In vivo effect of 1,25-dihydroxyvitamin D₃ on phagocyte function in hemodialysis patients

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In vivo effect of 1,25-dihydroxyvitamin D₃ on phagocyte function in hemodialysis patients. 1,25-dihydroxyvitamin D₃ (1,25(OH)₂D₃) has been shown to modulate the immune function of monocytes and macrophages. Patients with end-stage renal disease (ESRD) on chronic hemodialysis treatment usually present a deficiency of this active form of vitamin D₃. The aim of this study was to investigate the effect of 1,25(OH)₂D₃ replacement therapy on phagocytosis, bactericidal capacity, and oxidative metabolism of peripheral blood polymorphonuclear leukocytes (PMNL) and monocytes (MN) in chronic hemodialysis patients. Phagocyte function tests were performed before and after four weeks of oral replacement therapy with 0.5 µg/day of 1,25(OH)₂D₃ (Rocaltril®). The superoxide (O₂⁻) generation of monocytes, measured by cytochrome c reduction and lucigenin-enhanced chemiluminescence (CL) from patients receiving hemodialysis treatment was significantly diminished compared to healthy controls. After the replacement therapy with 1,25(OH)₂D₃, the O₂⁻ production showed a significant improvement, resulting in an increased cytochrome c reduction and lucigenin-CL response. The bactericidal capacity of MN was also impaired and exhibited a significant enhancement of their killing activity after the administration of 1,25(OH)₂D₃. On the other hand, the luminol-enhanced CL, which reflects the myeloperoxidase-dependent oxidative metabolism, and the phagocytic ability of MN was not affected by the hormone. The function of polymorphonuclear leukocytes (PMNL) from hemodialysis patients showed no impairment in the state of 1,25(OH)₂D₃ deficiency and the replacement of the hormone did not enhance their function. These results suggest that the deficiency of 1,25(OH)₂D₃ in patients with ESRD on chronic hemodialysis treatment may be responsible for an impaired monocyte function, which could be improved by an in vivo replacement of the hormone.

Infection is a frequent complication and a major cause of morbidity and mortality in patients with end-stage renal disease (ESRD) who are on regular dialysis treatment [1, 2]. Abnormalities of the immune system could partly contribute to an increased susceptibility for bacterial infections. Several alterations of leukocyte function in patients with ESRD have been demonstrated, including both impaired neutrophil and monocyte function [3]. A decreased chemotaxis and reduced production of reactive oxygen metabolites during the "respiratory burst" of polymorphonuclear leukocytes and monocytes have been reported [4, 5]. These functions seem to decrease further with duration of dialysis treatment [6].

The secosteroid hormone 1,25-dihydroxyvitamin D₃ [1,25(OH)₂D₃] is the active metabolite of vitamin D₃ and plays an important role in calcium hemostasis and skeletal metabolism. Recently it has been shown that 1,25(OH)₂D₃ exhibits immunomodulatory activities, interacting with lymphocytes and mononuclear phagocytes [7]. Peripheral blood monocytes and tissue macrophages show an enhancement of the oxidative metabolism after in vitro incubation with 1,25(OH)₂D₃ [8–11]. In addition, 1,25(OH)₂D₃ is capable of inducing monocyctic differentiation in various human [12] and murine [13] leukemic cell lines. Abnormal monocyte function with a decreased chemotaxis and phagocytosis has been demonstrated in vitamin D₃-deficient mice and could be corrected after in vitro and in vivo replacement of the hormone [14]. Similar phagocyte alterations have been shown in children with rickets [15]. Furthermore, an improvement of a diminished leukocyte chemotaxis has been reported in patients with ESRD on hemodialysis treatment after in vitro and in vivo administration of 1,25(OH)₂D₃ [16].

Patients with ESRD usually present a deficiency of active 1,25(OH)₂D₃ due to the loss of renoparenchymal function. The present study was undertaken to determine the effect of 1,25(OH)₂D₃ on phagocytosis and oxidative metabolism of polymorphonuclear leukocytes (PMNL) and peripheral blood monocytes (MN) after in vivo replacement therapy with oral 1,25(OH)₂D₃ (Rocaltril®) in patients with ESRD on regular hemodialysis treatment.

Methods

Patients

Twelve patients (7 male, 5 female; mean age 56.4 ± 13.1 years) with chronic renal failure on stable hemodialysis (3 times per week for 4 hours) who were not receiving any form of vitamin D therapy were investigated. The underlying kidney diseases were chronic glomerulonephritis (5), membranous nephropathy (1), tubular interstitial nephritis (2), polycystic kidney disease (2), reflux (1), and analgetic nephropathy (1).

Patients with diabetic nephropathy or with a medication of steroids, NSAID or immunosuppressive drugs were excluded from the study. Furthermore, patients with clinical evidence of infection and operations in the last four weeks prior to the entrance into the study were also excluded.