Review

Hypercalcemia and metastatic calcification

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1. Vitamin D intoxication

I grew up in Edinburgh, at the same latitude as Copenhagen, and then covered by a pall of coal smoke which gave it the sobriquet `auld reekie'. Many bandy-legged and dwarfed citizens carried the legacy of rickets contracted before the discovery of vitamin D, the fortification of food and the Clean Air Acts. However vitamin D, good in the right dose, is dangerous in overdose and there is no doubt that Gorm’s Vikings miscalculated the dose–response curve of cod liver oil; a teaspoon would have been a better implement than their ladle or Mrs. T’s tablespoon. In view of their formidable achievements, it is likely that the Vikings escaped the worst effects of vitamin D intoxication by irregular dosage and non-compliance. Their cavalier approach was repeated with more disastrous results after 1924 when high doses of tasteless ergocalciferol (vitamin D₂) from irradiated ergosterol became available and were indiscriminately prescribed for rheumatoid arthritis, tuberculosis, Paget’s disease and chilblains, in none of which it has been shown to produce benefit, and osteoporosis.

The effects of overdosage were described within four years of high dose ergocalciferol being released for sale; the condition was reviewed in a cluster of papers in the early 1950’s [1–3]. Diagnosis was often delayed because the commonest symptoms were the non-specific ones of hypercalcemia — nausea, vomiting, weight loss, colic, constipation, thirst, polyuria, headache, weakness, apathy and depression roughly in that order [1]. Once suspected, the diagnosis was confirmed by the presence of hypercalcemia and renal impairment. Although vitamin D stimulates phosphate absorption, serum phosphate was often normal, as in Mrs. T, unless the renal damage was severe. Reduction of serum calcium by administration of cortisol distinguished this cause of hypercalcemia from hyperparathyroidism; one action of cortisol is to inhibit the conversion of 25-(OH) vitamin D to 1,25-(OH)₂ vitamin D [4]. Once assays for 25-OH-vitamin D became available in 1974, they provided a more specific confirmation. Since the hydroxylation of vitamin D to 25-hydroxy-vitamin D is not tightly controlled by negative feedback, the plasma level of the hydroxylated vitamin rises with the degree of overload and may reach concentrations ten times the upper limit of normal; it remains high until vitamin D has been reabsorbed from fat stores, which may take several months [4]. Consequently the half-life of hypercalcemia, which is about 3 weeks when modest therapeutic overdose occurs [5], may be more prolonged in severe vitamin D toxicity [6]. One lady who took the Viking mixture of cod liver oil and milk required treatment for hypercalcemia for 21 months after withdrawal of vitamin D [5] and another elderly lady intoxicated with ergocalciferol had elevated blood vitamin D and 25(OH) vitamin D levels after 17 months [7].

Vitamin D intoxication causes an osteodystrophy which is still poorly understood. Aches and pains in the back and around joints are common symptoms [1]. The bone changes reported in radiological studies are puzzling; patients receiving the same dosage of vitamin D may have reduced or increased bone density [2,3]. Bone histology usually shows an increase in both calcified and uncalkified osteid and a combination of osteoblastic and osteoclastic activity [4] since vitamin D stimulates osteoclasts.

Tumoral calcinosis around joints was one of the first radiological signs described [2,3]. Many of the patients were receiving vitamin D for rheumatoid arthritis and therefore had damaged tissues in and around joints to act as a focus for metastatic calcification, as did Mrs. T; similar lesions were found in a few patients without arthritis [2] but the prevalence was much higher when vitamin D was given for rheumatoid arthritis [5]. Extensive calcification of ligaments and tendons and within joints often accompanied tumoral deposits. Analysis of one intra-articular mass showed predominant hydroxyapatite with some calcium carbonate and proteins [5]. At autopsy, metastatic
calcification was widespread, affecting large, medium and small arteries, lungs, liver, spleen, kidneys (as calculi and nephrocalcinosis), adrenals and mesentery [1–3]. Treatment consists of withdrawing vitamin D and drugs that exacerbate its effects on serum calcium and renal function (e.g. thiazides, non-steroidal anti-inflammatory agents) and rehydration where necessary. Depending on the severity and persistence of the hypercalcemia corticosteroids, calcitonin and bisphosphonates can be added sequentially.

The wide publicity given to vitamin D toxicity in the 1950’s did not end the story, for three reasons.

