Open Access Mini-Review

Journal of Renal Endocrinology

J Renal Endocrinol 2018;4:e8.

http://www.jrenendo.com

Nickan Research Institute

Vitamin D deficiency in chronic renal failure patients; current knowledge and new trends

Mohammad Amin Nasouti[1*], Aref Nasouti[2]

Abstract

Chronic kidney disease (CKD), or chronic renal failure at final stages requires hemodialysis treatment. One of complication of these patients on hemodialysis and even CKD is the deficiency of vitamin D. Inadequate exposure to sun rays and poor dietary containing vitamin D can lead to its deficiency. Vitamin D deficiency in these patients may lead to osteomalacia in adult and rickets in children. Appropriate levels of 25(OH)D and parathyroid hormone, can decrease complication of extra-renal disease and mortality in both hemodialysis and chronic kidney disease patients.

Keywords: Vitamin D, Chronic kidney disease, Hemodialysis, Osteomalacia, Vitamin D deficiency

Citation: Nasouti MA, Nasouti A. Vitamin D deficiency in chronic renal failure patients; current knowledge and new trends. J Renal Endocrinol. 2018;4:e08.

Introduction

There are two primary forms of vitamin D including dermal and dietary (cholecalciferol), that principally have non-functional activity. For activation of this vitamin and playing its important roles on the human body, these two primary forms need to be activated by specific hydroxylase enzymes that are located in the liver and kidney. Vitamin D transfers by the bloodstream to the liver and by hydroxylase enzyme, it converts to 25(OH) D (calcidiol). This form of vitamin D (cholecalciferol), that is also a prohormone, has not affinity as much as an activated form of vitamin D for binding to vitamin D receptors. Then, calcidiol is converted to calcitriol by 1 alpha-hydroxylase enzyme in the kidney. Studies showed that not only kidney can convert vitamin D to the activated form, but also other cells in different organ have this ability. For example, some immune cells like monocytes and macrophages can convert calcidiol to calcitriol. However, in this situations, calcitriol acts as cytokine for stimulating immune system (1). In addition, it is believed that the local activation of vitamin D has some positive physiological effects like lowering risk of autoimmune disease and cancer. Vitamin D receptor (VDR) exists in the many cell types including skin, gonads, prostate, breast, brain and heart (2). According to the expression of VDR in many organs, it assumes that this vitamin has various roles on cellular stage of this organ. It has been detected that the expression of VDR will diminish with aging (3,4). Binding of calcitriol to this receptor, can activate various functions depending on related cell. Vitamin D has very important roles in the body such as balancing of calcium absorption in the gastrointestinal system, bone formation and function of parathyroid hormone.

As different cells can convert calcidiol to the active form of vitamin D (calcitriol), other cells can convert cholecalciferol to calcidiol. Except for 1-a hydroxylase in liver, other cells in colon, parathyroid glands and even activated macrophage have also this enzyme (2,5-7).

Materials and Methods

For this mini-review, we used a variety of sources including PubMed, Embase, Scopus and directory of open access journals (DOAJ). The search was performed by using combinations of the following key words and or their equivalents; vitamin D, chronic kidney disease, hemodialysis, osteomalacia, chronic renal failure, vitamin D deficiency, 25(OH)D, 1-a hydroxylase, calcitriol, vitamin D receptor, parathyroid glands, parathormone, PTH, calcidiol, kidney and cholecalciferol.

Causes of vitamin D deficiency

Chronic kidney disease (CKD) at final stages requires hemodialysis treatment. One of complication of these patients on hemodialysis and even CKD is the deficiency of vitamin D. Inadequate exposure to sun rays and poor dietary containing vitamin D can lead to its deficiency. Vitamin D deficiency in these patients may lead to osteomalacia in adult and rickets in children. While we can categorize vitamin D deficiency in normal population into different subgroups like race, geographic latitude,

Received: 4 November 2017, Accepted: 19 Dec 2017, ePublished: 10 January 2018

[1]Chronic Renal Failure Research Center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran. [2]Iran University of Medical Science, Tehran, Iran.

