Nephron 30: 237–239 (1982)

Elevated Thrombocyte Calcium Content in Uremia and Its Correction by 1α(OH) Vitamin D Treatment[1]

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Key Words. Uremia · Vitamin D · Thrombocytes · Calcium · Hyperparathyroidism

Abstract. Intracellular calcium plays an important role in the regulation of platelet function. It has also been demonstrated that platelet functions are impaired in uremia. A rise in intracellular calcium has been shown in several tissues and has been held responsible for the impaired function of several organs seen in uremia. This study was undertaken to evaluate whether the calcium (Ca) content of thrombocytes is elevated in uremia and, if so, whether treatment with an active vitamin D metabolite might correct this abnormality. In 10 patients on chronic hemodialysis, platelet Ca content was determined by a technique utilizing consecutive freezing and thawing of platelet-rich plasma. The platelet Ca content of uremic patients was found to be markedly higher (20.86 ± 0.9 ng/200,000 platelets, $p < 0.001$) than that of a group of 20 normals (12.8 ± 1.2 ng/200,000 platelets). 1 month after treatment with 1α(OH) vitamin D at a dosage of 0.5–2.5 μg/day, the platelet Ca content of the dialysis patients decreased to 14.99 ± 2.14 ng/200,000 platelets ($p < 0.05$). The data show that in dialysis patients the platelet Ca content is markedly elevated in comparison with that of normals, and that treatment with 1α(OH) vitamin D may significantly reverse this abnormality. It is suggested that elevated Ca content may play a role in the pathogenesis of uremic platelet dysfunction, and that 1α(OH) vitamin D administration may be of benefit in correcting this disorder.

Introduction

Bleeding tendency, which is a major complication of the uremic syndrome [1], is a defect in which impaired platelet function plays a significant role [2]. The derangement of platelet activity is characterized primarily by reduced availability of platelet factor 3 and by impaired cellular aggregation and adhesiveness [3–5]. Evidence in the literature has increasingly pointed to the importance of Ca^{++} with respect to the regulation of platelet function [6]. Total Ca^{++} content and the flux of Ca^{++} between the cytosol and the various organelles appear to be a major factor contributing to cell shape and membrane surface changes and energy-producing reactions. Therefore, alterations in Ca^{++} content within the platelet may play an important role in the pathogenesis of uremic platelet dysfunction. Indeed, multiple studies have shown tissue content of Ca^{++} to be elevated in uremia [7, 8]. Recently, this elevation of tissue Ca^{++} has been shown to impair cellular function in other tissues [9]. For these reasons, the possibility of an increased platelet Ca^{++} content in uremic patients seemed to be of considerable relevance to us. Since elevated parathyroid hormone levels (PTH) are the hallmark in patients with chronic renal failure, and since PTH enhances translocation of calcium from the extracellular space to the cell [7, 8], it was suggested that the increased cellular content of calcium is due to the elevated PTH levels. Indeed, several investigators have shown that this is the case, and that reduction of PTH levels by either surgical removal or pharmacological means [administration of 1,25 $(OH)_2D_3$; 10, 11] will reduce the intracellular Ca^{++} concentration. Thus, the effects of treatment with an active vitamin D metabolite were used as a model in

[1] This work was read, in part, at the Annual Meeting of the American Society of Nephrology, New Orleans, La., 1979.

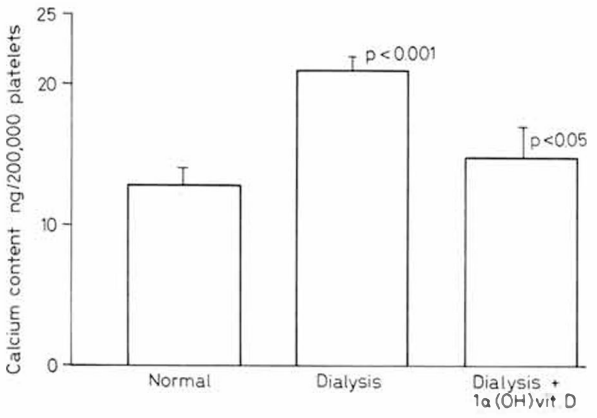

Fig. 1. Thrombocyte Ca^{++} content in normal volunteers, dialysis patients not receiving 1α(OH) vitamin D and the same patients after 1 month with 1α(OH) vitamin D treatment. Data are shown as mean ± SEM.

investigating the issue of platelet Ca^{++} behavior in uremic patients. This study was conducted to determine whether the Ca^{++} content of platelets was elevated in uremic patients and, if so, whether treatment with an active vitamin D metabolite would be of benefit in reducing platelet Ca^{++} content in such patients.