1.1. Mistakes in prescribing or follow-up

Ergocalciferol remains on the market in two strengths: microgram doses (10 μg = 400 IU) for dietary supplementation and milligram doses for treatment of hypoparathyroidism and vitamin D deficiency in intestinal malabsorption. The British National Formulary has always emphasised the need to distinguish carefully between these doses and to monitor progress. Despite this admonition, Davies and Adams [8] and Paterson [9] described 35 episodes of vitamin D poisoning in 29 British patients, all but one of them due to medical errors. These included confusing the two dose levels and administering high doses for inappropriate indications, but much the commonest error was inadequate follow-up, particularly of patients with hypoparathyroidism who require life-long treatment and monitoring. Another condition requiring permanent care is vitamin D resistant rickets for which high doses of vitamin D or its analogs, with phosphate supplements, were until recently standard life long treatment. Because of a substantial incidence of metastatic calcification and renal failure [10] these are now used more cautiously, particularly after growth has ceased.

1.2. Fortification of food

This public health measure played a leading role in eliminating rickets in Northern industrial cities. In general, it has proved remarkably safe. One possible exception was the increased incidence of hypercalcemia in infants taking a dose in the range 800–2000 IU per day from a combination of fortified milk and cod liver oil supplements in the 1950’s and 60’s [11], probably reflecting several forms of genetic sensitivity to vitamin D which were recently reviewed in Cardiovascular Research [12].

A recent outbreak of vitamin D intoxication in Massachusetts [13] was traced to erratic and excessive fortification of milk with ergocalciferol. A concentration of 232,565 IU/quart (946 ml) was recorded in homogenised whole milk, in place of the recommended 400–500 IU. Eight customers of one dairy presented with hypercalcemia; five had renal impairment. Subsequent reports showed that the outbreak was more widespread [14] and that under- and over-fortification of milk and infant formulas were common in the USA and Canada. Only a quarter of the milk samples lay within the prescribed range [15] and seventy per cent of infant formulas contained more than twice the stated dose [16]. Although serious overdosage was rare nationwide, there is a need for closer monitoring. A Medline search revealed no reports of similar outbreaks in other countries; milk is not fortified in Britain, Ireland and most West European countries despite a well-argued case for it [17].

1.3. Granulomatous disease

Since the recognition that the hypercalcemia of sarcoidosis is due to conversion of 25(OH) vitamin D into 1,25(OH)₂ vitamin D (calcitriol) in an unregulated manner in sarcoid granulomata, this phenomenon has been confirmed in lymphoma, Wegener’s granulomatosis [18] and infection with tuberculosis, Pneumocystis carinii, Candida albicans and Cryptococcus neoformans [19], silicone granulomata from breast implants and berylliosis, and hypercalcemia, probably of this origin, has been found in other granulomatous infections [18]. In these conditions hypercalcemia can occur with a normal serum 25(OH) vitamin D, implying normal dietary intake of vitamin D, but it is exacerbated by a high intake.

2. Milk-alkali syndrome

‘Bertram W Sippy powders’ are named after the pioneer who introduced antacid treatment for peptic ulcer in 1915. A few years later ‘toxic effects following alkaline treatment of peptic ulcer’ were reported [20] and subsequent authors added hypercalcemia and renal failure to the list of side effects. Until the 1960’s it was a fairly common cause of hypercalcemia but with the introduction of H2-blockers and proton-pump inhibitors it became a rarity, accounting for less than 1% of patients with hypercalcemia [21]. However, there has been a recent upsurge in the number of cases reported, mainly from consumption of calcium carbonate rather than alkalis and milk. In the USA the calcium carbonate has usually been taken for the treatment of osteoporosis [21] but in Britain the usual culprit is Rennies tablets, a popular, palatable antacid which contains 680 mg calcium carbonate per tablet with a recommended dose of up to 8 per day (about 5.5 g/day). This dose falls within the range of 4 to 12 g per day in the cases reported by Beall and Scofield [21]. There are many other products containing calcium carbonate available over the counter on both sides of the Atlantic. This new form of ‘milk alkali syndrome’ is characterised by hypercalcemia with normal or low serum phosphate, suppressed serum PTH (whole molecule assay, taken before rehydration), alkalosis and raised serum creatinine. Hypercalcemia may be exacerbated by other drugs such as thiazides. Treatment consists of initial rehydration with normal saline, which
often corrects — and may overcorrect — the hypercalcemia, further saline with loop diuretics and withdrawal of the offending medications. Corticosteroids, calcitonin, bisphosphonates and dialysis are all effective but seldom required, in contrast to vitamin D intoxication. Metastatic calcification in arteries and many organs is frequently described; the tumoral calcinosis experienced by Mr. S is well documented but unusual; his intake of powders at the rate of 130 g/day was unusually high though not unprecedented.

