Hyperphosphataemia—a silent killer of patients with renal failure?

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Introduction

For decades, it has been known that patients with end-stage renal failure have an excessive coronary and cardiac risk. There is also widespread consensus that coronary atherosclerosis and its complications are not fully explained by classical risk factors, e.g. dyslipidaemia, elevated homocysteine concentrations, hypertension, insulin resistance, high fibrinogen etc.

Studies on uraemia spring many surprises. In an early investigation, the paradoxical finding had been made [1] that high cholesterol concentrations are predictive of better survival. This observation subsequently has been confirmed [2] and the paradox is presumably explained by the fact that high cholesterol is a surrogate marker for adequate nutrition. Conversely, malnutrition turned out to be highly predictive of death including cardiac death [3].

Block et al. [4] sprang another surprise on the nephrological community when they found that hyperphosphataemia predicted reduced survival. This was accounted for by an excess of cardiac death. This observation has been confirmed and extended recently [5].

In the following, we discuss several possibilities of how elevated serum phosphate concentration may aggravate the cardiac risk and the impact that those observations will have on patient management.

Hyperphosphataemia and coronary plaques

Coronary plaques are not static lesions, but highly dynamic structures. They are initiated by injury to or dysfunction of the endothelial cell layer, migration of activated monocytes and local interaction with proliferating vascular smooth muscle cells. This sequence of injury and repair may occur on multiple occasions. The final outcome, i.e. stabilization or rupture with coronary thrombosis, will depend on the interplay between collagen fibre deposition (fibrous cap) on the one hand and proteolytic activity, released by activated macrophages and vascular smooth muscle cells, on the other hand [6]. Calciﬁcation is a feature of an advanced stage of plaque transformation. Recently, non-invasive technology, based on fast electron computed tomography (CT) led to the recognition that the number and the extension of calcified plaques [7] is a highly sensitive indicator of coronary atherosclerosis. The specificity of the lesions detected by fast electron CT is shown by the fact that they respond to interventions such as administration of statins [8]. Necrotic cores of plaques are known to calciﬁe easily. This is accompanied by expression of genes which potentially play a role in calcium metabolism, e.g. osteoponitin and osteocalcin, raising interesting issues about the mechanisms, direct or indirect, through which hyperphosphataemia promotes calciﬁcation. Autopsy studies [9] and clinical observations using electron-beam CT [10] showed a high prevalence of rapidly progressing calcified coronary plaques in uraemic patients. These ﬁndings with imaging procedures are supported by our own observations [11]. Figure 1 shows the heart of an uraemic patient with heavy calciﬁcation of the aortic valve and the aorta ascendens. Figure 2 shows a characteristic calciﬁed coronary artery of an uraemic patient. Figure 3 shows the histology of a calciﬁed coronary plaque. When comparing coronary plaques in 27

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Fig. 1. Calciﬁed aortic valve of a uraemic patient at autopsy.
Hyperphosphataemia may act per se or via excessive secretion of parathyroid hormone (PTH), in other words, some of the cardiac effects of hyperphosphataemia may be indirect [14,15]. This consideration would give another twist to the proposal of Massry that PTH is a potential cardiac and vascular ‘toxin’ [16]. A direct effect is a plausible possibility, however, in view of the observation that serum phosphate is correlated to angiographic levels of coronary disease and coronary occlusion in non renal patients [17]. In the past, we had studied a model of renal failure, i.e. the subtotally nephrectomized rat, and found that parathyroidectomy prevented, and infusion of the rat 1–34 N-terminal PTH fragment restored activation of interstitial cells [18] and thickening of the wall of cardiac arterioles [19]. Recently, we studied interstitial fibrosis and arteriolar wall thickness in the heart and noted striking differences between subtotally nephrectomized animals put on low phosphate compared with high phosphate diet [20]; currently, we cannot exclude the possibility that this finding is explained by differences in PTH.

In summary, hyperphosphataemia may adversely affect cardiac prognosis, first by modifying coronary plaque morphology, but, second, also by affecting the structure of the heart including the microvasculature. This would add an element of post-coronary microvascular disease with obvious repercussions on ischaemia tolerance [11]. These direct effects on the heart may be complemented by hyperphosphataemia-induced alterations in the elastic arteries, as suggested by the observation of London reported in this issue [21]. Since diminished aortic elasticity imposes greater work load upon the heart of the uraemic patient [22], it will be very important to provide further support for the preliminary findings in his cross-sectional observational study.

Clinical implications

Where does all this leave us today?

As discussed above, it remains unclear whether phosphate is injurious per se or whether the adverse effect is mediated via PTH. At any rate, it is appropriate that every effort is made to keep serum phosphate concentration and PTH concentration within or close to the normal range respectively. The recognition that hyperphosphataemia increases the cardiac risk gives an entirely new urgency to hyperphosphataemia control. The magnitude of the risk is illustrated by the fact that hyperphosphataemic compared with normophosphataemic patients have a 52% higher risk of death from coronary artery disease, a 26% higher risk of sudden death, a 34% higher risk from other cardiac causes and a 39% higher risk of death from cerebrovascular accidents [5]. From the patients’ perspective, prevention of cardiac death is far more important than prevention of renal osteodystrophy, which in the past has dominated the nephrologists’ perception of why hyperphosphataemia is dangerous.
References


Editor’s note

Please see also Preliminary Report by Marchais et al. (pp. 2178–2183 in this issue).