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Uremic calcifying arteriolopathy (calciphylaxis) with metabolic syndrome and diabetes mellitus. The current perspective

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The term uremic calcifying arteriolopathy (UCA), coined by Coates (1998),[1] should replace that of calciphylaxis, introduced by Seyles (1962).[2] Although widely used, this latter term corresponds to the reunion of two concepts, calcification and anaphylaxis, which express what the author observed in his experiments although they do not correspond with the clinical entity being the object of this editorial.

UCA develops within the dermis and the subcutaneous cellular tissue, generally in areas with high adiposity inducing the occurrence of ischemic ulcers. It manifests as a panniculitis with an initial stage in which purple nodules are observed and later on they get ulcerated. Ischemia of the deep vessels is reflected on the skin leading to livedo reticularis that shapes the characteristic anatomical distribution of the vessels. It is a fatal condition mainly associated to uremia although it may occur associated to other diseases (diabetes, systemic lupus erythematous, Crohn's disease, etc.).[3,4] In this issue of the Journal a review is presented analyzing the characteristics of 8 hemodialysis patients that developed UCA, with the aim of identifying the factors implicated in the pathogenesis. The predominant presence of diabetes mellitus (DM), metabolic syndrome (MS) and obesity makes the authors consider these associations as potential promoting factors.

Traditionally the role of mineral metabolism impairments has been emphasized in patients with chronic renal disease (CRD). In the review here commented and in other cases in the literature, the lack of increased Ca¥P product is striking. The sensitizing role of some of these factors (administration of calcium compounds, hyperphosphatemia, and increased doses of calcitriol) has been determinant in recent years due to the current management policies.[5,6] Today, adherence to K/DOQI guidelines and the new therapeutic tools (calcimimetics and paricalcitol) have minimized their importance. However, the change in the patients' profile, being older and with a higher proportion of diabetics, makes us formulate a more profound analysis of the factors relating to MS, DM, and obesity and that promote atheromatosis of the vascular tree, active calcification of the vascular wall, the accompanying inflammatory phenomena, and ultimately thrombosis.

By definition, UCA requires the existence of calcification of the wall of the arterioles within the dermis and the subcutaneous cellular tissue, although not all patients presenting it develop ischemic ulcers. Similarly, calcifications within the intermediate- and big-size arteries do not induce ischemia provided that the lumen is not compromised by atheromatous plaques. Atheromatosis is not present within the small-size arteries and arterioles, and the factors leading to ischemia are different. In order to better analyze this process, we should differentiate the phenomenon of generalized vascular calcification that slowly progresses through the years from those acute events that block the flow within the calcified vessels. Vascular calcification is a necessary factor although not sufficient for the disease manifesting clinically.

Figure 1 schematically shows the set of factors leading to ischemia in UCA: 1) The increase in the thickness of the vessel wall; 2) occupation of the vessel lumen; and 3) hemodynamic impairments causing the decrease in the peripheral flow.

1. According to the histological findings found in the vessels from ischemic ulcers biopsies, the increase in the thickness of the vessel wall is produced by the existence of extent areas of vascular calcification, endothelial proliferation, and fibrosis of the intimal layer. Occasionally, there is active inflammatory reaction that precedes fibrosis, with giant cells, which includes areas of calcification.[7] Inflammatory phenomena of septal distribution are also observed within the adipose panicle with small areas of extravascular calcification and cellular debris.[8] The presence of an inflammatory reaction is related to the earliness of biopsy collection. In advanced lesions, calcium alters the structure of the wall and occupies the lumen (fig. 2). We may highlight that in the review by Verdalles Guzman et al., the presence of changes of the inflammatory parameters in all patients is described, and this could be either the cause or the result of UCA.

