphate tissue deposition because it increases their solubility: when pH is reduced from 7.40 to 6.90 the solubility of hydroxyapatite rises two-to fourfold[11,12]. Metabolic acidosis modulates the activity of several enzymes, related to bone formation as well, thus preventing the production of hydroxyapatite and its soft tissue deposition. The cellular mechanisms are quite complex: recently it was described that metabolic acidosis blocks the effect of alkaline phosphatase and matrix gla-protein and suppresses the osteoblasts to form collagen and other protein components of the matrix. So that even if vascular smooth muscle cells are transformed to osteogenic cells, at acid medium they could not be able to produce bone-like tissue[1,12].

Another promoter of trans-differentiation of the vascular smooth muscle cells is hyperphosphatemia. Phosphate uptake through sodium-dependent phosphate cotransporter [Pit-1] has been reported as essential for vascular smooth muscle cells calcification. The measurement of Pit-1 in aortas of uremic rats not receiving ammonium chloride and in rats receiving ammonium chloride clearly has shown that Pit-1 and aortic calcification has increased in rats not receiving ammonium chloride[1,13,14]. It means that acidosis may prevent calcification by up-regulation of Pit-1 as well.

On the other hand acidosis is well known to promote inflammation of the arterial wall, releasing cytokines that could induce vascular calcification[1,3,8].

Finally, we could say that the effect of acidosis on cardiovascular system calcification in ESRD is ambivalent, but the preventive effect is prevailing, even when acidosis increases Ca x P product. The influence of acidosis is a complex one, acting as a stimulator of the solubility of Ca-P deposits, a suppressor of parathyroid secretion, an inhibitor of some osteogenic enzymes like alkaline phosphatase and matrix gla-protein, a blocker of formation of collagen and other proteins in bone matrix, a modulator of the up-regulation of Pit-1 and finally as a blocker of phosphate uptake by the smooth muscle cells.

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