***Corresponding Author:** Mohammad Amin Nasouti, Email: moam790@dr.com

Implication for health policy/practice/research/ medical education

Appropriate levels of 25(OH)D and PTH can decrease complication of extra-renal disease and mortality in both hemodialysis and CKD patients.

the rate of sun exposure, the rate of skin pigmentation and intake of dietary vitamin D, however in CKD patients requiring hemodialysis, these causes have a wider range (8,9). For example, decreased physical and outdoor activity (10,11) and lower rate of cholecalciferol skin synthesis (12) may be responsible. In addition, deficiency of vitamin D 25-hydroxylase enzyme which is located in kidney, is another important factor for this deficiency. Furthermore deficiency of activated form of vitamin D or deficiency of calcidiol is also detectable in CKD patients. For determining normal serum levels of 25(OH)D for both general population and CKD patients, there is no established reference. It should be noted that serum levels of calcidiol lower than 50 and 25 nmol/L should be regarded as insufficiency and deficiency of this hormone respectively. However, some other studies suggested serum levels of 25(OH)D of 30 ng/mL as optimal values. This recommended level for 25(OH)D is accompanied by maximal suppression rate for parathyroid hormone hypersecretion and other aspects like decreased rate of fracture and even health situation of dialysis patients (12-18). Recent investigations for insufficiency and deficiency of 25(OH)D in patients with stage 5 CKD demonstrated that low 25(OH)D is prevalent in CKD. Additionally, other conditions like gender, high BMI level and decreased rate of sun exposure can worsen serum levels of 25(OH)D too (19).

Many researches showed deficiency of both 25(OH)D and 1,25(OH)2D in hemodialysis patients. This deficiency in both forms of vitamin D is an independent factor for mortality in such patients beside other factors like residual renal function that is known as a predictor factor mortality in hemodialysis patients (20,21).

Vitamin D deficiency and other hormones

Studies demonstrated a reverse relationship between serum level of PTH with circulating 25(OH)D seasonal serum level variation (22). In addition, an association between serum level of 25(OH)D and sun exposure is also confirmed, however the variation in serum level of 25(OH)D, did not cause a significant effect on calcium absorption, fraction and urinary calcium excretion in healthy men (23). However, seasonal variation of 25(OH) D has relationship and mineral density of skeletal system (24). Although serum level of 25(OH)D in hemodialysis patients is usually low, studies demonstrated that by correction of food regimen for hemodialysis patients, the decreased serum level of 25(OH)D will improve. For example, giving cholecalciferol in hemodialysis patients can improve their decreased serum level of calcidiol (25). In a prospective study, an inverse correlation between 25(OH)D level and future insulin resistance and hyperglycemia status was detected (26). Evaluation of another aspect of 25(OH)D on endocrine system showed a significant inverse relationship between risk of diabetic type 2 and serum level of 25(OH)D (27).

Vitamin D deficiency and cancer

Nowadays, pathological findings of cancer causes revealed some hidden actions of 25(OH)D on prevention of cancers. In a study in the United Kingdom, a relationship between increased rate of breast cancer and lower serum level of 25(OH)D was detected (28). In addition, the rate of both breast cancer incidence and its metastases were decreased with higher 25(OH)D serum level compared to group with lower serum level (29). Evaluation of cholecalciferol on esophageal squamous cell carcinomas revealed that increased concentration of 25(OH)D has a linear relationship with risk of esophageal squamous cell carcinomas. However, the increased risk of esophageal squamous cell carcinomas was observed in men but not in women population. This study could not find any correlation between the serum level of this vitamin with risk of gastric adenocarcinoma (30). It is possible that the deficiency of 25(OH)D has various effects on different population. As an example, the effect of 25(OH)D on ovarian cancer was different among women. Overweight women with decreased pre-diagnostic serum level of 25(OH)D have higher risk of ovarian cancer, but this study on thinner women did not show any association (31). Individuals with higher serum level of 25(OH)D than 33 ng/mL have about 50% decrease in the incidence of colorectal cancers (32,33).

