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(54) Title: METHOD OF SAFELY AND EFFECTIVELY TREATING AND PREVENTING SECONDARY HYPERPARATHYROIDISM IN CHRONIC KIDNEY DISEASE

(57) Abrégé/Abstract:
A method of treating and preventing secondary hyperparathyroidism in CKD by increasing or maintaining blood concentrations of both 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D in a patient by administering 25-hydroxyvitamin D_3 with or without 25-hydroxyvitamin D_2 and, as necessary, 1,25-dihydroxyvitamin D_2 as a Vitamin D hormone replacement therapy.

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METHOD OF SAFELY AND EFFECTIVELY TREATING AND PREVENTING SECONDARY HYPERPARATHYROIDISM IN CHRONIC KIDNEY DISEASE

BACKGROUND

[0001] Secondary hyperparathyroidism is a disorder which develops primarily because of Vitamin D deficiency. It is characterized by abnormally elevated blood levels of parathyroid hormone (PTH) and, in the absence of early detection and treatment, it becomes associated with parathyroid gland hyperplasia and a constellation of metabolic bone diseases. It is a common complication of chronic kidney disease (CKD), with rising incidence as CKD progresses. Secondary hyperparathyroidism can also develop in individuals with healthy kidneys, due to environmental, cultural or dietary factors which prevent adequate Vitamin D supply.

[0002] "Vitamin D" is a term that refers broadly to the organic substances named Vitamin D_2, Vitamin D_3, Vitamin D_4, etc., and to their metabolites and hormonal forms that influence calcium and phosphorus homeostasis. "Vitamin D deficiency" is a term that broadly refers to reduced or low blood levels of Vitamin D, as defined immediately above.

[0003] The most widely recognized forms of Vitamin D are Vitamin D_2 (ergocalciferol) and Vitamin D_3 (cholecalciferol). Vitamin D_2 is produced in plants from ergosterol during sunlight exposure and is present, to a limited extent, in the human diet. Vitamin D_3 is generated from 7-dehydrocholesterol in human skin during exposure to sunlight and also is found, to a greater extent than Vitamin D_2, in the human diet, principally in dairy products (milk and butter), brain, certain fish and fish oils, and egg yolk. Vitamin D supplements for human use consist of either Vitamin D_2 or Vitamin D_3.

[0004] Both Vitamin D_2 and Vitamin D_3 are metabolized into prohormones by one or more enzymes located in the liver. The involved enzymes are mitochondrial and microsomal cytochrome P450 (CYP) isoforms, including CYP27A1, CYP2R1, CYP3A4, CYP2J3 and possibly others. These enzymes metabolize Vitamin D_2 into two prohormones known as 25-hydroxyvitamin D_2 and 24(S)-hydroxyvitamin D_2, and Vitamin D_3 into a prohormone known as 25-hydroxyvitamin D_3. The two 25-hydroxylated prohormones are more prominent in the blood, and are separately or collectively referred to as "25-hydroxyvitamin D". Vitamin D_2 and Vitamin D_3 can be metabolized into these same prohormones outside of the liver in certain epithelial cells, such as enterocytes, which contain the same (or similar) enzymes, but extrahepatic prohormone production probably contributes little to blood levels of 25-hydroxyvitamin D.

[0005] The rates of hepatic and extrahepatic production of the Vitamin D prohormones are not tightly regulated, and they vary mainly with intracellular concentrations of the precursors (Vitamin D_2 and Vitamin D_3). Higher concentrations of either precursor increase prohormone production, while lower concentrations decrease production. Hepatic production of prohormones is inhibited by high levels of 25-hydroxyvitamin D via a poorly understood mechanism apparently directed to prevention of excessive blood prohormone levels. However, there is little evidence of feedback regulation of extrahepatic prohormone production.

[0006] The Vitamin D prohormones are further metabolized in the kidneys into potent hormones by an enzyme known as CYP27B1 (or 25-hydroxyvitamin D_3-1α-hydroxylase) located in the proximal kidney tubule. The prohormones 25-hydroxyvitamin D_2 and 24(S)-hydroxyvitamin D_2 are metabolized into hormones known as 1α,25-dihydroxyvitamin D_2 and 1α,24(S)-dihydroxyvitamin D_2. Likewise, 25-hydroxyvitamin D_3 is metabolized into a hormone known as 1α,25-dihydroxyvitamin D_3 (or calcitriol). These hormones are secreted by the kidneys into the blood for systemic delivery. The two 25-hydroxylated hormones, usually far more prominent in the blood than 1α,24(S)-dihydroxyvitamin D_2, are separately or collectively referred to as "1,25-dihydroxyvitamin D". Vitamin D prohormones can be metabolized into hormones outside of the kidneys in keratinocytes, lung epithelial cells, enterocytes, cells of the immune system (e.g., macrophages) and certain other cells containing CYP27B1 or similar enzymes, but such extrarenal hormone production is incapable of sustaining normal blood levels of 1,25-dihydroxyvitamin D in advanced CKD. Extrarenal hormone production permits intracellular concentrations of 1,25-dihydroxyvitamin D to exceed and be independent of blood levels of 1,25-dihydroxyvitamin D.

[0007] Blood levels of 1,25-dihydroxyvitamin D are precisely regulated by a feedback mechanism which involves PTH. The renal 1α-hydroxylase (or CYP27B1) is stimulated by PTH and inhibited by 1,25-dihydroxyvitamin D. When blood levels of 1,25-dihydroxyvitamin D fall, the parathyroid glands sense this change via intracellular Vitamin D receptors (VDR) and secrete PTH. The secreted PTH stimulates expression of renal CYP27B1 and, thereby, increases production of Vitamin D hormones. As blood concentrations of 1,25-dihydroxyvitamin D rise again, the parathyroid glands attenuate further PTH secretion. As blood PTH levels fall, renal production of Vitamin D hormones decreases. Rising blood levels of 1,25-dihydroxyvitamin D also directly inhibit further Vitamin D hormone production by CYP27B1. PTH secretion can be abnormally suppressed in situations where blood 1,25-dihydroxyvitamin D concentrations become excessively elevated, as can occur in certain disorders or more commonly as a result of bolus (usually intravenous) doses of Vitamin D hormone replacement therapies. Oversuppression of PTH secretion can cause or exacerbate disturbances in calcium homeostasis and has been linked to vascular calcification. The parathyroid glands and the renal CYP27B1 are so sensitive to changes in blood concentrations of Vitamin D hormones that serum 1,25-dihydroxyvitamin D is tightly controlled, fluctuating up or down by less than 20% during any 24-hour period. In contrast to renal production of Vitamin D hormones, extrarenal production is not under precise feedback control.