Methods

Studies were done on 20 normal volunteers and on 10 patients aged 18–45, all with end-stage renal failure (GFR < 4 ml/min). All patients had been on chronic hemodialysis for at least 1 year and suffered from secondary hyperparathyroidism as demonstrated by subperiosteal bone resorption shown by X-ray. After the initial determination of platelet Ca^{++} content, the hemodialyzed patients were given 1α(OH) vitamin D (Teva, Israel) at a dosage of 0.5–2.5 μg/day. After 1 month of treatment, platelet Ca^{++} content was determined again.

All blood samples were obtained before dialysis was begun; platelet Ca^{++} content was measured by atomic absorption spectrophotometry in platelet-rich plasma after platelet destruction, using a technique of alternate freezing and thawing, as previously described by our laboratory [12]. The data were statistically evaluated using the unpaired t test.

Results

The platelet Ca^{++} content in normal volunteers (fig. 1) was 12.8 ± 1.2 ng/200,00 platelets (mean ± SEM), while in dialysis patients a significantly higher value of 20.86 ± 0.9 ng/200,000 platelets ($p < 0.001$) was found.

After 1 month of treatment with 1α(OH) vitamin D_3, serum Ca^{++} did not change significantly. However, as shown in figure 1, the patients' Ca^{++} content decreased markedly and significantly from 20.86 ± 0.9 ng/200,000 platelets to 14.99 ± 2.14 ng/200,000 platelets ($p < 0.05$), a value which did not differ significantly from that obtained in normal volunteers.

Discussion

Our data show that in dialysis patients platelet Ca^{++} content was significantly higher than in normal individuals, and was corrected following treatment with 1α(OH) vitamin D. The mechanism mediating this abnormality cannot be determined from our data since unfortunately PTH levels are not available to us. However, it is plausible to suggest secondary hyperparathyroidism, since in uremia hyperparathyroidism has been shown to be associated with elevated Ca^{++} content in tissue other than blood cells, such as skin and brain [7–9]. Therefore, it is possible that our findings in the platelets are also attributable to secondary hyperparathyroidism.

Because the importance of Ca^{++} with respect to platelet function cannot be overestimated [13], we are compelled to speculate that elevated platelet Ca^{++} content may be a cause of platelet dysfunction in our patients. We cannot at this point substantiate our conclusion since data regarding platelet function before and after vitamin D treatment are not available. However, several possible mechanisms should be suggested: (1) direct effect of 1α(OH) vitamin D on cellular Ca^{++}; data to substantiate this possibility are not available in the literature; (2) effects of 1α(OH) vitamin D and PTH levels. Currently, there is no consensus with regard to the effect of active vitamin D metabolites on PTH levels in uremics; some authors appear to believe that vitamin D metabolites lower PTH levels [14, 15] while others report that in acute studies this might not be the case [16]. Thus if 1α(OH) vitamin D inhibits PTH secretion, and since PTH is a major stimulant for influx of calcium into the cells, it is possible that the reduction in PTH levels might be a possible mechanism to mediate these changes.

Our data suggest that increased intracellular calcium levels may play a role in the impairment of platelet function in uremia, and the administration of an active vitamin D metabolite may be of beneficial effect in correcting this abnormality. Further investigations will be needed to evaluate the mechanisms and clinical importance of this observation.

Acknowledgements

The authors are indebted to *Nachman Brautbar*, MD, for his critical comments on this manuscript. The authors are grateful to Ms. *Dorothy Bodjanac* for her assistance in the preparation of the manuscript, and to the staff nurses at the Hasharon Hospital for their valuable assistance in this work.

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Accepted: July 22, 1981

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