Vitamin D deficiency and autoimmune disease

Except for cancers, autoimmune disease can also have a relationship with concentration of 25(OH)D. In a cohort study that divided individuals into three groups according to their 25(OH)D serum levels, in first group serum level was normal (more than 30 ng/mL) and second was in insufficient range lesser than 30 ng/mL and third group was in deficiency range (less than 15 ng/mL). In such study, comorbid autoimmune illness had a direct relationship with very low 25-hydroxyvitamin D. In the insufficient group, Fitzpatrick phototypes increased (34). The musculoskeletal system can also be under influence of vitamin D. A recent study carried out in the UK showed that the deficiency of vitamin D may be a common finding in patients who have psoriasis (35). Another study evaluating vitiligo and its associated comorbidity showed that more than half of patients have insufficiency of 25-OH vitamin D. These finding demonstrated the impact of vitamin D on autoimmune diseases (36).

Complication of 25(OH)D deficiency

There are numerous studies that evaluated serum level of 25(OH)D among many different diseases. Besides its significant effect of this vitamin on skeletal system,

it has been detected that low concentration of 25(OH) D is associated with worse prognosis of patients who have heart failure (37). There is also an increase in the incidence of cardiovascular disease and vitamin D deficiency (38-40). One of these reasons that deficiency of 25(OH)D has a significant effect on the cardiovascular system is due to detection of vitamin D receptors in many structures of this system like endothelial and cardiac myocytes (41). Regarding concentration of 25(OH) D and its association with systolic and diastolic blood pressure, there are no definitive studies. Some studies demonstrated its significant effect on blood pressure; however, other studies did not detect this result (42,43). Deficiency of this vitamin has also effect on psychological and mood disorders. Some studies evaluating serum level of 25(OH)D in such patients, showed that 25(OH) D has lesser concentration in patients having depression disorders. Interestingly, the severity of depression was directly related to low levels of 25(OH)D in such patients (44,45). Effect of this vitamin on muscular activity is also noted. In a study carried out on patients with lower serum level of 25(OH)D, the relationship of 25(OH)D level with inferior physical activity, low gait speed and balancing was demonstrated. Furthermore serum level of 25(OH)D less than 20 ng/mL can increase the risk of bone fracture in such patients (46). Decreased 25(OH)D has a negative impact on risk of surgery and complications of intestinal bowel disease (IBD). Importantly, the correction serum level of 25(OH)D decreased these complications. Correction of serum level of 25(OH)D had an ameliorative impact on inflammatory bowel disease (47). As deficiency of cholecalciferol has a relationship with prognosis and complication of several diseases, it is associated with early mortality among hemodialysis patients too (48). On the other hand, in a cohort study, parathyroid hormone (PTH) had a role in controlling of calcium, independent of vitamin D status. PTH acts on kidney and bone mass, which is associated with a higher mortality rate in aging population and hemodialysis patients too (49).

Conclusion

These studies showed that fine follow-up of some important elements like serum level of 25(OH)D and PTH can decrease complication of extra-renal disease and mortality in both hemodialysis and CKD patients.

Authors' contribution

MAN and AN contributed equally to wrote the manuscript.

Conflicts of interest

The authors declare no conflict of interest.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

Funding/Support

None.