An iatrogenic variant of milk-alkali syndrome (without metabolic alkalosis) is increasingly common on renal units where calcium carbonate has become the leading phosphate binder, and vitamin D is given as alfacalcidol or calcitriol. This combination is particularly prone to produce metastatic calcification in renal failure since serum phosphate is raised as well as serum calcium. The problem can be ameliorated by using low calcium dialysis fluid which allows larger doses of calcium carbonate or and calcitriol to be administered [22] or by substituting magnesium hydroxide for some of the calcium carbonate [23]. Several organic phosphate binders have been described which control plasma phosphate without causing hypercalcaemia. The most promising is poly(allylamine hydrochloride) (RenaGel); it has performed well in short term studies [24] and longer trials are in progress.

3. Calciphylaxis

This term was coined by Hans Selye [25] to describe a phenomenon he produced in mice and rats. They were ‘sensitised’, usually with dihydrotachysterol, and, at a critical time 1–2 days later received a ‘challenger’ — a subcutaneous injection or local trauma which caused subcutaneous calcification, or an intravenous injection which precipitated calcification at distant sites. Calcification was a rapid phenomenon, often developing within two days of the challenge. Selye clearly distinguished his phenomenon from slow metastatic calcification (e.g. in hyperparathyroidism). He discussed the possible relevance of calciphylaxis to 93 human diseases including vitamin D intoxication and milk alkali syndrome but did not describe the clinical lesion to which the name is now applied — infarction of the skin, subcutaneous tissues and occasionally muscle [26], accompanying small vessel calcification, of rapid onset — a serious and often lethal condition. It is preceded by mottling of the skin (livedo reticularis) and often by formation of tender nodules in the subcutaneous tissue; histologically these are areas of panniculitis — damage to fat cells which contain calcium and infiltration of subcutaneous tissue by lymphocytes and histiocytes [27]. The use of Selye’s term to describe this phenomenon is unfortunate since it implies an unproven similar pathogenesis.

Mr. R had a related syndrome — progressive aural gangrene — affecting his right hand. Distal ischaemia may necessitate amputation but is not as commonly lethal as the proximal lesion affecting the thighs [28]. In an autopsy study of a patient similar to Mr. R, the whole palmar arterial arch was dissected out to show a series of discrete rings of calcification throughout the length of these smaller arteries in contrast to the continuous calcification in medium sized arteries such as the brachial and anterior and posterior tibial [29]. These calcium deposits had fractured at many points and healed with callus formation, like bones. The aorta was remarkably normal in this young man suggesting that large and medium/small artery calcification are two separate phenomena, though they often coexist in renal failure.

The changes in human calciphylaxis are sometimes precipitated by occlusion of small vessels by thrombi [30] but search for a thrombotic state has usually been unsuccessful; an association with protein C deficiency described in 1990 has not been found in subsequent cases. In other cases severe progressive intimal thickening appears to be the major factor [30]. The localisation of lesions in calciphylaxis is sometimes explained by subcutaneous injection of heparin, insulin or erythropoietin [31] but other patients with similar pathology have no obvious explanation.

3.1. Treatment

Much the commonest explanation of hypercalcemia and hyperphosphatemia in reported cases has been secondary or tertiary hyperparathyroidism. Hafner and colleagues [32] reviewed the literature on parathyroidec tomy; 38/58 patients survived after this operation but only 13/37 without it. Pending the controlled trial they called for, parathyroidec tomy is the sensible choice if there is uncontrolled hyperparathyroidism. However there was a striking difference in prognosis between those with distal lesions (40/53 survivors) and proximal lesions (11/42 survivors); in the latter the value of parathyroid surgery is uncertain. ‘Medical parathyroidec tomy’ with intravenous [33] or high dose alfacalcidol or calcitriol is well established in managing recurrent hyperparathyroidism but potentially hazardous in calciphylaxis because both serum calcium and phosphate tend to rise [33]. A new vitamin D analog, 19-nor-1,25(OH)2 vitamin D2 produces less hypercalcemia and hyperphosphatemia while suppressing parathyroid secretion in rats [34] but human trials are awaited.