[0008] The Vitamin D hormones have essential roles in human health which are mediated by the intracellular VDR. In particular, the Vitamin D hormones regulate blood calcium levels by controlling intestinal absorption of dietary calcium and reabsorption of calcium by the kidneys. The Vitamin D hormones also participate in the regulation of cellular differentiation and growth and normal bone formation and metabolism. Further, Vitamin D hormones are required for the normal functioning of the musculoskeletal, immune and renin-angiotensin systems. Numerous other roles for Vitamin D hormones are being postulated and elucidated, based on the documented presence of intracellular VDR in nearly every human tissue.

[0009] The actions of Vitamin D hormones on specific tissues depend on the degree to which they bind to (or occupy) the intracellular VDR in those tissues. The three Vitamin D hormones specifically discussed herein have nearly identical affinities for the VDR and, therefore, have essentially equivalent VDR binding when present at the same intracellular concentrations. VDR binding increases as the intracellular concentrations of the hormones rise, and decreases as the intracellular concentrations fall. Intracellular concentrations of the Vitamin D hormones change in direct proportion to changes in blood hormone concentrations with the exception that in cells containing CYP27B1 (or similar enzymes), intracellular concentrations of the Vitamin D hormones also change in direct proportion to changes in blood and/or intracellular prohormone concentrations, as discussed above. In such cells, adequate intracellular prohormone concentrations can prevent reductions in intracellular 1,25-dihydroxyvitamin D concentrations due to low blood levels of 1,25-diydroxyvitamin D.

[0010] Vitamin D_2, Vitamin D_3 and their prohormonal forms have affinities for the VDR which are estimated to be at least 100-fold lower than those of the Vitamin D hormones. As a consequence, physiological concentrations of these hormone precursors exert little, if any, biological actions without prior metabolism to Vitamin D hormones. However, supraphysiological levels of these hormone precursors, especially the prohormones, in the range of 10 to 1,000 fold higher than normal, can sufficiently occupy the VDR and exert actions like the Vitamin D hormones.

[0011] Blood levels of Vitamin D_2 and Vitamin D_3 are normally present at stable, concentrations in human blood, given a sustained, adequate supply of Vitamin D from sunlight exposure and an unsupplemented diet. Slight, if any, increases in blood Vitamin D levels occur after meals since unsupplemented diets have low Vitamin D content, even those containing foods fortified with Vitamin D. The Vitamin D content of the human diet is so low that the National Institutes of Health (NIH) cautions "it can be difficult to obtain enough Vitamin D from natural food sources" [NIH, Office of Dietary Supplements, Dietary Supplement Fact Sheet: Vitamin D (2005)]. Almost all human Vitamin D supply comes from fortified foods, exposure to sunlight or from dietary supplements, with the last source becoming increasingly important. Blood Vitamin D levels rise only gradually, if at all, after sunlight exposure since cutaneous 7-dehydrocholesterol is modified by UV radiation to pre-Vitamin D_3 which undergoes thermal conversion in the skin to Vitamin D_3 over a period of several days before circulating in the blood.

[0012] Blood Vitamin D hormone concentrations also remain generally constant through the day in healthy individuals, but can vary significantly over longer periods of time in response to seasonal changes in sunlight exposure or sustained alterations in Vitamin D intake. Marked differences in normal Vitamin D hormone levels are commonly observed between healthy individuals, with some individuals having stable concentrations as low as approximately 20 pg/mL and others as high as approximately 70 pg/mL. Due to this wide normal range, medical professionals have difficulty interpreting isolated laboratory determinations of serum total 1,25-dihydroxyvitamin D; a value of 25 pg/mL may represent a normal value for one individual or a relative deficiency in another.

[0013] Transiently low blood levels of 1,25-dihydroxyvitamin D stimulate the parathyroid glands to secrete PTH for brief periods ending when normal blood Vitamin D hormone levels are restored. In contrast, chronically low blood levels of 1,25-dihydroxyvitamin D continuously stimulate the parathyroid glands to secrete PTH, resulting in a disorder known as secondary hyperparathyroidism. Chronically low hormone levels also decrease intestinal calcium absorption, leading to reduced blood calcium concentrations (hypocalcemia) which further stimulate PTH secretion. Continuously stimulated parathyroid glands become increasingly hyperplastic and eventually develop resistance to regulation by Vitamin D hormones. Without early detection and treatment, followed by consistent maintenance or preventative therapy, secondary hyperparathyroidism progressively increases in severity, causing debilitating metabolic bone diseases, including osteoporosis and renal osteodystrophy. Appropriate prophylactive therapy for early stage CKD can delay or prevent the development of secondary hyperparathyroidism.

[0014] Chronically low blood levels of 1,25-dihydroxyvitamin D develop when there is insufficient renal CYP27B1 to produce the required supply of Vitamin D hormones, a situation which commonly arises in CKD. The activity of renal CYP27B1 declines as the Glomerular Filtration Rate (GFR) falls below approximately 60 ml/min/1.73 m^2 due to the loss of functioning nephrons. In end-stage renal disease (ESRD), when the kidneys fail completely and hemodialysis is required for survival, renal CYP27B1 often becomes altogether absent. Any remaining CYP27B1 is greatly inhibited by elevated serum phosphorous (hyperphosphatemia) caused by inadequate renal excretion of dietary phosphorous.

[0015] Chronically low blood levels of 1,25-dihydroxyvitamin also develop because of a deficiency of Vitamin D prohormones, since renal hormone production cannot proceed without the required precursors. Prohormone production declines markedly when cholecalciferol and ergocalciferol are in short supply, a condition often described in the medical literature by terms such as "Vitamin D insufficiency", "Vitamin D deficiency" or "hypovitaminosis D". Therefore, measurement of prohormone (serum total 25-hydroxyvitamin D) levels in blood has become the accepted method among healthcare professionals to monitor Vitamin D status. Recent studies have documented that the great majority of CKD patients have low blood levels of 25-hydroxyvitamin D, and that the prevalence of Vitamin D insufficiency and deficiency increases as CKD progresses.