References

1. Adams JS, Hewison M. Update in vitamin D. J Clin Endocrinol Metab. 2010;95:471-8.
2. Holick MF. Sunlight and vitamin D for bone health and prevention of autoimmune diseases, cancers, and cardiovascular disease. Am J Clin Nutr. 2004;80:1678S-88S.
3. Bischoff-Ferrari HA, Borchers M, Gudat F, Durmuller U, Stahelin HB, Dick W. Vitamin D receptor expression in human muscle tissue decreases with age. J Bone Miner Res. 2004;19:265-9.
4. Bischoff HA, Borchers M, Gudat F, Duermueller U, Theiler R, Stahelin HB, et al. In situ detection of 1,25-dihydroxyvitamin D3 receptor in human skeletal muscle tissue. Histochem J. 2001;33:19-24.
5. Segersten U, Holm PK, Bjorklund P, Hessman O, Nordgren H, Binderup L, et al. 25-Hydroxyvitamin D3 1alpha-hydroxylase expression in breast cancer and use of non-1alpha-hydroxylated vitamin D analogue. Breast Cancer Res. 2005;7:R980-6.
6. Correa P, Segersten U, Hellman P, Akerstrom G, Westin G. Increased 25-hydroxyvitamin D3 1alpha-hydroxylase and reduced 25-hydroxyvitamin D3 24-hydroxylase expression in parathyroid tumors--new prospects for treatment of hyperparathyroidism with vitamin d. J Clin Endocrinol Metab. 2002;87:5826-9.
7. Segersten U, Correa P, Hewison M, Hellman P, Dralle H, Carling T, et al. 25-hydroxyvitamin D(3)-1alpha-hydroxylase expression in normal and pathological parathyroid glands. J Clin Endocrinol Metab. 2002;87:2967-72.
8. Mager DR, Jackson ST, Hoffmann MR, Jindal K, Senior PA. Vitamin D3 supplementation, bone health and quality of life in adults with diabetes and chronic kidney disease: Results of an open label randomized clinical trial. Clin Nutr. 2017;36:686-696. doi: 10.1016/j.clnu.2016.05.012.
9. Holick MF. Vitamin D for health and in chronic kidney disease. Semin Dial. 2005;18:266-75.
10. Clayton P, Singer R. 25-Hydroxyvitamin D levels in prevalent Australian dialysis patients. Nephrology (Carlton). 2009;14:554-9.
11. Korkor AB, Eastwood D, Bretzmann C. Effects of gender, alcohol, smoking, and dairy consumption on bone mass in Wisconsin adolescents. WMJ. 2009;108:181-8.
12. Michaud J, Naud J, Ouimet D, Demers C, Petit JL, Leblond FA, et al. Reduced hepatic synthesis of calcidiol in uremia. J Am Soc Nephrol. 2010;21:1488-97.
13. Kimlin M, Harrison S, Nowak M, Moore M, Brodie A, Lang C. Does a high UV environment ensure adequate vitamin D status? J Photochem Photobiol B. 2007;89:139-47.
14. Bischoff-Ferrari HA, Giovannucci E, Willett WC, Dietrich T, Dawson-Hughes B. Estimation of optimal serum concentrations of 25-hydroxyvitamin D for multiple health outcomes. Am J Clin Nutr. 2006;84:18-28.
15. Martins D, Wolf M, Pan D, Zadshir A, Tareen N, Thadhani R, et al. Prevalence of cardiovascular risk factors and the serum levels of 25-hydroxyvitamin D in the United States: data from the Third National Health and Nutrition Examination Survey. Arch Intern Med. 2007;167:1159-65.
16. Martins D, Tareen N, Zadshir A, Pan D, Vargas R, Nissenson A, et al. The association of poverty with the prevalence of albuminuria: data from the Third National Health and Nutrition Examination Survey (NHANES III). Am J Kidney Dis. 2006;47:965-71.
17. Zadshir A, Tareen N, Pan D, Norris K, Martins D. The prevalence of hypovitaminosis D among US adults: data from the NHANES III. Ethn Dis. 2005;15:S5-97-101.
18. Hayati F, Nasouti MA, Shayanpour S, Ahmadi Halili S, Karimpourian H, Mousavi ZB. Vitamin D and chronic kidney disease. J Parathyr Dis. 2016;4:25-30.
19. Del Valle E, Negri AL, Aguirre C, Fradinger E, Zanchetta JR. Prevalence of 25(OH) vitamin D insufficiency and deficiency in chronic kidney disease stage 5 patients on hemodialysis. Hemodial Int. 2007;11:315-21.