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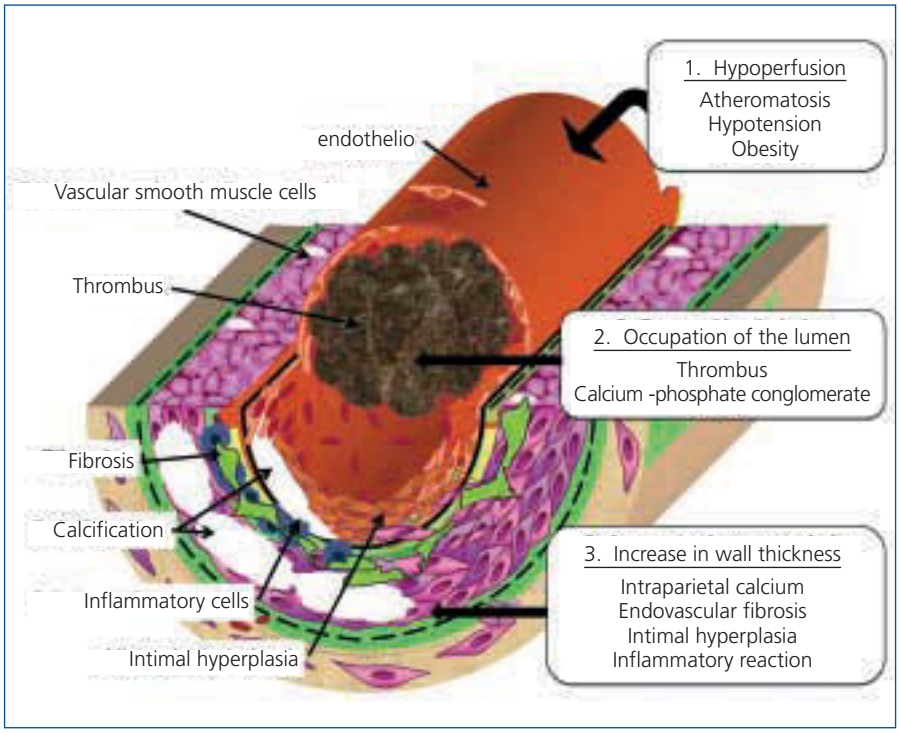

Figure 1. It shows the three components leading to clinical manifestation of uremic calcifying arteriopathy. 1) Peripheral hypoperfusion; 2) Occupation of the vessel lumen; and 3) increase of the vascular wall thickness.

2. Occupation of the vessel lumen. The phenomena previously described are frequently accompanied by thrombosis of the small arteries and arterioles. Hypercoagulability conditions (deficits of proteins C or S, anti-phospholipidic syndrome) promote this phenomenon. Thrombosis within the venules also occurs, usually underestimated, which may favor ischemia due to secondary edema. Within the microvasculature, intravascular calcium conglomerates also contribute to lumen occlusion (figs. 1 and 2).
3. Blood flow decrease to peripheral areas may be a consequence of circulation compromise at more proximal sites due to atheromatous disease. Hypotension or any other hemodynamic cause or volume depletion favoring peripheral hypoperfusion may aggravate tissular ischemia. In the patients presented in the series by Verdalles Guzman et al. there are risk factors for atheromatous disease, obesity, and MS in 100% of the cases, and DM in 85%. In addition, the authors underscore a mechanism present in these patients, which is systolic blood pressure values < 100 mmHg induced by an strict volume control (maybe excessive?) at the beginning of dialysis. This mechanism is worsened by the stiffness of the vessel wall due to vascular calcification that prevents peripheral vasodilation in response to hypoperfusion. Besides, in obese female patients there may coexist a mechanical factor produced by traction of the vascular tracts within the adipose panicle due to its volume increase.[9]

PHENOMENA PROMOTING VASCULAR CALCIFICATION IN DM AND MS

UCA more commonly occurs in female diabetic patients.[10,11] Vascular calcification in CRD and DM affects the intermediate and intimal layers.[12,13] It starts at the big and medium size arteries progressing until it affects the small arteries and the arterioles, which are the ones irrigating the subcutaneous cellular tissue and the skin. These pathologies give way to bone formation within the vascular wall as a result of an unbalance between promoting and inhibiting factors. The study of such factors is an active research area with excellent review works to which the reader is conferred.[12,13]