[0016] It follows that individuals most vulnerable to developing chronically low blood levels of 1,25-dihydroxyvitamin D are those with CKD. Most CKD patients typically have decreased levels of renal CYP27B1 and a shortage of 25-hydroxyvitamin D prohormones. Not surprisingly, most CKD patients develop secondary hyperparathyroidism. Unfortunately, early detection and treatment of secondary hyperparathyroidism in CKD is rare, let alone prevention.

[0017] The National Kidney Foundation (NKF) has recently focused the medical community's attention on the need for early detection and treatment of secondary hyperparathyroidism by publishing Kidney Disease Outcomes Quality Initiative (K/DOQI) Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease [*Am. J. Kidney Dis.* 42:S1-S202, 2003)]. The K/DOQI Guidelines identified the primary etiology of secondary hyperparathyroidism as chronically low blood levels of 1,25-dihydroxyvitamin and recommended regular screening in CKD Stages 3 through 5 for elevated blood PTH levels relative to stage-specific PTH target ranges, which for Stage 3 is 35-70 pg/mL (equivalent to 3.85-7.7 pmol/L), for Stage 4 is 70-110 pg/mL (equivalent to 7.7-12.1 pmol/L), and for Stage 5 is 150-300 pg/mL (equivalent to 16.5-33.0 pmol/L) (defined in K/DOQI Guideline No. 1). In the event that screening revealed an iPTH value to be above the ranges targeted for CKD Stages 3 and 4, the Guidelines recommended a follow-up evaluation of serum total 25-hydroxyvitamin D to detect possible Vitamin D insufficiency or deficiency. If 25-hydroxyvitamin D below 30 ng/mL was observed, the recommended intervention was Vitamin D repletion therapy using orally administered ergocalciferol. If 25-hydroxyvitamin D above 30 ng/mL was observed, the recommended intervention was Vitamin D hormone replacement therapy using oral or intravenous Vitamin D hormones or analogs.

[0018] Current Vitamin D hormone replacement therapies available for use in CKD patients contain 1,25-dihydroxyvitamin D_3, 19-nor-1,25-dihdroxyvitamin D_2, or 1-alpha-hydroxyvitamin D_2 and are formulated for quick or immediate release in the gastrointestinal tract or for bolus intravenous administration. When administered at chronically high doses (usually 0.25 to 2.0 mcg orally, or 1.0 to 10 mcg intravenously), as is usually required for adequate hormone replacement, these products can effectively restore serum total 1,25-dihydroxyvitamin D to levels above 20 pg/mL and lower iPTH by at least 30% in the majority of patients. However, they cannot be administered in high enough doses to control elevated iPTH in all patients and they sporadically cause side effects, including hypercalcemia, hyperphosphatemia, hyercalciuria and oversuppression of iPTH, in a significant minority of the patients. Health care professionals are cautious in raising the dose of these hormone replacement therapies for purposes of improving the control of secondary hyperparathyroidism in patients with excessive iPTH levels due to the increasing risk of causing such side effects.

[0019] As explained above, all CKD patients eventually develop decreased levels of renal CYP27B1 as kidney insufficiency becomes more severe, making it even more difficult, and eventually impossible, to treat secondary hyperparathyroidism with Vitamin D repletion therapies alone. The safe and effective use of Vitamin D hormone replacement therapies, therefore, is essential in the later stages of CKD.

[0020] Clearly, a novel alternative approach to Vitamin D hormone replacement for the treatment and prevention of secondary hyperparathyroidism in CKD Stages 3-5 is sorely needed, in view of the problems encountered with the currently available oral and intravenous Vitamin D hormone therapies.

[0021] BRIEF DESCRIPTION OF THE INVENTION

[0022] In one aspect the present invention provides a method of treating and preventing secondary hyperparathyroidism in CKD by increasing or maintaining blood concentrations of both 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D in a patient by administering 25-hydroxyvitamin D_3 with or without 25-hydroxyvitamin D_2 and, as necessary, 1,25-dihydroxyvitamin D_2 as a Vitamin D hormone replacement therapy. The blood concentrations of 25-hydroxyvitamin D are increased to and maintained at or above 30 ng/mL, with 25-hydoxyvitamin D_3 being the predominant hormone, and blood concentrations of serum total 1,25-dihydroxyvitamin D_2 are increased to or maintained within a patient's normal historical physiological range for serum total 1,25-dihydroxyvitamin D without causing side effects, including hypercalcemia, hyperphosphatemia, hypercalciuria and oversuppression of iPTH, in a significant minority of the patients.

[0023] In another aspect, the invention provides a method of concurrently lowering or maintaining plasma iPTH levels, increasing or maintaining serum calcium levels, maintaining serum phosphorous levels, increasing or maintaining serum 25-hydroxyvitamin D, or increasing or maintaining serum 1,25-dihydroxyvitamin D levels in a human patient by administering to the early stage CKD patient, 25-hydroxyvitamin D_3 with or without 25-hydroxyvitamin D_2 and, as necessary, 1,25-dihydroxyvitamin D_2, so that the blood concentrations of 25-hydroxyvitamin D are increased to and maintained at or above 30 ng/mL, with 25-hydoxyvitamin D_3 being the predominant hormone, and blood concentrations of 1,25-dihydroxyvitamin D are increased to or maintained within a patient's normal historical physiological range for 1,25-dihydroxyvitamin D.

[0024] In yet another aspect, the invention provides a method of reducing the risk of over suppression of plasma iPTH levels in a patient undergoing treatment for elevated levels of plasma iPTH, or maintenance/prevention therapy for secondary hyperparathyroidism by administering 25-hydroxyvitamin D_3 with or without 25-hydroxyvitamin D_2 and, as necessary, 1,25-dihydroxyvitamin D_2, so that the blood concentrations of 25-hydroxyvitamin D are increased to and maintained at or above 30 ng/mL, with 25-hydoxyvitamin D_3 being the predominant hormone, and blood concentrations of 1,25-dihydroxyvitamin D are increased to or maintained within a patient's normal historical physiological range for 1,25-dihydroxyvitamin D, and elevated plasma iPTH levels are decreased or controlled while avoiding an abnormally low bone turnover rate.

