Published in final edited form as:

Curr Opin Nephrol Hypertens. 2008 November ; 17(6): 566–572. doi:10.1097/MNH.0b013e32830fe377.

Vitamin D and glucose metabolism in chronic kidney disease

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Abstract

Purpose of review—Impaired glucose metabolism is common in chronic kidney disease and contributes to poor clinical outcomes. Vitamin D may improve insulin secretion and insulin sensitivity, thus helping to prevent cardiovascular disease and death.

Recent findings—Mounting evidence from observational studies links vitamin D with both glucose metabolism and decreased mortality. Intervention studies assessing effects of vitamin D therapy on glucose metabolism have yielded mixed results.

Summary—Vitamin D therapy holds promise for improving health outcomes in chronic kidney disease. Improved glucose metabolism is one potential mechanism through which vitamin D may exert beneficial effects. However, further data from clinical trials are needed to test whether vitamin D has clinically relevant long-term effects on glucose metabolism and overall clinical outcomes.

Keywords

vitamin D; glucose intolerance; insulin resistance; chronic kidney disease

Introduction

People with chronic kidney disease (CKD) have a markedly increased mortality rate. Treatment with vitamin D may improve health outcomes. Recently, potential pleiotropic actions of vitamin D, beyond those traditionally described for maintenance of bone health, have attracted increasing interest. As one of these pleiotropic actions, vitamin D may improve glucose metabolism, which may in turn help prevent cardiovascular disease and death. The purpose of this review is to examine the evidence supporting a role for vitamin D therapy in improving glucose metabolism in CKD, highlighting advances over the last year.

Vitamin D deficiency in CKD

In healthy individuals, cutaneous synthesis is the predominant source of vitamin D, with smaller quantities coming from diet.¹ Cholecalciferol and ergocalciferol from these sources are converted in the liver to 25-hydroxyvitamin D (25-OHD), and circulating 25-OHD reflects cutaneous and dietary vitamin D intake. 25-OHD is filtered at the glomerulus and actively reabsorbed into renal tubular cells via megalin and cubulin, where it is converted to the potent hormone 1,25-dihydroxyvitamin D (calcitriol) by the enzyme 1- α hydroxylase.²

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Vitamin D metabolism is profoundly disordered in CKD. (In this review, “CKD” encompasses all stages of disease, including stages 1–5 CKD and ESRD, unless otherwise specified.) Abnormalities begin during early CKD stages, i.e. stage 3 or sooner, and progress as renal function declines.³ The central feature of this process is a decline in circulating calcitriol, which occurs early and is due to diminished 1- α hydroxylase substrate, mass, and activity (Figure 1).^{3, 4} While CKD is not an independent risk factor for 25-OHD insufficiency, it is clear that low 25-OHD concentrations are common in all CKD stages.^{5–7} Contributing factors may include decreased cutaneous synthesis (due to older age, comorbidities, and decreased physical activity), decreased dietary intake of fortified dairy products, obesity, and renal 25-OHD losses, which are most severe with heavy proteinuria.^{4, 8, 9} Diminished 1- α hydroxylase activity is probably the most important cause of declining calcitriol levels in CKD. Hyperphosphatemia, hyperuricemia, metabolic acidosis, and diabetes are associated with decreased 1- α hydroxylase activity.^{3, 4, 10–12} Elevated levels of fibroblast growth factor-23, which act to maintain serum phosphorous concentration as GFR falls, potentially suppress 1- α hydroxylase activity.^{13, 14}

Vitamin D deficiency and clinical outcomes

Patients with CKD have a markedly increased mortality rate, due in large part to increased risk for cardiovascular disease (CVD).^{15, 16} Vitamin D deficiency may contribute to poor clinical outcomes. Recently, low circulating 25-OHD and calcitriol concentrations were associated with increased risk for short-term mortality among incident hemodialysis patients,⁶ and low circulating 25-OHD levels were associated with increased risk for long-term CVD events in the general population.¹⁷ Moreover, a number of cohort studies have reported that treatment with calcitriol or an activated vitamin D analogue is associated with decreased risk for mortality and CVD events in CKD. Specifically, three large studies have reported an approximate 20% lower risk of death among chronic hemodialysis patients treated with intravenous calcitriol or its analogues.^{18–20} Two studies have observed 26% and 65% lower mortality risks in stage 3–5 CKD patients treated with oral calcitriol.^{21, 22} It has been suggested that vitamin D may slow progression of CKD,^{22, 23} though this finding is not consistent across studies.²¹

