MD Thesis: Acidosis and Bone Disease in Chronic Renal Failure

Addendum: August 2018

http://etheses.bham.ac.uk/486/
MD Thesis, 1974

The work considered the evidence that metabolic acidosis in chronic renal failure (CRF) inhibited bone formation by hindering mineralisation, contributing to the osteomalacic component of Renal Bone Disease.

We had previously reported that osteomalacia in CRF occurred in subjects with clear metabolic acidosis and a somewhat lower plasma phosphate level than was usual for that degree of CRF (1). Robertson, investigating kidney stone disease and precipitation of calcium salts, pointed out how exquisitely sensitive the calcium phosphate association was to pH changes. The active phosphate species was the trivalent phosphate PO4''' and whose concentration fell as the H+ increased, shifting the equilibrium towards HPO4'' and HP2O4' (2). Thus, minor decrease in pH led to a substantial fall in the available phosphate concentration for mineral precipitation. This provided a reasonable explanation for the mineralisation failure. However, we also noted the very similar pattern for alkaline phosphatase, whose enzymatic activity was almost completely inhibited at pH 7.2, a level seen among patients with renal acidosis. At that time, the role of alkaline phosphatase in mineralisation was unknown but it had long been suspected that it provided phosphate from some some source. We therefore suggested that the mineralisation failure in acidosis could be explained by either, or both, of these mechanisms. This was the central idea put forward in the MD Thesis.

It was also already known that pyrophosphate inhibited calcium phosphate crystallisation (3) but we did not consider this possible link. In fact, it became clear that pyrophosphate was the substrate for alkaline phosphatase (4), so indeed a metabolic acidosis would indirectly inhibit pyrophosphate breakdown, thus contributing to mineralisation failure. It follows that there are three mechanisms that operate around the pH of renal acidosis, all tending to inhibit bone mineralisation.

This last concept was not included in the MD as submitted in 1973.

1. The role of acidosis in renal osteomalacia. Cochran M, Nordin BEC. Brit Med J. 1969; 2: 276-279

2. Octocalcium phosphate: the phase governing the solubility equilibrium in apatitic calculi. MacGregor J, Robertson WG, Nordin BE. Br J Urol. 1965 Oct;37(5):518-24.

3. The urinary excretion of inorganic pyrophosphate by normal subjects and patients with renal calculus. Russell RG, Hodgkinson A. Clin Sci. 1966 Aug;31(1):51-62.

4. Pyrophosphate activity of alkaline phosphatase. Casey P, Russell RG, Fernley HN, Birkett D, Bisaz S, Fleisch H. Helv Physiol Pharmacol Acta. 1967; 25 (2): CR 174-6