

*Editorial Review*

## Does obesity play a role in the pathogenesis of calcific uraemic arteriolopathy?

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### Introduction

*Calcific uremic arteriolopathy* (CUA) [1] refers to calcification of the media of small terminal arteries and arterioles and associated fibrotic intimal thickening and lumen narrowing, thereby increasing the risk of ischaemic necrosis. As the term suggests, CUA is reported in patients with chronic kidney disease (CKD) ‘nearly exclusively’ [2]. Identical clinical and pathologic features have developed with hyperphosphataemia from other causes [3–7].

CUA develops silently [1,5,8], sometime presenting only with subcutaneous plaques and/or nodules. But with ischaemic complications it presents acutely with foci with discoloured skin progressing to necrosis and deep ulcers; hereafter designated *complicated CUA*. Once mistakenly likened to an allergic reaction by Selye (and therefore inappropriately termed ‘calciphylaxis’ [9]), complicated CUA is uncommon but is recognized increasingly in dialysis patients and renal transplant patients [3,8]. The lesions have appeared in ‘proximal’ body areas – abdominal wall, thighs, flanks, buttocks and breasts – and are generally more devastating than ‘distal’ ones localizing mainly in the lower legs [1,5,9–12]. Both may coexist [5].

### The association of proximal lesions with obesity

Complicated CUA has been reported in a distinctive subgroup: at least 69 obese and overweight patients, mostly female, with proximal lesions [3–6,8–34] and, when specified, corresponding to sites of greatest

adiposity [1,3,9–12]. Two case-controlled studies [10,13] revealed obesity to be a significant risk factor (another study [35] based on different calculations did not).

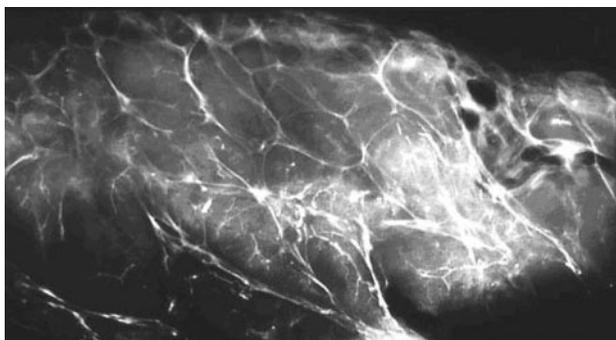
Our early clinical-pathological experiences with 10 patients [3,4,6,16,17] suggested excessive adipose tissue accumulations may underlie the selection of proximal sites [5].

Recent experiences with an additional 9 patients (unpublished) fortify this notion, which is now based on (a) 17 females, 14 moderately to morbidly obese and 2 overweight, and 2 males, 1 morbidly obese. All obese and overweight patients had proximal lesions, mostly extensive, and distal lesions, mostly limited. This quantitative distribution was reversed in the two non-obese patients; (b) histologic and X-ray studies of tissue samples from all 19 (numerous biopsies and/or debridements, amputated legs from three and five autopsies). Collectively, these revealed calcification of the subcutaneous septa and arterioles that surround adipose tissue lobules, most evident in sites of greatest adiposity, whether or not ulcerated (Figures 1–3). There were also sometimes lobules with calcified foci without overlying skin necrosis.

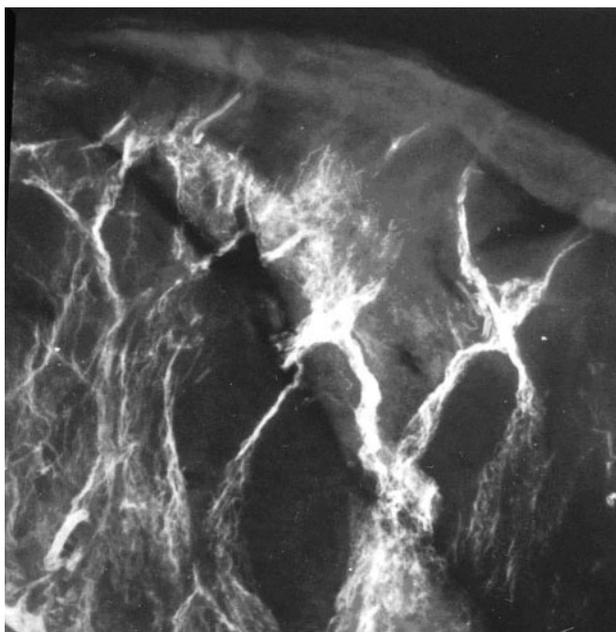
### Relevance of the calcified septal–arteriolar tandem