Why might vitamin D have broad health benefits? Vitamin D receptors are present throughout the body in diverse tissues, and hundreds of human genes contain vitamin D response elements.²⁴ Pleiotropic actions have been described for vitamin D, beyond those traditionally described for maintenance of bone health (Figure 2).²⁴ These include suppression of the renin-angiotensin-aldosterone system and blood pressure reduction as well as modulation of immune function and cellular proliferation.^{24–27} Additional beneficial effects prior to ESRD may include podocyte survival, albuminuria reduction, and prevention of glomerulosclerosis.^{28–30} These important potential mechanisms are beyond the scope of this review. Here, focus is placed on the potential benefit of vitamin D on glucose metabolism in CKD.

Glucose metabolism in CKD

In general, glucose metabolism can be impaired by defects in insulin secretion (pancreatic beta cell) and/or defects in insulin sensitivity (muscle and/or liver). Either type of defect, or both in combination, may result in hyperglycemia (elevated fasting glucose or hemoglobin A1c) and diminished glucose tolerance (elevated circulating glucose concentrations after an oral or intravenous glucose challenge). Thus, fasting glucose measurements and oral glucose tolerance tests are routinely used to identify clinical disease, e.g. type 2 diabetes.³¹ More invasive diagnostic tests can be used to define underlying pathophysiology, usually for research purposes.³² These tests include glucose clamp studies and the intravenous glucose tolerance test (IVGTT). In addition, fasting insulin concentrations or indices calculated from fasting insulin and glucose (e.g. the Homeostasis Model Assessment, HOMA33), can be used to estimate insulin sensitivity under basal conditions in large epidemiologic studies.

The hyperinsulinemic euglycemic clamp procedure is the gold standard for quantifying insulin sensitivity.^{32, 34} During administration of exogenous insulin, an infusion of glucose is titrated to a rate which maintains peripheral glucose concentration at the normal fasting level. In this setting, the glucose infusion rate equals the rate of glucose utilization by the body, a measure of insulin sensitivity. In the hyperglycemic clamp, insulin secretion is measured in response to a steady, high concentration of glucose maintained via titrated glucose infusion. Insulin sensitivity can also be calculated from hyperglycemic clamp studies by relating glucose infusion rate to insulin concentration. In the IVGTT, glucose and insulin concentrations are observed after a standard intravenous glucose bolus. The insulin response reflects insulin secretion, while modeling relates glucose disappearance to insulin concentrations to calculate insulin sensitivity.³⁵

Glucose metabolism is frequently impaired in CKD.³⁶ In ESRD, defects in insulin sensitivity (i.e. insulin resistance) appear to be the most profound disturbance, as demonstrated by deFronzo et al using euglycemic and hyperglycemic clamp techniques.³⁴ Specifically, ESRD is characterized by reduced insulin-mediated glucose uptake in skeletal muscle.³⁷ Some ESRD patients are able to compensate for insulin resistance by increasing insulin secretion. However, defects in insulin secretion are also common in ESRD.^{34, 38} A recent epidemiologic study using data from the Third National Health and Nutrition Examination Survey (NHANES III) reported that insulin resistance (elevated fasting insulin, hemoglobin A1c, and HOMA-insulin resistance score) was also associated with CKD in its earlier stages.³⁹ It is not clear whether impaired glucose metabolism contributes to the pathogenesis of CKD and its progression (in the absence of overt diabetes), whether impaired renal function causes impaired glucose metabolism, or both.