20. Wolf M, Shah A, Gutierrez O, Ankers E, Monroy M, Tamez H, et al. Vitamin D levels and early mortality among incident hemodialysis patients. Kidney Int. 2007;72:1004-13.
21. Hayati F, Nasouti MA, Shayanpour S, Halili SA, Karimpourian H, Mousavi ZB**.** Survival of patients with end-stage renal disease in Iran. Ann Res Dial. 2016;1:e01.
22. Vanderschueren D, Gevers G, Dequeker J, Geusens P, Nijs J, Devos P, et al. Seasonal variation in bone metabolism in young healthy subjects. Calcif Tissue Int. 1991;49:84-9.
23. Barger-Lux MJ, Heaney RP**.** Effects of above average summer sun exposure on serum 25-hydroxyvitamin D and calcium absorption. J Clin Endocrinol Metab. 2002;87:4952-6.
24. Rosen CJ, Morrison A, Zhou H, Storm D, Hunter SJ, Musgrave K, et al. Elderly women in northern New England exhibit seasonal changes in bone mineral density and calciotropic hormones. Bone Miner. 1994;25:83-92.
25. Boylan M, Behrens J, Burt B, Clements L, Pannell R, Macha L, et al. Mean serum 25 hydroxy vitamin D levels are higher in hemodialysis subjects given a renal multivitamin with cholecalciferol at dialysis. Journal of the Academy of Nutrition and Dietetics. 2012;112:A36.
26. Forouhi NG, Luan Ja, Cooper A, Boucher BJ, Wareham NJ**.** Baseline serum 25-hydroxy vitamin d is predictive of future glycemic status and insulin resistance the medical research council ely prospective study 1990–2000. Diabetes. 2008;57:2619-25.
27. Song Y, Wang L, Pittas AG, Del Gobbo LC, Zhang C, Manson JE, et al. Blood 25-hydroxy vitamin D levels and incident type 2 diabetes a meta-analysis of prospective studies. Diabetes Care. 2013;36:1422-8.
28. Lowe LC, Guy M, Mansi JL, Peckitt C, Bliss J, Wilson RG, et al. Plasma 25-hydroxy vitamin D concentrations, vitamin D receptor genotype and breast cancer risk in a UK Caucasian population. Eur J Cancer. 2005;41:1164-9.
29. Goodwin P, Ennis M, Pritchard K, Koo J, Hood N, Lunenfeld S**.** Vitamin D deficiency is common at breast cancer diagnosis and is associated with a significantly higher risk of distant recurrence and death in a prospective cohort study of T1-3, N0-1, M0 BC. J Clin Oncol. 2008;26:511.
30. Chen W, Dawsey S, Qiao Y, Mark S, Dong Z, Taylor P, et al. Prospective study of serum 25 (OH)-vitamin D concentration and risk of oesophageal and gastric cancers. Br J Cancer. 2007;97:123-8.
31. Tworoger SS, Lee I-M, Buring JE, Rosner B, Hollis BW, Hankinson SE**.** Plasma 25-hydroxyvitamin D and 1, 25-dihydroxyvitamin D and risk of incident ovarian cancer. Cancer Epidemiol Biomarkers Prev. 2007;16:783-8. doi: 10.1158/1055-9965.EPI-06-0981
32. Gorham ED, Garland CF, Garland FC, Grant WB, Mohr SB, Lipkin M, et al. Vitamin D and prevention of colorectal cancer. J Steroid Biochem Mol Biol. 2005;97:179-94.
33. Cross HS, Bises G, Lechner D, Manhardt T, Kallay E**.** The Vitamin D endocrine system of the gut--its possible role in colorectal cancer prevention. J Steroid Biochem Mol Biol. 2005;97:121-8.
34. Silverberg JI, Silverberg AI, Malka E, Silverberg NB**.** A pilot study assessing the role of 25 hydroxy vitamin D levels in patients with vitiligo vulgaris. J Am Acad Dermatol. 2010;62(6):937-41.