[0025] In another aspect, the invention provides a method of proactively administering 25-hydroxyvitamin D_3 with or without 25-hydroxyvitamin D_2, and/or

Vitamin D_3 with or without Vitamin D_2, to an early stage CKD patient having the potential to develop secondary hyperparathyroidism due to Vitamin D insufficiency or deficiency.

[0026] Given this invention, which is described in more detail herein, it becomes possible, for the first time, to (1) effectively and safely use 25-hydroxyvitamin D_3 with or without 25-hydroxyvitamin D_2, and/or Vitamin D_3 with or without Vitamin D_2, to treat secondary hyperparathyroidism due to Vitamin D insufficiency or deficiency in the early stages of CKD; (2) concurrently apply these Vitamin D repletion therapies and Vitamin D hormone replacement therapies for more effective treatment of secondary hyperparathyroidism in this population; (3) prevent the recurrence of secondary hyperparathyroidism due to Vitamin D insufficiency of deficiency after initial diagnosis and treatment with Vitamin D repletion therapies; and (4) prevent the development of Vitamin D insufficiency and deficiency altogether by proactive administration of Vitamin D repletion therapy.

[0027] A fuller appreciation of the specific attributes of this invention will be gained upon an examination of the following detailed description of preferred embodiments, and the appended claim. Before the embodiments of the invention are explained in detail, it is to be understood that the invention is not limited in its application to the details of construction and the arrangements of the components set forth in the following description. The invention is capable of other embodiments and of being practiced or being carried out in various ways. Also, it is understood that the phraseology and terminology used herein are for the purpose of description and should not be regarded as limiting. The use of “including”, “having” and “comprising” and variations thereof herein is meant to encompass the items listed thereafter and equivalents thereof as well as additional items and equivalents thereof.

DETAILED DESCRIPTION OF THE INVENTION

[0028] The present invention relates to treating and preventing secondary hyperparathyroidism and the underlying chronically low blood levels of 1,25-dihydroxyvitamin D by administering safe and effective amounts of Vitamin D repletion therapy with, as necessary, 1,25-dihydrovitamin D_2. It has been discovered that secondary hyperparathyroidism arising in CKD is frequently unresponsive to Vitamin D repletion therapy unless such therapy specifically elevates serum total 25-hydroxyvitamin D to levels of at least 30 ng/mL and consistently maintains such levels in a manner which ensures that the predominant circulating prohormone is 25-hydroxyvitamin D_3. Without ensuring the predominance of circulating 25-hydroxyvitamin D_3, adequate production of 1,25-dihydroxyvitamin D by the remaining renal CYP271B is not fully supported, making control of chronically elevated PTH (or secondary hyperparathyroidism) incomplete or unlikely. Current approaches to administering Vitamin D replacement therapies to CKD patients overwhelmingly favor or promote the elevation of serum total 25-hydroxyvitamin D in such a manner that 25-hydroxyvitamin D_2 becomes the predominant circulating prohormone, due to its perceived safety advantage.

[0029] It has been further found that elevated levels of circulating either 25-hydroxyvitamin D_2 or 25-hydroxyvitamin D_4, in the presence of 25-hydroxyvitamin D_3, do not strongly support the production of 1,25-dihydroxyvitamin D_2 or 1,25-dihydroxyvitamin D_4, respectively, and instead support the predominant production of other metabolites, including 24,25-dihydroxyvitamin D_2 and 24,25-dihydroxyvitamin D_4. Unlike 1,25-dihydroxyvitamin D_2 or 1,25-dihydroxyvitamin D_4, these alternative metabolites do not potently inhibit the secretion of PTH by the parathyroid glands in secondary hyperparathyroidism.

[0030] In one aspect the present invention consists of increasing and then maintaining blood concentrations of 25-hydroxyvitamin D at or above 30 ng/mL, and blood concentrations of 1,25-dihydroxyvitamin D to within a patient's normal historical physiological range for 1,25-dihydroxyvitamin D by administering 25-hydroxyvitamin D_3 with or without a lesser amount of 25-hydroxyvitamin D_2 and/or Vitamin D_3 with or without a lesser amount of Vitamin D_2. As noted hereinbefore, many circumstances can lead to chronically low blood levels of 1,25-dihydroxyvitamin D, including the development of CKD, living in northern latitudes and insufficient intake of cholecalciferol and/or ergocalciferol. It has been found that chronic treatment of those CKD patients in need thereof with appropriate, effective and progressively adjusted Vitamin D repletion therapy with, as necessary, 1,25-dihydroxyvitamin D_2, can provide blood concentrations of 25-hydroxyvitamin D consistently at or above 30 ng/mL, with 25-hydroxyvitamin D_3 being the predominant circulating hormone, and blood concentrations of 1,25-dihydroxyvitamin D consistently within the patient's normal historical physiological range, which together can reduce and often normalize elevated plasma PTH levels and subsequently maintain reduced or normalized plasma PTH levels.

[0031] In another aspect, the invention provides a method of concurrently lowering or maintaining plasma iPTH levels, increasing or maintaining serum calcium levels, maintaining serum phosphorous levels, increasing or maintaining serum 25-hydroxyvitamin D levels, and increasing or maintaining serum 1,25-dihydroxyvitamin D levels in a human patient by chronically administering to the patient appropriate, effective and progressively adjusted amounts of Vitamin D repletion therapy with, as necessary, one or more Vitamin D hormone replacement therapies. Many diseases manifest abnormal blood levels of one or more prohormones, hormones and minerals. In CKD, for example, patients may experience decreases in serum total 25-hydroxyvitamin D, and/or 1,25-dihydroxyvitamin D, increases in plasma iPTH, decreases in serum calcium and increases in serum phosphorous. Consistent therapeutic and, then, prophylactic treatment in accordance with the present invention presents concurrent leveling and/or maintaining of the prohormone, hormone and mineral levels.