Anatomically, under the skin fibro-elastic septa extend from the deep fascia through the subcutis to the dermis and, *en route*, both divide the subcutaneous adipose tissue into lobules (Figure 4) and provide a scaffolding for attached arteries/arterioles that supply the skin as well as the lobules. Functionally, the septa anchor the skin to the body, and they resist expansion of the interposed subcutis by adipose tissue. However, with obesity both septa and arterioles are under a chronic stretch tension – we found abdominal pannus thicknesses of 6–14 cm – with a taut overlying skin. On incision, skin edges and septa quickly retract, the

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**Fig. 1.** Ulcerated area (top, far right) with adjacent intact skin to the left. There is perilobular calcification of septa and arterioles in both ulcerated and non-ulcerated parts. The diffuse opacities on the right represent calcification of infarcted adipose tissue. Small, barely evident calcified foci are to the left.

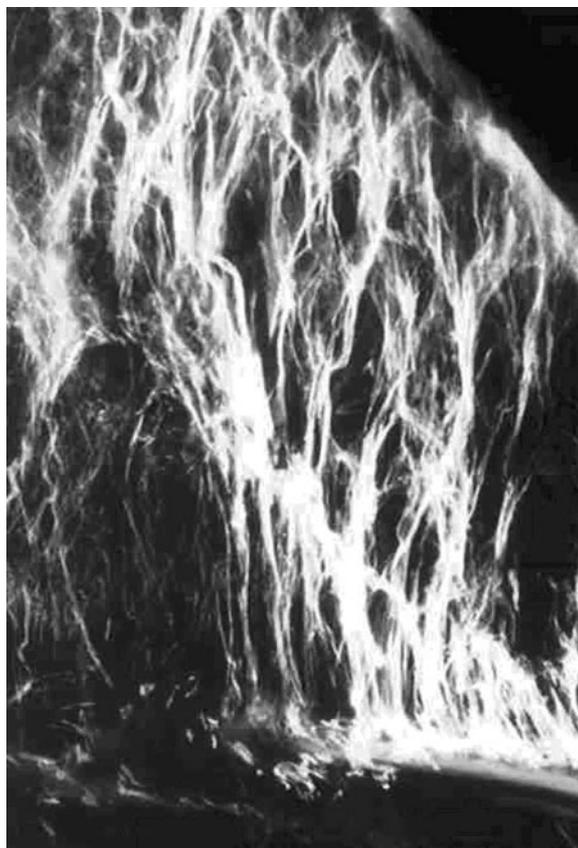


**Fig. 2.** Non-ulcerated specimen with non-infarcted subcutis. The skin (top) is slightly folded over, an artefact. In addition to the perilobular calcifications there are small calcific foci in lobules, upper right (Reprinted from 'Massive necrosis of fat and skin as complication of obesity' — *CMAJ* 15-Mar-89; Vol. 140, Page(s) 665–668 by permission of the publisher. © 1989 CMA Media Inc).

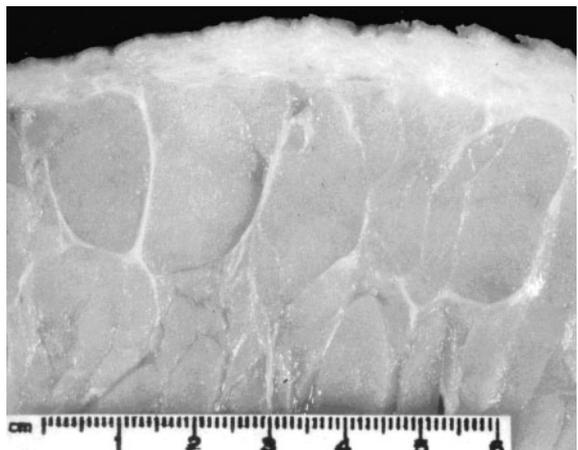
lobules bulge above the cut surfaces and any edema fluid escapes: a fasciotomy effect. Suspensory ligaments in the female breast serve a function similar to that of skin septa in skin, and these and mammary arterioles (and arteries) were calcified in pendulous breasts from morbidly obese women [3,17].

Injured or disturbed soft tissues are potential targets for pathologic (dystrophic) calcification through the action of circulating factors, including factors in uraemic serum [2].

