POSSIBLE ROLE OF INORGANIC SULPHATE IN THE PATHOGENESIS OF HYPERPARATHYROIDISM IN CHRONIC RENAL FAILURE

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Summary

In order to investigate the role of hypersulphataemia in the development of hyperparathyroidism the blood levels of inorganic sulphate (SO$_4^{2-}$) and phosphate (HPO$_4^{2-}$) were compared with total and ionised calcium (Ca) and parathyroid hormone (PTH) in 20 patients with chronic renal failure (CRF). There was a positive correlation between plasma SO$_4^{2-}$ and serum creatinine. Ionised Ca was inversely correlated with HPO$_4^{2-}$, SO$_4^{2-}$ and PTH, respectively. The best correlation was found between ionised Ca and the ion product of HPO$_4^{2-}$ and SO$_4^{2-}$. It is suggested that hypersulphataemia might be involved in the pathogenesis of secondary hyperparathyroidism and osteodystrophy in CRF by complex formation with Ca, thereby aggravating the effect of HPO$_4^{2-}$ on ionised Ca and the resulting PTH stimulation.

Introduction

Hyperparathyroidism in chronic renal failure (CRF) is thought to be due to a fall in the blood level of ionised calcium (Ca) [1]. One factor believed to play an important role in causing hypocalcaemia is phosphate retention and hyperphosphataemia because of the formation of soluble CaHPO$_4$ complexes [2]. But the increase of complexed calcium is not related to the degree of hyperphosphataemia in all patients with CRF [3]. Therefore other factors must account for the decrease of plasma ionised Ca, one of which may be inorganic sulphate (SO$_4^{2-}$), since it is the other important divalent anion in human blood, which is able to complex with Ca and is accumulated in uraemia even more than phosphate (HPO$_4^{2-}$) [4].

Patients and methods

In order to investigate the possible role of hypersulphataemia in the development of secondary hyperparathyroidism we determined the plasma levels of SO$_4^{2-}$ and
$\text{HPO}_4^{2-}$ in relation to total and ionised Ca and parathyroid hormone (PTH) in 20 children and adolescents, eight to 20 years old, with CRF of various origins. Serum creatinine ($S_{\text{Cr}}$) and $\text{HPO}_4^{2-}$ were measured by a Gemseac autoanalyser and total Ca and $\text{SO}_4^{2-}$ by atomic absorption spectrophotometry (PE 400) as described previously [5]. Serum ionised Ca was determined by sensitive electrodes (SS 20, Orion) after blood sampling in deaerated tubes (Vacutainer), and PTH by radioimmunoassay directed to the $\text{COOH}$ terminal. Simultaneously measured total protein and blood pH were within the normal range and, therefore, did not interfere with the determination of serum ionised Ca.

Results

The plasma levels of $\text{SO}_4^{2-}$ were elevated ($> 0.75\text{mEq/L}$) in 18 patients. This rise of $\text{SO}_4^{2-}$ was significantly related to $S_{\text{Cr}}$ (Figure 1). In advanced renal failure the concentration of plasma $\text{SO}_4^{2-}$ was increased to $5.6\text{mEq/L}$, which is approximately eight times the upper normal limit for healthy children [5]. In contrast, serum $\text{HPO}_4^{2-}$ was normal or even decreased in most patients and failed to correlate with $S_{\text{Cr}}$.

Ionised Ca was decreased ($< 2.24\text{mEq/L}$) in seven patients. The fall was inversely correlated with $\text{HPO}_4^{2-}$ ($r = -0.71$, $p < 0.01$) and with plasma $\text{SO}_4^{2-}$ ($r = -0.63$, $p < 0.01$) but not with $S_{\text{Cr}}$. Whereas ionised Ca was found to be

![Plasma sulphate vs Serum-creatinine](image)

Figure 1. Relationship between plasma inorganic sulphate and serum creatinine
lowered even in the presence of normal serum HPO$_4^{2-}$ levels, it began to decrease only at a moderate degree of hypersulphataemia (> 2mEq/L). Since both anions are able to bind to Ca, the effect of HPO$_4^{2-}$ on ionised Ca might be intensified by the concomitant increase of SO$_4^{2-}$ and vice versa. If ionised Ca was compared

\[ y = 2.62 - 0.06x \]
\[ r = -0.84 \quad p < 0.001 \]
\[ n = 20 \]

Figure 2. Relationship between serum ionised calcium and the ion product of inorganic phosphate and sulphate. Hatched areas represent normal range

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with the ion product of $\text{HPO}_4^{2-}$ and $\text{SO}_4^{2-}$ (Figure 2), the correlation between these parameters was more significant ($r = -0.84$, $p < 0.001$) than that observed after comparison of ionised Ca with each individual anion.