[0032] In yet another aspect, the invention provides a method of proactively administering 25-hydroxyvitamin D_3 with or without a lesser amount of 25-hydroxyvitamin D_2, and/or Vitamin D_3 with or without a lesser amount of Vitamin D_2, to an early stage CKD patient having the potential to develop secondary hyperparathyroidism due to Vitamin D insufficiency or Vitamin D deficiency with the result that blood concentrations of 25-hydroxyvitamin D are maintained consistently at or above 30 ng/mL, with 25-hydroxyvitamin D_3 being the predominant circulating hormone, and blood concentrations of 1,25-dihydroxyvitamin D are maintained consistently within the patient's normal historical physiological range, and plasma PTH is maintained at reduced or normal levels.

[0033] Preferably blood concentrations of 25-hydroxyvitamin D are maintained consistently at or above 30 ng/mL, with 25-hydroxyvitamin D_3 being the predominant circulating hormone, for at least 14 days, at least 1 month, at least 30 days, at least 2 months, at least three months, at least 90 days, or at least 6 months. Further preferably, blood concentrations of 1,25-dihydroxyvitamin D are maintained consistently within the patient's normal historical physiological range, and plasma PTH is maintained at reduced or normal levels, for at least 14 days, at least 1 month, at least 30 days, at least 2 months, at least three months, at least 90 days, or at least 6 months.

[0034] "Vitamin D insufficiency and deficiency" is generally defined as having serum 25-hydroxyvitamin D levels below 30 ng/mL (equivalent to about 75 nmol/L) (National Kidney Foundation guidelines, NKF, Am. J. Kidney Dis. 42:S1-S202 (2003)).

[0035] The term "vitamin D_2 compound" as used herein refers to a precursor, analog or derivative of ergocalciferol, 25-hydroxyvitamin D_2 or 1,25-dihydroxyvitamin D_2.

[0036] The term "vitamin D_3 compound" as used herein refers to a precursor, analog or derivative of vitamin D_3 (cholecalciferol), 25-hydroxyvitamin D_3, or 1α,25-dihydroxyvitamin D_3, including, 1α-hydroxyvitamin D_3, that activates the vitamin D receptor or that can be metabolically converted in a human to a compound that activates the vitamin D receptor.

[0037] As used herein, the term "patient's normal historical physiological range of serum 1,25-dihydroxyvitamin D" refers to the average blood concentration range of 1,25-dihydroxyvitamin D of a patient based on at least two annual or biannual readings of serum 1,25-dihydroxyvitamin D levels taken while the kidneys are healthy.

[0038] As used herein the term "hypercalcemia" refers to condition in a patient wherein the patient has corrected serum levels of calcium above 10.2 mg/dL. Normal corrected serum levels of calcium for a human are between about 8.6 to 10.2 mg/dL.

[0039] As used herein the term "hyperphosphatemia" refers to a condition in a patient having normal kidney function, or Stage 1-4 CKD, wherein the patient has serum phosphorous levels above 4.6 mg/dL. In a patient who has Stage 5 CKD, hyperphosphatemia occurs when the patient has serum levels above 5.5 mg/dL. Normal values for serum phosphorous in a human are 2.4-4.5 mg/dL.

[0040] As used herein the term "over suppression of plasma iPTH" refers to a condition in a patient having adequate kidney function, or Stage 1-3 CKD, wherein the patient has levels of plasma iPTH below 15 pg/mL. In a patient having Stage 4 CKD, over suppression of plasma iPTH occurs when the patient has levels of plasma iPTH below 30 pg/mL. In a patient having Stage 5 CKD, over suppression of plasma iPTH occurs when the patient has levels of plasma iPTH below 150 pg/mL.

[0041] As used herein, the term "Vitamin D repletion therapy" refers to the administration to a patient of an effective amount of a vitamin D_3 compound with a vitamin D compound, e.g., cholecalciferol with or without a lesser amount of ergocalciferol, and/or 25-hydroxyvitamin D_3 with or without a lesser amount of 25-hydroxyvitamin D_2 via any route of administration.

[0042] As used herein, the term "Vitamin D hormone replacement therapy" refers to the administration to a patient of an effective amount of 1,25-dihydroxyvitamin D_2, 1,25-dihydroxyvitamin D_3, 1,25-dihydroxyvitamin D_4, or other metabolites and analogs of Vitamin D which can substantially occupy the intracellular VDR.

[0043] The term "therapeutically effective amount" depends on the patient's condition and is an amount effective to achieve a desired clinical effect, e.g. to maintain a laboratory test value within the normal range or the recommended range for that patient's condition, or an amount effective to reduce the occurrence or severity of a clinical sign or symptom of disease. In some embodiments, a therapeutically effective amount is an amount effective on average to maintain serum 25-hydroxyvitamin D levels or 25-hydroxyvitamin D_3 levels at about 30 ng/mL (equivalent to about 75 nmol/L) or higher. Such levels may be maintained for an extended period, for example at least one month, at least three months, at least six months, nine months, one year, or longer. In other embodiments, a therapeutically effective amount is an amount effective on average to achieve at least a 15%, 20%, 25% or 30% reduction in serum parathyroid hormone levels (iPTH) from baseline levels without treatment. In yet other embodiments, a therapeutically effective amount is an amount effective on average to reach CKD stage-specific iPTH target ranges which for Stage 3 is 35-70 pg/mL (equivalent to 3.85-7.7 pmol/L), for Stage 4 is 70-110 pg/mL (equivalent to 7.7-12.1 pmol/L), and for Stage 5 is 150-300 pg/mL (equivalent to 16.5-33.0 pmol/L) (defined in K/DOQI Guideline No. 1). When used in reference to an amount of a vitamin D_3 compound, "therapeutically effective" can refer either to the effective amount of vitamin D_3 supplement when administered alone, or to the effective amount of vitamin D_3 compound when administered in combination with a vitamin D_2 compound.

[0044] It also is specifically understood that any numerical value recited herein includes all values from the lower value to the upper value, i.e., all possible combinations of numerical values between the lowest value and the highest value enumerated are to be considered to be expressly stated in this application. For example, if a concentration range or a beneficial effect range is stated as 1% to 50%, it is intended that values such as 2% to 40%, 10% to 30%, or 1% to 3%, etc., are expressly enumerated in this specification. These are only examples of what is specifically intended.