To explain the increased risk for proximally distributed CUA lesions in the obese, we propose that chronic tension on both subcutaneous septa and



**Fig. 3.** Non-ulcerated, non-necrotic specimen with skin at top and partially calcified deep fascia at bottom right. There is marked septal calcification outlining elongated, distorted lobules. (The apparent calcification of intact skin at top right is an artefact due to its retraction below the cut surface).



**Fig. 4.** Gross specimen. Skin (top) and subcutaneous adipose tissue from lower abdominal wall from an obese female without CKD and prepared after formaldehyde fixation, showing thickened subcutaneous septa partitioning adipose tissue into lobules (associated arterioles are not evident).

companion arterioles imposed by excess adipose tissue localizes the calcifying activity of such serum factors. There is a parallel for this proposed biophysical impact: the well-known predominant distribution of

coumarin-induced skin necrosis in sites of greatest adiposity, with or without CKD.

### Subcutaneous plaques and nodules in CUA

These are among the earliest clinical presentations, and skin necrosis does not always follow [8]. The pathologic basis for plaques and nodules has not, to our knowledge, been established. More study is needed, but focally intensive septal calcification (Figure 3) appears to correlate with some plaques – isolated calcified microinfarcts in lobules with some nodules.

### Limitations of the hypothesis

The hypothesis is based on cumulative, observational data without case-control studies. However, it addresses the specific question of what determines the predominant proximal distribution of CUA in the obese. It is true that not all patients with proximal lesions are obese or overweight, including two in our series with very limited proximal lesions and extensive distal lesions. This discrepancy is presently unexplained, but a role for local edema in the subcutaneous evolution of CUA might fruitfully be explored: like excess adipose tissue, edema fluid can expand the subcutis to a considerable extent, as witnessed by ‘pitting’ on pressure.

### Conclusion

Expansion of the subcutaneous compartment by excess adipose tissue of obesity exerts a chronic stretch tension on the septa and associated arterioles. Coexisting edema adds to that burden. This biophysical effect appears to target both structures for pathological calcification; a hypothesis that explains the increased risk of obese patients for the proximal locations of CUA.

*Conflict of interest statement.* None declared.