Impaired glucose metabolism is an established risk factor for CVD and mortality, and thus represents an important potential therapeutic target in CKD. Among nondiabetic Modification of Diet in Renal Disease Study participants with stage 3–4 CKD, higher hemoglobin A1c (presumably representing mild chronic hyperglycemia) was associated with increased mortality over long-term follow-up.⁴⁰ Among ESRD patients with diabetes, most studies have observed that higher hemoglobin A1c levels are associated with increased mortality.^{41–45} Insulin resistance and frank hyperglycemia may lead to CVD and mortality through endothelial dysfunction, renin-angiotensin-aldosterone system activation, increased formation of reactive oxygen species, dyslipidemia, and systemic inflammation.³⁶

Vitamin D and glucose metabolism

Existing data suggest that vitamin D may have beneficial effects on both insulin secretion and insulin sensitivity (Figure 3). In seminal work by Norman et al, administration of cholecalciferol to vitamin D-deficient rats more than doubled insulin secretion from isolated perfused pancreas.⁴⁶ Subsequent studies have suggested that the mechanism for this effect is increased insulin release through stimulation of intracellular free calcium.⁴⁷ Modulation of the immune system has been proposed as an additional mechanism through which vitamin D may preserve long-term beta-cell function (and prevent type 1 diabetes), and vitamin D could potentially protect beta cells through effects on cell proliferation, differentiation, and apoptosis.²⁴ Vitamin D may also affect insulin sensitivity through actions on the insulin receptor. A vitamin D response element has been described in the promoter region of the human insulin receptor gene, and calcitriol stimulated insulin receptor expression and insulin responsiveness for glucose transport in cultured human promonocytic cells.^{48–50}

A large number of cross-sectional human studies have demonstrated associations of vitamin D deficiency with impaired glucose metabolism. For example, circulating 25-hydroxyvitamin D concentrations have been directly correlated with glucose tolerance, beta-cell function, and

insulin sensitivity, measured using oral glucose tolerance tests and hyperglycemic clamps.^{51, 52} In NHANES III, lower circulating 25-hydroxyvitamin D concentrations were independently associated with higher HOMA-insulin resistance scores, the metabolic syndrome, and overt diabetes.^{5, 53, 54} These cross-sectional studies suggest that effects of vitamin D on insulin secretion and/or sensitivity observed in animal-experimental studies may be clinically relevant. They do not demonstrate causality, but they do raise the important question whether vitamin D therapy improves glucose metabolism in humans. This question must be addressed with clinical trials.

Clinical trials evaluating vitamin D therapy and glucose metabolism

Clinical trials of vitamin D in CKD have focused primarily on parathyroid hormone, calcium, and phosphorous. However, glucose metabolism has been examined as an outcome in a number of small studies of maintenance hemodialysis patients (Table 1).^{55–63} Each of these studies employed before-after treatment comparisons to demonstrate improvement of glucose metabolism after a relatively short duration of calcitriol therapy. In studies which included a comparison group without kidney disease, measures of glucose metabolism were substantially worse among hemodialysis patients and returned to normal or near-normal with calcitriol.^{56–61, 63} As a group, these studies demonstrate the principle that vitamin D therapy favorably alters glucose metabolism in ESRD. However, the long-term effects of vitamin D on glucose metabolism in ESRD and earlier stages of CKD, and how these effects translate to clinical health outcomes, are not clear.

Further data regarding vitamin D interventions and glucose metabolism are available in the general population. This subject was recently reviewed.⁶⁴ Spanning 1984–2005, five controlled trials evaluated effects of vitamin D compounds on glucose metabolism. These trials were generally small (n = 14–151), enrolled study populations with heterogeneous baseline vitamin D and diabetes status, treated participants with different compounds for varying lengths of time (4 days–2 years), and assessed glucose metabolism using diverse methods. Results of these studies were mixed and inconclusive.

