A clinical approach to the uraemic patient with extraskeletal calcifications

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Abstract. Soft tissue calcifications are a frequent complication in patients with chronic renal failure. In most instances they remain clinically silent. However, in a minority of patients they are responsible for complications and may even become life-threatening. Various locations and types of calcium deposits have been characterized. Numerous underlying factors are thought to favour their formation, in particular increased calcium x phosphate product and advanced age. In most cases, local factors probably are involved as well. Tumoral calcinosis is a rarely observed form of extraskeletal calcification which is often invalidating. Since treatment is generally difficult, prevention should be the preferred goal.

Key words: calcification; soft tissues; chronic uraemia; dialysis

Extraskeletal (or 'soft tissue') calcifications are frequently seen in uraemic patients [1], especially in patients with end-stage renal failure whose life expectancy has considerably increased since the introduction of renal replacement therapy [2-4]. They can be classified according to various criteria, including degree of development and clinical repercussion, distribution across organs and tissues, physicochemical nature, and relation to the uraemic state. At present, their pathogenesis is still incompletely understood, and their treatment and prevention poses a formidable problem in many of these patients. The optimal clinical approach to soft tissue calcifications requires identification of the underlying factors, whenever possible.

Anatomical and physicochemical description of extraskeletal calcifications in uraemic patients

Soft tissue calcium deposits may be small or large, depending on the length of time during which they developed, on their location and on their nature. Generally, large deposits have been small first, except in calcifications of the metastatic type where they may be large from the beginning, such as in large calcified intramuscular or periartricular haematomas. Whereas in some patients small deposits nearly inevitably evolve towards large deposits, in others they do not. In cases of extremely large and voluminous soft tissue calcification, the term 'tumoural calcinosis' is appropriate.

Localization of calcium deposits

According to organ and tissue localization, one can distinguish schematically several varieties of extraskeletal calcification related to the uraemic state: (1) periartricular calcifications; (2) calcifications of medium sized arteries; (3) visceral calcifications mainly affecting the heart, the lung, and the kidney; (4) cutaneous and subcutaneous calcifications; and (5) ocular calcifications. Whereas calcifications of medium sized and small vessels are most often related to the uraemic state (except in diabetic patients where they may be of mixed origin), those of the aorta and large arteries generally are not. Calcium deposits in the former are abundant in the vessel media, whereas they are essentially limited to atherosclerotic plaques of the vessel intima in the latter. Calcifications of heart valves (especially mitral and aortic valves) may be classified as 'vascular' calcium deposits. They are relatively frequent and may contribute to heart failure [5,6].

Nature of calcium deposits

As to physicochemical composition, two major types of soft tissue calcium deposits have been characterized, namely hydroxyapatite, with a molar ratio similar to that of bone, and amorphous (CaMg)3(PO4)2, resembling whithlockite, with a much greater magnesium content [7,8]. The latter is the type generally found in visceral organs, while hydroxyapatite prevails in vascular and periartricular deposits. Other types of extraskeletal calcification may occur in uraemic patients, but they are observed much less frequently. Calcium oxalate deposits are generally seen in dialysis patients with primary hyperoxaluria, when they may be extensive and massive. However, they also may occur in other dialysis patients as visceral deposits [9] and more rarely as chondrocalcinosis [10], probably in association with excessive ascorbic acid supplements. Calcium pyro-
phosphate dihydrate (CPPD) deposits are occasionally diagnosed in cases with microcrystalline arthritis [11]. The main types of soft tissue calcification are shown in Table 1.

Tumoral calcinosis

Tumour-like calcifications are made of massive calcium phosphate deposits that are usually periaxial in location but do not involve the joints or their capsules. The deposits are encapsulated with a thick fibrous wall, are multiloculated [12] and induce a foreign body reaction with histiocytes and osteoclast-like giant cells [13]. Electron microscopy and X-ray diffraction studies show that the deposits are mainly composed of hydroxyapatite, with a calcium/phosphate molar ratio of 1.64 [12,13].

Pathogenesis of the calcification process

The pathogenesis of soft tissue calcification in uraemic patients is as yet poorly understood. It is almost certainly more complex than was thought initially.

Calcium x phosphate product

One of the most important factors associated with extraskeletal calcifications, at least for non-visceral localizations, is an elevation of serum phosphate and/or an increase of the Ca x P product in serum beyond the saturation point [4,5,14-16]. This clearly reflects common clinical experience in most centres including ours [17], although it has not been a constant finding in all centres [3,18]. Whether an increase of the Ca x P product also plays a role in visceral calcifications is not clear. In a recent study, no difference was found between dialysis patients who had evidence of pulmonary calcifications and those who had not [19].