The serum PTH levels were increased in all but one patient. This increase was related to the fall of ionised Ca in a nonlinear fashion ($r = -0.68$, $p < 0.01$) (Figure 3). Total Ca was within the normal range in 18 patients and failed to correlate with any parameter investigated.

![Figure 3](image)

**Figure 3.** Relationship between serum concentrations of parathyroid hormone and serum ionised calcium. Dotted line represents the upper normal limit of PTH.

**Discussion**

The pathogenesis of hyperparathyroidism in CRF is very complex. Because of the mutual influences, the separate investigation of one pathogenetic factor is almost impossible and, the interpretation of our results is difficult. The inverse correlation between serum PTH and ionised Ca indicates that hyperparathyroidism is, indeed, caused by a fall in ionised Ca as suspected previously [6]. The slope of the curve suggests exhaustion of PTH secretion from the parathyroid gland in more advanced renal failure. But since our patients were rather heterogeneous with respect to the duration and cause of CRF, the observed PTH level of each patient may reflect his individual state of Ca homeostasis rather than be caused by an actual change in ionised Ca. Nevertheless, the feedback mechanism between serum ionised Ca

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and the parathyroid gland seems to be still functioning in CRF.

Although hyperphosphataemia was rare in our patients, we could confirm the observation that serum HPO$_4^{2-}$ may influence ionised Ca [3] but not total Ca [7]. But since ionised Ca was lowered even in normophosphataemic patients, other factors must have been responsible for the hypocalcaemia in these cases. The inverse correlation between ionised Ca and plasma SO$_4^{2-}$ suggests that hypersulphataemia might be one of these factors. As can be calculated from the plasma levels of HPO$_4^{2-}$ and SO$_4^{2-}$ and the dissociation constants of CaHPO$_4$ (0.003M) and CaSO$_4$ (0.006M) [8], SO$_4^{2-}$ has to accumulate in plasma to concentrations four times higher than HPO$_4^{2-}$ to exert the same effect on Ca as HPO$_4^{2-}$. In fact, hypersulphataemia exceeded hyperphosphataemia by about this amount in our patients with advanced renal failure. The close correlation between ionised Ca and the ion product of HPO$_4^{2-}$ and SO$_4^{2-}$ is compatible with the hypothesis that hypocalcaemia in CRF is due to the combined action of both anions. Obviously further studies are necessary to evaluate the role of hypersulphataemia in the development of secondary hyperparathyroidism in CRF.

Acknowledgment

We are very much obliged to Prof. Dr. H Schmidt-Gayk, Department of Medicine, University of Heidelberg, for the determination of parathyroid hormone.

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Open Discussion

DRUEKE (Paris) The presentation of a relationship between two variables is very interesting but not a demonstration of a direct relationship. Do you know of any experimental work in uraemic animals showing whether a restriction in sulphate in the diet leads to less hyperparathyroidism than in the unrestricted animals, such as the experiments which have been done for phosphate?

MICHALK No, there are no data about sulphate restriction in humans nor in animals. There is some data obtained from calcium infusions in dogs with normal renal function and in these dogs severe hypercalcaemia could be obtained by the infusion, but I think this was due to combined calcium and sulphate excretion and not to the effect in the serum.
GUILLET (Heidelberg) I would agree with Dr Drüeke that demonstration of a relationship does not determine the mechanism involved, since the fact that the higher the sulphate the higher the PTH could just mean that the patients were more uraemic. Do you have evidence that the solubility product for calcium sulphate was exceeded? Is there any evidence for precipitation of gypsum or calcium sulphate in the bone or soft tissue?

MICHALK It is assumed that there is no deposition of calcium sulphate as well as calcium phosphate, but only an ion association making the calcium ion unavailable to the parathyroid gland. There is no direct evidence that the sulphate content of, for example, the arteries is increased. One can say that the dissociation constant of calcium phosphate is twice that of calcium sulphate. We found that sulphate concentration increases four times more than phosphate but since the plasma levels of phosphate are twice those of sulphate in normals, sulphate concentration has to increase to four or five times that of phosphate to be comparable and this is exactly what happens in uraemia.

DRÜEKE Would you suggest uraemic patients take sulphate binders?

MICHALK I think it is too early to do this! I am working with a diet low in methionine and other sulphur-containing amino acids. I only want to say that there is another anion which should be studied.