[0045] Ergocalciferol, cholecalciferol, 25-hydroxyvitamin D_2 and/or 25-hydroxyvitamin D_3, 1,25-dihydroxyvitamin D_2,, and analogs thereof are useful as pharmacologically active compounds of this invention. The pharmacologically active compounds of this invention can be processed in accordance with conventional methods of pharmacy to produce pharmaceutical agents for administration to patients, e.g., in admixtures with conventional excipients such as pharmaceutically acceptable organic or inorganic carrier substances suitable for parenteral, enteral (e.g., oral), topical or transdermal application which do not deleteriously react with the active compounds. Suitable pharmaceutically acceptable carriers include, but are not limited to, water, salt (buffer) solutions, alcohols, gum arabic, mineral and vegetable oils, benzyl alcohols, polyethylene glycols, gelatin, carbohydrates such as lactose, amylose or starch, magnesium stearate, talc, silicic acid, viscous paraffin, perfume oil, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, hydroxy methylcellulose, polyvinyl pyrrolidone, etc.

[0046] The pharmaceutical preparations can be sterilized and, if desired, mixed with auxiliary agents, e.g., lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, coloring, flavoring and/or aromatic active compounds. If a pharmaceutically acceptable solid carrier is used, the dosage form of the analogs may be tablets, capsules, powders, suppositories, or lozenges. If a liquid carrier is used, soft gelatin capsules, transdermal patches, aerosol sprays, topical creams, syrups or liquid suspensions, emulsions or solutions may be the dosage form.

[0047] For parenteral application, particularly suitable are injectable, sterile solutions, preferably oily or aqueous solutions, as well as suspensions, emulsions, or implants, including suppositories. Ampoules are convenient unit dosages.

[0048] For enteral application, particularly suitable are tablets, dragées, liquids, drops, suppositories, or capsules such as soft gelatin capsules. A syrup, elixir, or the like can be used wherein a sweetened vehicle is employed.

[0049] Sustained or directed release compositions can be formulated, e.g., liposomes or those wherein the active compound is protected with differentially degradable coatings, such as by microencapsulation, multiple coatings, etc. It is also possible to freeze-dry the new compounds and use the lypolizates obtained, for example, for the preparation of products for injection. Transdermal delivery of pharmaceutical compositions of the compounds of the invention is also possible.

[0050] For topical application, there are employed as nonsprayable forms, viscous to semi-solid or solid forms comprising a carrier compatible with topical application and having a dynamic viscosity preferably greater than water. Suitable formulations include, but are not limited to, solutions, suspensions, emulsions, creams, ointments, powders, liniments, salves, aerosols, etc., which are, if desired, sterilized or mixed with auxiliary agents, e.g., preservatives, etc.

[0051] It is possible, if desired, to produce the metabolites of certain ones of the compounds of the invention, in particular by nonchemical means. For this purpose, it is possible to convert them into a suitable form for administration together with at least one vehicle or auxiliary and, where appropriate, combined with one or more other active compounds.

[0052] The dosage forms may also contain adjuvants, such as preserving or stabilizing adjuvants. They may also contain other therapeutically valuable substances or may contain more than one of the compounds specified herein and in the claims in admixture.

[0053] As described hereinbefore, Vitamin D repletion and Vitamin D hormone replacement therapies are preferably administered to the human patients in oral or intravenous dosage formulations. The administration of such therapies, in accordance with the present invention, can be on an episodic basis, suitably from daily, to 1 to 3 times a week. Suitably the dosage of Vitamin D replacement therapy or Vitamin D hormone replacement therapy is about 0.5 μg to about 400 μg per week, depending on the agent selected. Suitably such therapies can be given in a unit dosage form between about 0.5 μg to about 100 μg, or about 0.5 μg to about 10 μg in a pharmaceutically acceptable carrier per unit dosage. Episodic doses can be a single dose or, optionally, divided into 2-4 subdoses which, if desired, can be given, e.g., twenty minutes to an hour apart until the total dose is given.

[0054] Those of ordinary skill in the art will readily optimize effective doses and co-administration regimens as determined by good medical practice and the clinical condition of the individual patient. Regardless of the manner of administration, it will be appreciated that the actual preferred amounts of active compound in a specific case will vary according to the efficacy of the specific compound employed, the particular compositions formulated, the mode of application, and the particular situs and organism being treated. For example, the specific dose for a particular patient depends on age, sex, body weight, general state of health, on diet, on the timing and mode of administration, on the rate of excretion, and on medicaments used in combination and the severity of the particular disorder to which the therapy is applied. Dosages for a given patient can be determined using conventional considerations, e.g., by customary comparison of the differential activities of the subject compounds and of a known agent, such as by means of an appropriate conventional pharmacological protocol. A physician of ordinary skill can readily determine and prescribe the effective amount of the drug required to counter or arrest the progress of the condition. Optimal precision in achieving concentrations of drug within the range that yields efficacy without toxicity requires a regimen based on the kinetics of the drug's availability to target sites. This involves a consideration of the distribution, equilibrium, and elimination of a drug. The dosage of active ingredient in the compositions of this invention may be varied; however, it is necessary that the amount of the active ingredient be such that an efficacious dosage is obtained. The active ingredient is administered to patients (animal and human) in need of treatment in dosages that will provide optimal pharmaceutical efficacy.

[0055] Bulk quantities of Vitamin D and Vitamin D analogs in accordance with the present invention can be readily obtained in accordance with the many widely known processes.

[0056] The compositions, methods and kits of the invention are useful for treating any subject in need of vitamin D supplementation, either prophylactically to prevent vitamin D insufficiency or deficiency, or therapeutically to replete low serum vitamin 25(OH)D levels to normal range or above. The compositions and methods of the invention are also useful for preventing or treating secondary hyperparathyroidism resulting from low vitamin D levels. In general, serum 25(OH)D values less than 5 ng/mL indicate severe deficiency associated with rickets and osteomalacia. Although 30 ng/mL has been suggested as the low end of the normal range, more recent research suggests that PTH levels and calcium absorption are not optimized until serum total 25(OH)D levels reach approximately 40 ng/mL. [See also Vieth, R. Prog Biophys Mol Biol. 2006 Sep;92(1):26-32.] The term "subject" or "patient" as used herein includes humans, mammals (e.g., dogs, cats, rodents, sheep, horses, cows, goats), veterinary animals and zoo animals.