Secondary hyperparathyroidism

Another important factor is parathyroid gland overfunction [14,15]. It has long been known that the severe secondary hyperparathyroidism of chronic uraemia favours the mobilization of calcium, magnesium and phosphate from bone, leading to an increase of these ions in the plasma and to their deposition in soft tissues. Several recent reports again demonstrate that PTH excess remains an important cause of extraskeletal calcifications in chronic renal failure [6,20,21].

Age

Age clearly is a factor which favours the occurrence of calcium deposits in atherosclerotic lesions of large artery walls. Older age has been found to favour heart valve and pulmonary calcification in dialysis patients [5,6,19] but it is less clear whether it also plays a role in other uraemia-related soft tissue calcification. It is well established that even very young age does not procure absolute protection. Thus, children with end-stage renal disease in a centre in Los Angeles, California have been shown to develop soft tissue calcification, in conjunction with long-standing vitamin D therapy at probably supraphysiological levels [4], even though uraemic children appeared to be relatively protected in two European centres [22,23]. Interestingly, the dialysed and/or transplanted children of the American study who had extraskeletal calcium deposits had an older age at onset of renal failure than those who had no calcification [4].

Aluminium overload, hypoparathyroidism, and adynamic bone disease

During the last decade, soft tissue calcification increasingly has been shown to occur or to worsen in dialysis patients in the absence of severe secondary hyperparathyroidism, sometimes even after successful surgical parathyroidectomy (PTX), with an actually diminished Ca x P product compared with before PTX [17,18,24]. Interestingly, the Newcastle group was unable to observe a significant correlation between the Ca x P product and the presence of periaxial calcifications in haemodialysis or CAPD patients [3,18]. This clearly indicates that at least in certain dialysis centres other factors must be more important than PTH Ca or P excess. It is of note that many patients in the Newcastle centre suffered from heavy aluminium intoxication during the decade that preceded the publication of these reports. We recently made similar observations of an association between large soft tissue calcium deposits and aluminium intoxication in dialysis patients [17]. On the other hand, we observed an aluminium-overloaded patient in whom soft tissue calcifications resolved under desferrioxamine treatment even though the degree of hyperparathyroidism worsened [25]. Since severe aluminium intoxication leads to a mineralization defect, we hypothesized that the disturbance of the skeletal calcification process by aluminium or aluminium itself, which was shown to initiate the precipitation of calcium apatite [26], might somehow lead to soft tissue deposition of calcium and phosphate. The lack of demonstration by microprobe analysis of aluminium in the removed deposits would however argue against a direct involvement in nucleation of crystals. It has been suggested by others that an aluminium-induced increase in collagen cross-
linking might predispose collagen to develop dystrophic or metastatic calcification [27]. Removal of aluminium by deferoxamine chelation therapy could lead to a decrease of abnormal collagen cross-linking and hence to the disappearance of soft tissue calcinosis.

It is possible that the link is not directly with aluminium, but with the state of ‘adynamic’ (or ‘aplastic’) bone disease which may be due to aluminium overload or to other, hitherto ill-defined causes, with chronic hypoparathyroidism being a common denominator. The decrease in calcium influx into and calcium efflux out of bone in the setting of low-turnover bone disease, compared with that of high-turnover bone disease, would favour calcium deposition in soft tissues [28]. Several recent reports have drawn attention to the fact that at present extraskeletal calcifications are often observed in dialysis patients in the absence of hypoparathyroidism, generally in association with adynamic bone disease [20,29].

**Vitamin D**

A potential role for vitamin D in the pathogenesis of soft tissue calcifications is supported by numerous clinical observations in patients with vitamin D intoxication. Even though serum 25(OH) vitamin D and 1,25(OH)2 vitamin D (calcitriol) are generally low in patients with advanced chronic renal failure, this is not the case in all such individuals, even in the absence of vitamin D therapy. Thus inappropriately high serum calcitriol together with hyperphosphataemia have been observed in two dialysis patients with tumoral calcinosis [30]. The cause of high calcitriol production could not be identified in one of them, whereas granulomatous tissue was probably the source in the other. In a retrospective study in 120 uraemic children, prior treatment with native vitamin D or vitamin D derivatives showed the strongest independent association with soft tissue calcification, and was found in 72 (60%) children [4]. It must be pointed out that the time period over which this study was performed, namely from 1960 to 1983, preceded in the majority of these children the introduction of modern, highly active vitamin D derivatives which have a much shorter half-life than native vitamin D. Nevertheless, such findings raise the possibility that the administration of active vitamin D derivatives to uraemic patients leads to or aggravates pre-existing soft tissue calcification, probably even in the absence of increased plasma calcium or phosphorus. This may occur through an enhancement of intestinal calcium and phosphorus absorption with subsequent direct precipitation in soft tissues, and/or via an increase in the expression of calcification-regulating proteins, such as osteopontin in the skin [31] or in atheromatous blood vessels [32,33]. Vitamin D derivatives also stimulate intestinal oxalate absorption, increase plasma oxalate saturation and thereby enhance the risk of ectopic calcium oxalate crystal deposition [34].