35. Gisondi P, Rossini M, Di Cesare A, Idolazzi L, Farina S, Beltrami G, et al. Vitamin D status in patients with chronic plaque psoriasis. Br J Dermatol. 2012;166:505-10.
36. Sheth VM, Guo Y, Qureshi AA**.** Comorbidities associated with vitiligo: a ten-year retrospective study. Dermatology. 2013;227:311-5.
37. Liu LC, Voors AA, van Veldhuisen DJ, van der Veer E, Belonje AM, Szymanski MK, et al. Vitamin D status and outcomes in heart failure patients. Eur J Heart Fail. 2011;13:619-25.
38. Wang TJ, Pencina MJ, Booth SL, Jacques PF, Ingelsson E, Lanier K, et al. Vitamin D deficiency and risk of cardiovascular disease. Circulation. 2008;117:503-11.
39. Ohman K, Larsson T, Spaak J**.** [Vitamin D deficiency in kidney failure. Risk factor for cardiovascular disease]. Lakartidningen. 2010;107:2884-7.
40. Anderson JL, May HT, Horne BD, Bair TL, Hall NL, Carlquist JF, et al. Relation of vitamin D deficiency to cardiovascular risk factors, disease status, and incident events in a general healthcare population. Am J Cardiol. 2010;106:963-8.
41. O'Connell TD, Berry JE, Jarvis A, Somerman M, Simpson R**.** 1, 25-Dihydroxyvitamin D3 regulation of cardiac myocyte proliferation and hypertrophy. Am J Physiol. 1997;272:H1751-8. doi: 10.1152/ajpheart.1997.272.4.H1751.
42. Judd SE, Nanes MS, Ziegler TR, Wilson PW, Tangpricha V**.** Optimal vitamin D status attenuates the age-associated increase in systolic blood pressure in white Americans: results from the third National Health and Nutrition Examination Survey. Am J Clin Nutr. 2008;87:136-41.
43. Snijder M, Lips P, Seidell J, Visser M, Deeg D, Dekker J, et al. Vitamin D status and parathyroid hormone levels in relation to blood pressure: a population-based study in older men and women. J Intern Med. 2007;261:558-65.
44. Hoogendijk WJ, Lips P, Dik MG, Deeg DJ, Beekman AT, Penninx BW. Depression is associated with decreased 25-hydroxyvitamin D and increased parathyroid hormone levels in older adults. Arch Gen Psychiatry. 2008;65:508-12.
45. Jorde R, Waterloo K, Saleh F, Haug E, Svartberg J**.** Neuropsychological function in relation to serum parathyroid hormone and serum 25–hydroxyvitamin D levels. J Neurol. 2006;253:464-70.
46. Gerdhem P, Ringsberg K, Obrant K, Akesson K**.** Association between 25-hydroxy vitamin D levels, physical activity, muscle strength and fractures in the prospective population-based OPRA Study of Elderly Women. Osteoporosis Int. 2005;16:1425-31. doi: 10.1007/s00198-005-1860-1.
47. Ananthakrishnan AN, Cagan A, Gainer VS, Cai T, Cheng S-C, Savova G, et al. Normalization of plasma 25-hydroxy vitamin D is associated with reduced risk of surgery in Crohn's disease. Inflamm Bowel Dis. 2013;19:1921-7. doi: 10.1097/MIB.0b013e3182902ad9.
48. Wolf M, Shah A, Gutierrez O, Ankers E, Monroy M, Tamez H, et al. Vitamin D levels and early mortality among incident hemodialysis patients. Kidney Int. 2007;72:1004-13.
49. Sambrook P, Chen J, March L, Cameron I, Cumming R, Lord S, et al. Serum parathyroid hormone is associated with increased mortality independent of 25-hydroxy vitamin d status, bone mass, and renal function in the frail and very old: a cohort study. J Clin Endocrinol Metab. 2004;89:5477-81. doi: 10.1210/jc.2004-0307