[0057] Patients in need of vitamin D supplementation include healthy subjects and subjects at risk for vitamin D insufficiency or deficiency, for example, subjects with stage 1, 2, 3, 4 or 5 chronic kidney disease; infants, children and adults that do not drink vitamin D fortified milk (e.g. lactose intolerant subjects, subjects with milk allergy, vegetarians who do not consume milk, and breast fed infants); subjects with rickets; subjects with dark skin (e.g., in the U.S., 42% of African American women between 15 and 49 years of age were vitamin D deficient compared to 4% of white women); the elderly (who have a reduced ability to synthesize vitamin D in skin during exposure to sunlight and also are more likely to stay indoors); institutionalized adults (who are likely to stay indoors, including subjects with Alzheimer's disease or mentally ill); subjects who cover all exposed skin (such as members of certain religions or cultures); subjects who always use sunscreen (e.g., the application of sunscreen with an Sun Protection Factor (SPF) of 8 reduces production of vitamin D by 95%, and higher SPFs may further reduce cutaneous vitamin D production); subjects with fat malabsorption syndromes (including but not limited to cystic fibrosis, cholestatic liver disease, other liver disease, gallbladder disease, pancreatic enzyme deficiency, Crohn's disease, inflammatory bowel disease, sprue or celiac disease, or surgical removal of part or all of the stomach and/or intestines); subjects with inflammatory bowel disease; subjects with Crohn's disease; subjects who have had small bowel resections; subjects with gum disease; subjects taking medications that increase the catabolism of vitamin D, including phenytoin, fosphenytoin, phenobarbital, carbamazepine, and rifampin; subjects taking medications that reduce absorption of vitamin D, including cholestyramine, colestipol, orlistat, mineral oil, and fat substitutes; subjects taking medications that inhibit activation of vitamin D, including ketoconazole; subjects taking medications that decrease calcium absorption, including corticosteroids; subjects with obesity (vitamin D deposited in body fat stores is less bioavailable); subjects with osteoporosis and/or postmenopausal women. According to the Institute of Medicine's report on the Dietary Reference Intakes for vitamin D, food consumption data suggest that median intakes of vitamin D for both younger and older women are below current recommendations; data suggest that more than 50% of younger and older women are not consuming recommended amounts of vitamin D. Optionally excluded from the methods of the invention are therapeutic treatment of subjects suffering from renal osteodystrophy (including osteomalacia and osteitis fibrosa cystica).

[0058] In other aspects, the compositions and methods of the invention are useful for prophylactic or therapeutic treatment of vitamin D-responsive diseases, i.e., diseases where vitamin D, 25(OH)D or active vitamin D (e.g., 1, $25(OH)_2D$) prevents onset or progression of disease, or reduces signs or symptoms of disease. Such vitamin D-responsive diseases include cancer (e.g., breast, lung, skin, melanoma, colon, colorectal, rectal, prostate and bone cancer). $1,25(OH)_2D$ has been observed to induce cell differentiation and/or inhibit cell proliferation in vitro for a number of cells. Vitamin D-responsive diseases also include autoimmune diseases, for example, type I diabetes, multiple sclerosis, rheumatoid arthritis, polymyositis, dermatomyositis, scleroderma, fibrosis, Grave's disease, Hashimoto's disease, acute or chronic transplant rejection, acute or chronic graft versus host disease, inflammatory bowel disease, Crohn's disease, systemic lupus erythematosis, Sjogren's Syndrome, eczema and psoriasis, dermatitis, including atopic dermatitis, contact dermatitis, allergic dermatitis and/or chronic dermatitis. Vitamin D-responsive diseases also include other inflammatory diseases, for example, asthma, chronic obstructive pulmonary disease, polycystic kidney disease

(PKD), polycystic ovary syndrome, pancreatitis, nephritis, hepatitis, and/or infection. Vitamin D-responsive diseases have also been reported to include hypertension and cardiovascular diseases. Thus, the invention contemplates prophylactic or therapeutic treatment of subjects at risk of or suffering from cardiovascular diseases, for example, subjects with atherosclerosis, arteriosclerosis, coronary artery disease, cerebrovascular disease, peripheral vascular disease, myocardial infarction, myocardial ischemia, cerebral ischemia, stroke, congestive heart failure, cardiomyopathy, obesity or other weight disorders, lipid disorders (e.g. hyperlipidemia, dyslipidemia including associated diabetic dyslipidemia and mixed dyslipidemia hypoalphalipoproteinemia, hypertriglyceridemia, hypercholesterolemia, and low HDL (high density lipoprotein)), metabolic disorders (e.g. Metabolic Syndrome, Type II diabetes mellitus, Type I diabetes mellitus, hyperinsulinemia, impaired glucose tolerance, insulin resistance, diabetic complication including neuropathy, nephropathy, retinopathy, diabetic foot ulcer and cataracts), and/or thrombosis.

[0059] The present invention is further explained by the following example which should not be construed by way of limiting the scope of the present invention. The following example demonstrates that the concomitant administration of Vitamin D repletion and Vitamin D hormone replacement therapies has improved efficacy in reducing or preventing elevated blood PTH levels as well as maintaining adequate and appropriate levels of serum calcium, serum phosphorous, serum total 25-hydroxyvitamin D and serum total 1,25-dihydroxyvitamin D.

Example 1: Efficacy Study in Patients With Stage 4 CKD and Secondary Hyperparathyroidism Associated With Vitamin D Insufficiency

[0060] The effectiveness of 25-hydroxyvitamin D_3 and, as necessary, 1,25-dihydroxyvitamin D_2 in restoring serum total 25-hydroxyvitamin D to optimal levels (> 30 ng/mL) and serum total 1,25-dihydroxyvitamin D to adequate levels (> 25 pg/mL) is examined in an open-ended study of adult male and female patients with Stage 4 CKD and secondary hyperparathyroidism associated with vitamin D insufficiency. Two formulations are used in the study. One of the formulations (Formulation #1) is a soft gelatin capsule containing 30 μg of 25-hydroxyvitamin D_3. The second formulation (Formulation #2) is a soft gelatin capsule containing 0.25 μg of 1,25-dihydroxyvitamin D_2.