**Magnesium**

The role of increased plasma magnesium in bone metabolism and soft tissue calcification remains uncertain [35]. Magnesium is a natural inhibitor of crystallization [36]. Thus, theoretically, increased plasma magnesium should rather inhibit soft tissue deposits of crystalline apatite salts. This is in line with one study where increased plasma magnesium in haemodialysis patients was associated with a lower prevalence of vascular calcification [37]. However, since magnesium also stabilizes amorphous calcium phosphate [38], this could explain why in one experimental study magnesium was able to potentiate metastatic calcifications in vitamin D-treated rats [39]. On the other hand, magnesium could also favour the generation of extraskeletal calcium deposits indirectly via its interference with the skeletal calcification process [35]. More work is clearly needed to better delineate the precise role of this cation in the deposition of extraskeletal calcifications.

**Other systemic factors**

A number of other factors have been incriminated, the relative roles of which are however still uncertain, at least with respect to soft tissue calcification associated with uraemia. They include the following: black race compared with white race [16]; metabolic alkalosis, especially during and after the haemodialysis session [1]; excessive generation of growth factors such as TGF-β which stimulates osteoblast-like vascular cells to calcify [40] and which can be induced by acetate dialysis, compared with bicarbonate dialysis [41]; high plasma vitamin K; capable of increasing the synthesis of vitamin K-dependent Gla-containing tissue proteins having a high affinity for calcium, such as osteocalcin and atherocalcin [42].

**Local factors**

Focal tissue injury of known or unknown nature is necessarily involved in several types of soft tissue calcification. Such lesions could be accompanied by local changes of pH and of the affinity of tissue proteins for calcium. This would explain particular predilection sites for soft tissue calcification, as seen in many patients, such as periarticular or visceral calcium deposits. Periarticular or intramuscular haematomas may favour focal calcium phosphate deposition, as may local injections of calcium heparin [43]. A high expression of genes for calcification-regulating proteins such as osteopontin and matrix Gla protein has been found in human atherosclerotic plaques of non-uraemic subjects [32,33]. It is possible that such proteins are overexpressed in chronic renal failure subsequent to increased plasma vitamin K [42], but this issue has never been addressed in uraemic patients at the tissue level.

Tables 2 and 3 summarize the factors which may be involved in soft tissue calcification of chronic renal failure.
The dialysate calcium concentration may allow to avoid be reviewed in case of hyperphosphataemia. Lowering proves to be impractical in patients who already have soft tissue calcifications. In dialysis patients, the efficacy be reduced by changing dietary habits, but this often
tently in all uraemic patients. This can be achieved by several means \[45,46\]. Excessive protein intake should
Focal tissue injury (haematoma, infection, heparin injection)
Local changes of pH and of normal tissue proteins
De novo local development of calcifying cells
De novo expression of proteins with high affinity for calcium (osteopontin, matrix Gla protein)
Local expression of growth factors (TGF-\(\beta\))

### Clinical repercussion and management

**Clinical expression**

Radiologically visible vascular, periarticular or visceral calcifications of small size most often have no apparent clinical expression. However, they generally are of concern because they may progress to larger deposits, and because they make the prevention and the treatment of a concomitantly present secondary hyperparathyroidism more difficult. In a minority of cases, soft tissue calcifications lead to clinically important, sometimes even life-threatening complications. Thus myocardial or valvular calcifications may be comorbid factors in atrioventricular block and cardiac failure [5,6,16,44], calcification of small peripheral arteries may be responsible for bone and soft tissue necrosis, and tumoural calcinosis may become infected and lead to sepsicaemia, especially after surgical evacuation (personal unpublished observations).

