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Review

Vitamin D compounds and diabetic nephropathy

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ABSTRACT

Vitamin D therapies for renal disease have been used for over a half century and are likely to be utilized for many more years. Past roles have been to alter calcium and phosphorus metabolism to prevent or lessen bone disease and reduce PTH levels in dialysis patients and more recently, pre-dialysis patients. However, emerging evidence indicates new applications for vitamin D compounds are likely to exist for this patient population. In addition to the possible new targets in this therapeutic area, a popularly debated topic is the ideal form of vitamin D for use in renal disease. Because the vitamin D metabolism system is severely altered in kidney disease, a thorough understanding of the disease progression relative to the vitamin D signaling pathway is necessary. The current state of knowledge in this area with the primary focus on patients with diabetic nephropathy will be the scope of this review.

History of vitamin D compounds for renal disease

Vitamin D compounds have a lengthy and successful history in renal disease therapy (Table 1). During the middle of the 20th century, vitamin D itself was prescribed to renal patients at pharmacological doses – 50,000–500,000 IU daily [1,2]. At the time, the understood problems of chronic renal disease were altered calcium homeostasis and bone metabolism and thought to be due to a problem in intestinal uptake of calcium. The discovery that vitamin D must be metabolized to an active form changed the view of vitamin D therapy. Calcidiol or $25(OH)D_3$ was thought initially to be the hormonal form of the vitamin and was proposed as a therapy for chronic kidney disease (CKD) because there was a known vitamin D resistance present in CKD patients [3]. Once it was realized that $1,25(OH)_2D_3$ was the hormone produced in the kidney, calcitriol or $1,25(OH)_2D_3$ became the standard of care. Due to the narrow therapeutic window, new compounds were sought and subsequently the vitamin D analogs Hectorol® (doxercalciferol) and Zemplar® (paricalcitol) were developed for the US market. In addition, two other compounds, $1\alpha(OH)D_3$ (alphacalcidol) and 22-oxa-$1,25(OH)_2D_3$ were developed outside the US. Initially, the indication for vitamin D therapy in renal disease was for treatment of renal osteodystrophy. Recognition that the PTH gland was a direct target of vitamin D resulted in a switch to secondary hyperparathyroidism as the marketed indication. A fluorinated derivative, $1,25(OH)_226,27\text{-}F_6$-vitamin D_3 was most recently developed in Japan for this market based on the understanding that the catabolic enzyme for vitamin D compounds could not act on this compound thus increasing the lifetime of the drug.

In 2003, Thadhani and colleagues provided the first epidemiological evidence that vitamin D compounds not only lowered PTH levels, but reduced overall mortality in CKD patients on dialysis [4,5]. This increase in survival could not be explained wholly by PTH suppression and precipitated exploration into other possible therapeutic actions of vitamin D compounds in renal disease beside the suppression of secondary hyperparathyroidism.

The pathology of diabetic nephropathy

Renal disease afflicts more than 20 million adults in the US [6]. The predominant cause of end stage renal disease (ESRD) is diabetes with over 40% of the ESRD population comprised of patients suffering from type 1 or 2 diabetes [7]. Clinically, protein loss in the urine (microalbuminuria) has been used as a guide for identification of nephropathy [8]. Decreases in estimated glomerular filtration rates (eGFR) and increases in blood pressure are also used to diagnose nephropathy. Renal biopsies, when performed in nephropathy patients, show thickening of the basement membrane of the glomerulus and accumulation of extracellular matrix molecules, primarily from mesangial cells (smooth muscle cells controlling blood flow through the capillaries), so that expansion of the mesangium and podoctye damage occurs (Fig. 1). Once the podocyte damage becomes extensive, microalbuminuria progresses to overt proteinuria and after enough insult, fibrosis develops in the interstitium [9,10]. It should be noted that fibrosis is a more prominent feature of type 2 than type 1 diabetes [11]. In addition, recent reports show that there are significant numbers of individuals that do not exhibit albuminuria but have other signs of nephropathy

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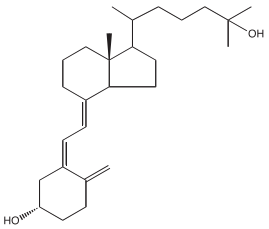
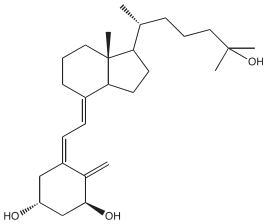
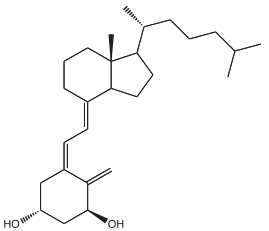
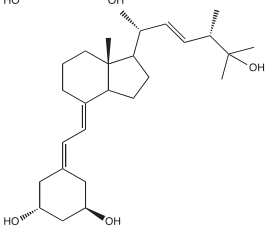
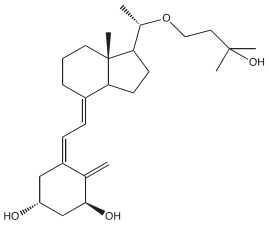
Table 1
Marketed or previously marketed vitamin D therapies for renal disease.

Chemical structure	Compound	Product name®	Company	Indication	Year of approval (information source)
	25(OH)D_3 calcidiol	Calderol®	UpJohn	Renal osteodystrophy	1976 (Trademark registration)
	1,25$(OH)_2D_3$ calcitriol	Rocaltrol® Calcijex®	Roche Abbott	Renal osteodystrophy Renal osteodystrophy	1978 (Drugs@FDA) 1986 (Drugs@FDA)
	1(OH)D_3 alfacalcidol	Alfarol® One-Alpha®, EinsAlpha®, Etalpha® Alfa D_3®	Chugai Leo pharma Teva pharmaceuticals	Renal osteodystrophy Renal osteodystrophy, Secondary hyperparathyroidism Renal osteodystrophy	1981 (Chugai Pharmaceuticals Website) 1979 (Trademark registration) 2002 (Teva Pharmaceuticals Website)
	1,25$(OH)_2$-19-nor-vitamin D_2 paricalcitol	Zemplar®	Abbott	Secondary hyperparathyroidism	1998 (Drugs@FDA)
	22-oxa-1,25$(OH)_2D_3$ oxacalcitriol[a]	Oxarol® Injection	Chugai	Secondary hyperparathyroidism	2000 (Chugai Pharmaceuticals Website)