A total of 100 subjects participate in this study, all of whom are aged 30 to 70 years and have serum 25-hydoxyvitamin D levels between 15 and 29 ng/mL (inclusive) and serum intact parathyroid hormone (iPTH) levels above the target levels published in the current K/DOQI Guidelines at the time of enrolment. All subjects abstain from taking other Vitamin D supplements for 60 days before study start and continuing through study termination, and from significant sun exposure. All subjects begin daily dosing with two capsules of Formulation #1. Serum total 25-hydroxyvitamin D is measured at biweekly intervals and serum iPTH is determined at quarterly invervals. After 1 month, the daily dosage of Formulation #1 is maintained unchanged in patients whose serum total 25-hydroxyvitamin D is between 50 and 90 ng/mL, increased by one capsule in patients whose serum total 25-hydroxyvitamin D is below 50 ng/mL, and decreased by one capsule per day in patients whose serum total 25-hydroxyvitamin D is above 90 ng/mL. Further adjustments in the daily dose are made as needed in order to maintain serum total 25-hydroxyvitamin D between 50 and 90 ng/mL. After 6 months, subjects whose serum iPTH levels are above K/DOQI targets also begin receiving a daily dose of one capsule of Formulation #2. The dosage of Formulation #2 is adjusted upwards in one capsule increments at monthly intervals until serum iPTH levels are lowered progressively into K/DOQI targets. Dosing with both Formulation #1 and #2 is continued indefinitely, provided that hypercalcemia, hypercalciuria and hyperphosphatemia do not develop, in which case appropriate adjustments in dosage are made. After 1 year, the subjects' ongoing serum total 25-hydroxyvitamin D levels are found to remain stable between 50 and 90 ng/mL, serum total 1,25-dihydroxyvitamin D levels are found to remain stable at levels that are within the subjects' normal historical range prior to the onset of advanced CKD and serum iPTH is found to remain stable at levels consistent with targets published in the K/DOQI Guidelines. The incidence of hypercalcemia, hypercalciuria and hyperphosphatemia are rare once stable dosing has been achieved.

What is claimed is:

1. A use of 25-hydroxyvitamin D_3 and optionally 25-hydroxyvitamin D_2 for the treatment of secondary hyperparathyroidism in a patient suffering from chronic kidney disease Stage 3 or Stage 4, wherein the 25-hydroxyvitamin D_3 and optionally 25-hydroxyvitamin D_2 are for use once a week, wherein the 25-hydroxyvitamin D_3 and optionally 25-hydroxyvitamin D_2 are formulated for sustained release and wherein the 25-hydroxyvitamin D_2, when used, is used in a lesser amount than the 25-hydroxyvitamin D_3.

2. A use of 25-hydroxyvitamin D_3 and optionally 25-hydroxyvitamin D_2 in the manufacture of a medicament for the treatment of secondary hyperparathyroidism in a patient suffering from chronic kidney disease Stage 3 or Stage 4, wherein the medicament is for use once a week, wherein the 25-hydroxyvitamin D_3 and optionally 25-hydroxyvitamin D_2 are formulated for sustained release and wherein the 25-hydroxyvitamin D_2, when used, is used in a lesser amount than the 25-hydroxyvitamin D_3.

3. The use of claim 1 or claim 2, wherein the patient suffering from chronic kidney disease Stage 3 or Stage 4 also has a serum total concentration of 25-hydroxyvitamin D less than 30 ng/ml.

4. The use of any one of claims 1-3, wherein the 25-hydroxyvitamin D_3 is for use in an amount between about 0.5 μg and about 400 μg per week.

5. The use of any one of claims 1-4, wherein the 25-hydroxyvitamin D_3 is for use in an amount between about 210 μg and about 630 μg per week.

6. The use of any one of claims 1-5, wherein the 25-hydroxyvitamin D_3 is for use transdermally.

7. A use of 25-hydroxyvitamin D_3 and optionally 25-hydroxyvitamin D_2 to treat and/or prevent secondary hyperparathyroidism in a patient suffering from chronic kidney disease, wherein the 25-hydroxyvitamin D_3 and optionally 25-hydroxyvitamin D_2 are formulated for sustained release and wherein the 25-hydroxyvitamin D_2, when used, is used in a lesser amount than the 25-hydroxyvitamin D_3, and wherein the patient is receiving one or more: medications

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that increase the catabolism of vitamin D; or phenytoin, or fosphenytoin, or phenobarbital, or carbamazepine, or rifampin; or one or more medications that reduce absorption of vitamin D; or cholestyramine, or colestipol, or orlistat, or a fat substitute; or one or more medications that inhibit activation of vitamin D; or ketoconazole; or one or more medications that decrease calcium absorption; or a corticosteroid; or any combination of the foregoing.

8. The use of claim 7, wherein the patient is receiving one or more medications that increase the catabolism of vitamin D, or phenytoin, or fosphenytoin, or phenobarbital, or carbamazepine, or rifampin.

9. The use of claim 8, wherein the patient is receiving phenytoin.

10. The use of claim 8, wherein the patient is receiving fosphenytoin.

11. The use of claim 8, wherein the patient is receiving phenobarbital.

12. The use of claim 8, wherein the patient is receiving carbamazepine.

13. The use of claim 8, wherein the patient is receiving rifampin.

14. The use of claim 7, wherein the patient is receiving one or more medications that reduce absorption of vitamin D, or cholestyramine, or colestipol, or orlistat, or a fat substitute.

15. The use of claim 14, wherein the patient is receiving cholestyramine.

16. The use of claim 14, wherein the patient is receiving colestipol.

17. The use of claim 14, wherein the patient is receiving orlistat.

18. The use of claim 14, wherein the patient is receiving a fat substitute.

19. The use of claim 7, wherein the patient is receiving one or more medications that inhibit activation of vitamin D, or ketoconazole.

20. The use of claim 19, wherein the patient is receiving ketoconazole.

21. The use of claim 7, wherein the patient is receiving one or more medications that decrease calcium absorption, or a corticosteroid.

22. The use of claim 21, wherein the patient is receiving a corticosteroid.

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