### References

- Coates T, Kirkland GS, Dymock RB *et al.* Cutaneous necrosis from calcific uremic arteriopathy. *Am J Kidney Dis* 1998; 32: 384–391
- Moe SM. Calcific uremic arteriopathy: a new look at an old disorder. *Nephropathol* 2004; 3: 77–83
- Moe SM, Chen NX. Pathophysiology of vascular calcification in chronic kidney disease. *Circ Res* 2004; 95: 560–567
- Janigan DT, Prokopetz RD, Chawla S, Durning RG. Massive necrosis of fat and skin as complication of obesity. *Can Med Assoc J* 1989; 140: 665–668
- Janigan DT, Perey, Marrie TJ, Chiasson, Hirsch D. Skin necrosis: an unusual complication of hyperphosphatemia during parenteral nutrition therapy. *J Parenter Enterol Nutr* 1997; 21: 50–52
- Janigan DT, Hirsch DJ, Klassen GA, MacDonald AS. Calcified subcutaneous arterioles with infarcts of the subcutis and skin (‘calciphylaxis’) in chronic renal failure. *Am J Kidney Dis* 2000; 35: 588–597
- Chapman DM, Boskey AL, Tesch M, Janigan DT. Subcutaneous microvascular (capillary) calcification. Another basis for livedo-like skin changes? *Clin Exp Dermatol* 1995; 20: 213–217
- Fine A, Zacharias J. Calciphylaxis is usually non-ulcerating: risk factors, outcome and therapy. *Kidney Int* 2002; 61: 2210–2217
- Anderson DC, Stewart WK, Piercy DM. Calcifying panniculitis with fat and skin necrosis in a case of uremia with autonomous hyperparathyroidism. *Lancet* 1968; 2: 323–325
- Chan YL, Mahoney JF, Turner JJ, Posen S. The vascular lesions associated with skin necrosis in renal disease. *Br J Dermatol* 1983; 109: 85–95
- Bleyer AJ, Choi M, Igweze B, de la Torre, W, White WL. A case control study of proximal calciphylaxis. *Am J Kidney Dis* 1998; 32: 376–383
- Bleyer AJ, White WL, Choi MJ. Calcific small vessel ischemic disease (calciphylaxis). *Int J Artif Organs* 2000; 23: 351–355
- Ahmed S, O’Neill KD, Hood A, Evan AP, Moe SM. Calciphylaxis is associated with hyperphosphatemia and increased osteopontin expression by vascular smooth muscle cells. *Am J Kidney Dis* 2001; 37: 1267–1276
- Goodman WG and London G, on behalf of the Vascular Calcification Work Group. *Am J Kidney Dis* 2004; 43: 572–579
- Moe SM, Chen NX. Calciphylaxis and vascular calcification: a continuum of extra-skeletal osteogenesis. *Pediatr Nephrol* 2003; 18: 969–975
- Janigan DT, Morris J, Hirsch D. Acute skin and fat necrosis during sepsis in a patient with chronic renal failure and subcutaneous arterial calcification. *Am J Kidney Dis* 1992; 20: 643–646
- Janigan DT, Hirsch DJ, Parkhill WS, MacDonald AS. Breast infarction in a patient with chronic renal failure. *Can J Surg* 1996; 39: 507–509
- Walsh JS, Fairley JA. Correspondence. Calciphylaxis. *J Am Acad Dermatol* 1996; 35: 786
- Cooksley WGE, Craswell OW. Involvement of the skin and subcutaneous tissue in azotaemic hyperparathyroidism. *Aust N Z J Med* 1972; 2: 142–147
- Laurent R, Thiery F, Saint-Hillier Y *et al.* Calcifying panniculitis with renal failure: a tissue calciphylaxis syndrome [in French]. *Ann Dermatol Venereol* 1987; 114: 1073–1081
- Asmundsson P, Elfasson GJ, Pordarson H. A case report of calciphylaxis. *Scand J Urol Nephrol* 1988; 22: 155–157
- Bourland A, Eggers S, Wilcox D *et al.* Calciphylaxie? Nécroses cutanées étendue associées à une calcinose artériolaire et sous-cutanées importante dans le cadre d’une insuffisance rénale chronique. *Dermatologica* 1989; 179: 165–169
- Grob JJ, Legre R, Bertochio P, Pyan MJ *et al.* Calcifying panniculitis and kidney failure: considerations on pathogenesis and treatment of calciphylaxis. *Int J Dermatol* 1989; 28: 129–131
- Buchet S, Blanc D, Humbert PH *et al.* Calcifying Panniculitis [in French]. *Ann Dermatol Venereol* 1992; 119: 659–666
- Fischer AH, Morris DJ. Pathogenesis of calciphylaxis: study of three cases with literature review. *Hum Pathol* 1995; 26: 1055–1064
- Rostaing L, El Feki S, Delisle M-B *et al.* Calciphylaxis in a chronic hemodialysis patient with protein S deficiency. *Am J Nephrol* 1995; 15: 524–547
- Elamin EM, McDonald AB. Calcifying panniculitis with renal failure: a new management approach. *Dermatologica* 1996; 192: 156–159
- Ruggian JC, Maesaka JK, Fishbane S. Proximal calciphylaxis in four insulin-requiring hemodialysis patients. *Am J Kidney Dis* 1996; 28: 409–419

29. Whittam LR, McGibbon DH, MacDonald DM. Proximal cutaneous necrosis in association with chronic renal failure. *Br J Dermatol* 1996; 135: 778–781
30. Braden G, Goerdts P, Pekow P *et al.* Calciphylaxis in hemodialysis patients: patient profiles and temporal association with IV iron dextran. *J Am Soc Nephrol* 1997; 8: 549A
31. Angelis M, Wong LL, Myers SA *et al.* Calciphylaxis in patients on hemodialysis: a prevalence study. *Surgery* 1997; 122: 1083–1090 (personal communication L. Wong)
32. Kalaaji AN, Douglass MC, Chaffins *et al.* Calciphylaxis: a cause of necrotic ulcers in renal failure. *Cutan Med Surg* 1998; 2: 242–244
33. Gilson, RT, Milum, E. Calciphylaxis: case report and treatment. *Cutis* 1999; 63: 149–153
34. Alain J, Poulin YP, Cloutier, RA *et al.* Calciphylaxis: seven new cases. *J Cutan Med Surg* 2000; 4: 529–543
35. Buxant F, Jedwab J, Noel JC. Bilateral extensive vascular calcification of the breast associated with coagulative necrosis: a calciphylaxis-like syndrome. *The Breast* 2004; 13: 213–238

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