4. Other metastatic calcification in renal failure

While calciphylaxis is fortunately rare in renal failure, more slowly progressive metastatic calcification is very common when sought by radiology or 99mTc-diphosphonate isotopic scanning. Common sites are the blood vessels, periaricular regions, heart, lungs, kidneys, gastric mucosa, central nervous system, breasts and eyes; the
liver, spleen, skeletal muscle, small and large bowel, peritoneal cavity, tongue and larynx are less commonly affected. Only the sites of major concern to cardiologists will be reviewed.

4.1. Vascular calcification

Small vessel calcification is the precursor of calciphylaxis, discussed above. It is partially reversible by parathyroidectomy in some patients, in contrast to large vessel calcification. An uncommon aspect is involvement of the penis, causing impotence and eventual gangrene. The prognosis of patients with widespread small vessel calcification in dismal. Linear calcification of medium and large arteries develops gradually during renal failure, causes narrowing of the lumen and ends in amputation for a significant minority of patients. Most authors identify high calcium phosphate product as the main aetiologic factor in vascular calcification. Traditionally the product is of serum phosphate and total serum calcium though ionised serum calcium would be more logical. However several studies have shown no correlation [35,36] suggesting that there are other important risk factors still to be discovered.

4.2. Cardiac calcification

Calcification affects the myocardium, coronary arteries and valves. Mitral valve annulus calcification is not uncommon in the elderly, especially diabetics, with normal renal function but its prevalence is substantially raised in renal failure even before dialysis. It is associated with mitral valve calcification, mitral systolic murmurs, left ventricular dilatation and reduced function [37]. Progression to mitral stenosis during dialysis has been documented [38]. Aortic valve calcification, affecting tricuspid valves, is less common but not rare in the ageing dialysis population, leading to aortic stenosis [39]. Age and raised calcium phosphate product, serum PTH and alkaline phosphatase are risk factors for both mitral and aortic valve calcification [39,40].

4.3. Pulmonary calcification

This is a common complication estimated to affect over half adult [41] and a third of paediatric [42] patients on regular dialysis. The usual change on chest radiographs is non-specific mottling, but CT scan shows scattered calcified nodules often accompanied by vascular calcification in the intercostal arteries [43]; the most sensitive diagnostic technique is the diphasonate scan. Heavy calcification reduces vital capacity, CO diffusing capacity and PO$_2$ [44]; a few episodes of respiratory failure have been reported particularly in the immediate aftermath of renal transplantation [42]. Thereafter the lung changes improve remarkably after renal transplantation [43].

5. The enigma of metastatic calcification

Metastatic calcium is found in many forms including carbonate, phosphate, oxalate, whitlockite [44] and apatite [6,29]. The observation that apatite, the building block of bone, is found in several forms of metastatic calcification, including atheromatous plaques [45], heart valves [46] and breast cancer [47] has led to a search at these sites for the non-collagenous proteins which are present in uncacified osteoid in bone and are essential for bone formation. These include osteonectin, bone sialoprotein and osteopontin. Osteopontin has attracted most interest because it is strongly expressed at the mineralisation front and is therefore likely to play a vital role in initiating ossification. It is highly phosphorylated and the phosphate groups are arranged in a pattern which is thought to be optimal for binding calcium and forming apatite; it can also inhibit apatite formation [48]. It contains the Arg–Gly–Asp sequence of amino acids that binds with integrins, a characteristic which may be important when it is expressed in breast cancer [47]. Although widespread during development, osteopontin is largely confined to bone in adult life but persists in the kidney and aorta, two common sites of calcification. Although absent from bioprosthetic heart valves when they are implanted [46], it appears *puri passu* with the onset of calcification in heart valves and is found adjacent to the calcium deposits [46,48]. Messenger RNA for osteopontin, osteocalcin and osteonectin was found in osteoblast-like cells at the mineralisation front in calcified valves [48]. The origin of these cells is uncertain but several authors suggest they are derived from macrophages and that the origin of the calcified lesions is inflammatory rather than degenerative. Very similar observations have been made on calcifying atheromatous plaques in coronary arteries [45,49]. It is apparent that metastatic calcification is far from a simple physico-chemical phenomenon due to supersaturation with calcium and phosphate.

References


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