**General measures to avoid or treat extraskeletal calcification**

Since hyperphosphataemia and/or an increase of the Ca \(\times\) P product are most often involved, a strict control of plasma phosphorus to less than 1.5 mM (that is the predialysis concentration in dialysis patients) and the avoidance of an increase of plasma calcium greater than 2.7 mM should be the goal to be attained permanently in all uraemic patients. This can be achieved by several means [45,46]. Excessive protein intake should be reduced by changing dietary habits, but this often proves to be impractical in patients who already have soft tissue calcifications. In dialysis patients, the efficacy of the dialysis procedure can be improved and should be reviewed in case of hyperphosphataemia. Lowering the dialysate calcium concentration may allow to avoid or correct the hypercalcaemia induced by calcium and/or vitamin D supplements. A better control of metabolic acidosis may be helpful. The ingestion of more or less massive doses of calcium salts with meals often allows to obtain a better control of plasma phosphorus, but the danger of a concomitant calcium overload is not discarded, despite claims to the contrary [47]. Magnesium salts may be efficacious in some cases but gastrointestinal side effects are of concern. Aluminium-containing compounds are most often efficacious but they bear the danger of conferring an aluminium overload which may actually induce or aggravate extraskeletal calcium deposits. Whenever active vitamin D compounds are administered, great care should be taken to avoid an increase of plasma calcium or phosphorus above the upper limit of the normal range.

In our view, the presence of soft tissue calcifications precludes the administration of calcium supplements and/or vitamin D compounds by the oral or intravenous route, except perhaps in case of calcium deposits limited to atherosclerotic plaques in the intima of the aorta and proximal arteries. Even in the latter condition, prolonged treatment with calcium and/or vitamin D cannot be considered to be entirely innocuous. The administration of both calcium supplements and vitamin D derivatives together must be avoided in the great majority of uraemic patients, except of course in cases of vitamin D deficiency with hypocalcaemia, because of the increased risk of developing soft tissue calcification.

Soft tissue calcium deposits which are associated with parathyroid overfunction can be improved and sometimes even cured by parathyroidectomy [48,49]. It must be stressed, however, that parathyroidectomy is only indicated in case of severe secondary hyperparathyroidism, characterized by plasma intact PTH greater than 600 pg/ml (for a normal range between 10 and 65 pg/ml) and patent osteitis fibrosa. Surgical parathyroidectomy is not helpful in case of mild or no hyperparathyroidism. Table 4 summarizes general measures for the prevention and treatment of extraskeletal calcifications.

**Treatment of tumoral calcinosis**

The treatment of tumour-like calcifications in dialysis patients is particularly difficult and remains often tot-

### Table 2. Systemic and general factors potentially predisposing to soft tissue calcifications in CRF

- Increase of Ca \(\times\) P product
- Secondary hyperparathyroidism
- Age
- Aluminium overload
- Hyperparathyroidism—dynamic bone disease
- Vitamin D or vitamin D derivatives
- Magnesium
- Acetate vs bicarbonate in dialysis fluid
- Other general and systemic factors (race, metabolic acidosis, TGF-\(\beta\), vitamin K)
- Action of local factors

### Table 3. Local factors potentially predisposing to soft tissue calcifications in CRF

- Focal tissue injury (haematoma, infection, heparin injection)
- Local changes of pH and of normal tissue proteins
- De novo local development of calcifying cells
- De novo expression of proteins with high affinity for calcium (osteopontin, matrix Gla protein)
- Local expression of growth factors (TGF-\(\beta\))
ally unsuccessful, thereby exposing the patients to the risk of major complications and death. In addition to a more intensive application of all the general measures mentioned above, more specific interventions have been proposed. An increase of the haemodialysis frequency from three to seven times a week has been shown to obtain a full regression of the deposits [50] whereas an increase to only four or five times a week is not efficacious (personal unpublished observations). A switch from intermittent haemodialysis to daily CAPD treatment with a relatively low dialysate calcium concentration may be an alternative approach.

Various types of drugs have been considered for the treatment of severe soft tissue calcification in uraemic patients during the last two decades, including bisphosphonates, steroidal and non-steroidal anti-inflammatory agents, heparin, and vitamin K antagonists. Any conclusion as to their potential efficacy is however difficult since no controlled studies are available. Recently, two new types of drug have been proposed for treatment, on the basis of non-randomized studies in haemodialysis patients with untractable tumoral calcinosis, namely sodium thiosulfate [51] and vinpocetine [52]. The authors of both clinical trials claimed that these compounds were highly effective in allowing tumour-like calcium deposits to regress or even fully resolve.

It must be noted that the performance of controlled studies will be difficult, if not impossible, when considering the relatively small number of dialysis patients who develop extensive extraskeletal calcifications and who would therefore be eligible for prospective treatment trials.

References