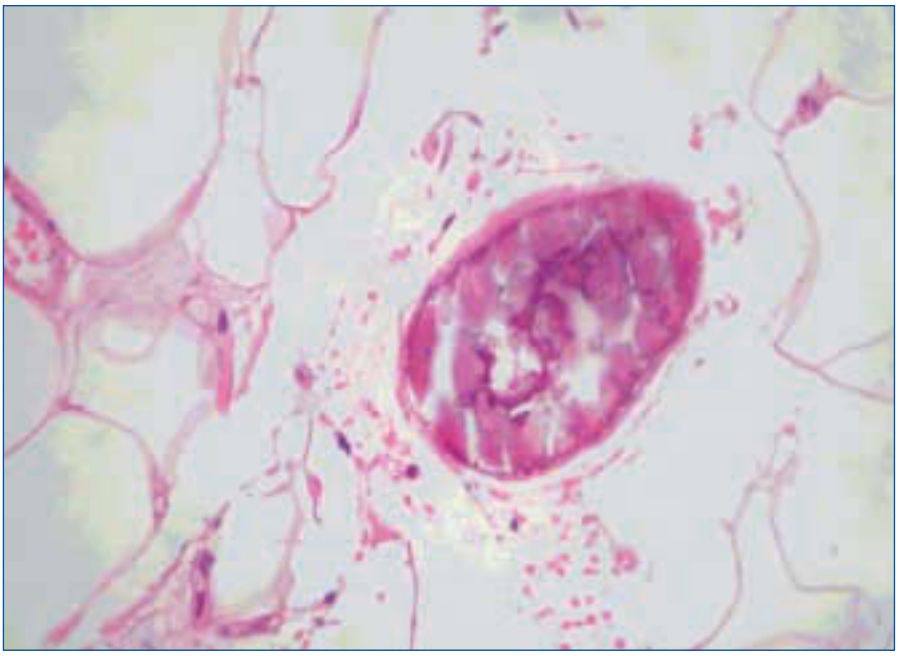

Figure 2. Unstructured arteriole due to massive calcification of the wall. Calcium deposition completely occludes the vessel lumen (H & E, X 200).

Vesicle formation within the lipid core of the atheromatous plaque or within the intermediate layer is the beginning of vascular calcification. These matrix vesicles are replaced by osteoid tissue synthesized by osteoblast-like cells, which origin is mesenchymal cells derived from the vascular smooth muscle (VSMC) or the pericytes. Further mineralization takes place through a neo-vascularization phenomenon by which the vasa vasorum of the adventitia, which normally penetrate down to the intermediate layer, also invade the intimal layer and bring inflammatory mediators, mineral salts (calcium, phosphorus…) and growth factors that promote mineralization.[11]

The onset of this process requires previous vascular damage. The analysis of factors such as hemodynamic stress induced by AHT or infections are beyond the scope of this editorial. I will refer here to multiple metabolic toxicity induced by MS and DM, which generates reactive oxygen species (ROS) that play a key role in atherosclerosis development. CRD shares some of these factors and brings others that are unique to it (calcium, phosphorus, and PTH) acting by «sensitizing» the arterial wall for the development of the process of bone formation within it (table I). I will outline next some of these toxic metabolic factors, invariably present in patients with higher risk for UCA, that is to say those coexisting with CRD and MS or DM:

Glucotoxicity induces a phenotypic change of VSMC to osteoblast-like cells.[14,15] Ishimura et al.[15] were able to demonstrate that for each 1% increase in HbA1c there is 2.1 times higher risk for developing vascular calcification.

High uric acid levels interfere with normal functioning of the enzyme nitric oxide synthetase (ONS), and thus with normal endothelial production of nitric oxide (eNO).[16,17]

Hyperhomocysteinemia induces fibrosis within the vascular wall through various mechanisms including activation and proliferation of VSMC and activation of ROS.[18-20]

Mediators of inflammation (CRP, cytokines, etc.) are associated to vascular calcification within the aorta and hands of hemodialysis patients.[21] Fetuin A, a negative acute phase reactant and a potent inhibitor of vascular calcification,[22] is increased in patients with renal disease, and interleukine-10, which has anti-inflammatory activity, is decreased in CRD.[23]

Obesity is a source of metabolic toxicity due to hyperlipidemia and increased levels of leptin, resistin, and adipocytokines that also lead to the production of ROS.[24]

Hyperinsulinemia, hyperproinsulinemia and the increase in insulin-like growth factor (IGF-I) may increase osteogenesis within the intermediate layer. Amylin, another hormone secreted by beta cells from the pancreas and also increased in CRD, is a physiologic regulator of bone remodeling, and thus it may be involved in vascular calcification.[11,25]

Dyslipidemia (increased LDL-C, triglycerides, and free fatty acids, together with decreased HDL-C). These oxidized lipid products, within a milieu full of ROS, form the lipidic core where calcification of the atheromatous plaque begins.[11,23,24]

Endothelial disease: through the synthesis and secretion of a number of molecules, the endothelium regulates the vascular tone, inflammation, lipid metabolism, angiogenesis, remodeling of the arterial/arteriolar wall, coagulation, and fibrinolysis. A particular enzyme (eNOS) and its anti-oxidant and anti-inflammatory gas product (eNO) play a key role. When this system fails, due to the multiple metabolic toxicity previously mentioned, superoxide and ROS molecules are produced instead of the beneficial gas eNO. This endothelial dysfunction at the small arteries and arterioles leads to a pro-thrombotic state at the same time that it promotes calcification of the vessels wall. Besides, endothelial dysfunction and calcification render the vessels unable to regulate their tone and adapt to hemodynamic changes.[26]

FUTURE DIRECTIONS IN PREVENTION AND MANAGEMENT

The current profile of patients and the knowledge of the factors described make us taking into account other preventive measures and therapies beyond those aiming at strictly controlling the changes in mineral metabolism. Reduction of oxidative stress is achieved by putting into practice the measures leading to reduction of the whole cardiovascular risk.

We have recently started using intravenous sodium thiosulfate that has an anti-oxidant function and calcium-chelating effect. It has a tetrahedral chemical structure with a central sulfur atom surrounded by three oxygen atoms and another sulfur atom. It is currently used as a chemo-protector when using cisplatinum therapy. In the cases described, there is a rapid (days) improvement in pain and a slower resolution of ischemic ulcers (months), when used with other measures such as hyperbaric chamber.[27] Its anti-oxidant properties help to correct endothelial dysfunction and pro-

Table I. Metabolic toxicities producing ROS.

Shared by both pathologies	Metabolyc syndrome and/or diabetes mellitus	Renal failure
Hypertension	Hyperglycemia	Anemia (hypoxia)
Chronic Inflammation	AGEs/AFEs	Hyperphosphatemia
Hyperuricemia	Adipocytokines	Hypercalcemia
Hyperhomocysteinemia	Increased leptin and resistin	Hyperparathyroidism
Oxidative stress	Decreased adiponectin	Therapy with Calcitriol
Dyslipidemia		and calcium compounds
ADMA		
Hyperinsulinemia, IGF-I		

mote vasodilatation. In addition, it forms together with calcium, calcium thiosulfate, which is 3,600 times more soluble than calcium phosphate (present in CV), which may promote the clearance of vascular calcium deposits. The rapid improvement in pain may be due to the effects on the vasa nervorum and endoneurium, which are also calcified.[11] The lack of other effective therapies and the low toxicity make us consider this drug as first line in UCA, together with other measures such as hyperbaric chamber and strict control of mineral metabolism.

There exist recent data relating nanobacteria with the development of atherosclerotic disease vascular calcification. These are bacteria belonging to the gram-negative family, although they are 100 times smaller and have been visualized by immunohystochemical techniques in human calcified cardiovascular tissue.[28] Significant improvement in calcification of the coronary arteries has been shown in patients treated with tetracyclines for four months. These facts open new treatment possibilities.

The association between osteoporosis and vascular calcification also suggests that anti-reabsorption therapies such as biphosphonates and other new drugs that will be soon introduce in the clinical practice such as anti-RankL antibodies, may have a beneficial effect.[29] The outcomes of biphosphonate therapy in patients with UCA are controversial.[30,31]

In the meanwhile, the best tool is preventing UCA-induced ischemia, by identifying early the patient at risk of developing it: obese women with MS or DM. Especially in them, strict control of multiple metabolic toxicity (reduction of global vascular risk: statins, renin-angiotensin-aldosterone system inhibitors, ASA, glycemic control and arterial hypertension) should be carried out. In parallel, those factors predisposing to UCA (local trauma, obesity, treatment with oral dicoumarin anti-coagulant agents, hypotension, etc.) should be avoided. Only the knowledge of all of them by the professional team treating the patient may prevent the occurrence of this severe disease.

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