Three recent studies in people without CKD provide additional data. First, a meta-analysis of clinical trials including 57,311 participants, predominantly post-menopausal women, reported that vitamin D supplementation (cholecalciferol or ergocalciferol) was associated with a statistically significant 7% reduction in total mortality.⁶⁵ Effects on glucose metabolism were not reported for evaluation as a potential mediator. Second, effects of cholecalciferol plus calcium supplementation (700 u plus 500 mg daily, respectively) on glucose metabolism were evaluated among 314 postmenopausal women as a post-hoc analysis of a three-year trial designed for bone-related outcomes.⁶⁶ Benefits with regard to changes in fasting glucose and insulin sensitivity (estimated using HOMA) were observed for 92 women with impaired fasting glucose at baseline, but not for women with normal fasting glucose at baseline. Third, the effect of cholecalciferol plus calcium supplementation (400 u plus 1000 mg daily, respectively) on the risk of incident drug-treated diabetes over seven years of follow-up was evaluated among 33,951 post-menopausal women who participated in the Women's Health Initiative (WHI) Calcium/Vitamin D Trial.⁶⁷ Results of this study were robustly null, with a hazard ratio of 1.01 (95% confidence interval 0.94, 1.10) and no effects observed in subgroups, sensitivity analyses, or analyses of fasting glucose and insulin levels. A potential limitation of the WHI trial is the low prescribed dose of vitamin D.

Synthesizing the heterogeneous data provided by clinical trials of vitamin D and glucose metabolism is challenging, but several conclusions can be made. Data from the hemodialysis population consistently suggest that calcitriol improves short-term insulin secretion and insulin sensitivity in ESRD. Data addressing long-term outcomes are only available in the general

population, in which vitamin D supplementation may lead to a small but significant improvement in mortality but did not appear to prevent the development of diabetes in the largest clinical trial to date (the WHI). One potential explanation is that patients with CKD may derive more benefit from vitamin D interventions, given their more profound deficiencies in vitamin D at baseline. In particular, vitamin D therapy may be most effective when intrinsic 1- α hydroxylase activity is most impaired. Further long-term clinical trials in CKD are warranted to test this hypothesis.⁶⁸ The form of administered vitamin D may also be important. It is not clear whether/when calcitriol or activated vitamin D analogues are needed, instead of or in addition to cholecalciferol or ergocalciferol. Cholecalciferol and ergocalciferol may best augment paracrine and/or autocrine actions of vitamin D, but, among people with CKD, they may not be converted to calcitriol in sufficient quantities to optimize systemic endocrine effects.

Conclusions and future directions

Data from observational studies and animal-experimental models suggest that vitamin D therapy holds promise for improving health outcomes in CKD. Improved glucose metabolism is one potential mechanism through which vitamin D may exert beneficial effects. However, further data from clinical trials in humans are needed to test whether vitamin D has clinically relevant long-term effects on glucose metabolism and, more importantly, on overall clinical outcomes.

Acknowledgments

This publication was made possible by Grant Number 1KL2RR025015-01 from the National Center for Research Resources (NCRR), a component of the National Institutes of Health (NIH) and NIH Roadmap for Medical Research. Its contents are solely the responsibility of the authors and do not necessarily represent the official view of NCRR or NIH.

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Figure 1.

Vitamin D metabolism and mechanisms through which vitamin D metabolism is deranged in chronic kidney disease. FGF-23 = fibroblast growth factor-23.

Figure 2. Potential pleiotropic effects of vitamin D, beyond those described for maintenance of calcium, phosphorous, and bone homeostasis. RAAS = renin-angiotensin-aldosterone system, BP = blood pressure.

Figure 3.
Mechanisms through which vitamin D therapy may improve glucose metabolism in chronic kidney disease.

Table 1

Clinical trials assessing the effect of calcitriol therapy on glucose metabolism in hemodialysis patients.

First author (year)	N	Calcitriol Dose	Duration	Outcome (method of ascertainment)
Quesada (1990) ⁵⁵	9	0.5 µg/d	2 weeks	↑insulin secretion (OGTT)
Mak (1992) ⁵⁶	11	2 µg/m ²	Single dose	↑glucose tolerance (IVGTT), ↑insulin secretion (hyperglycemic clamp)
Mak (1992) ⁵⁷	7	2 µg/m ²	Single dose	↑insulin sensitivity (hyperglycemic clamp)
Allegra (1994) ⁵⁸	17	0.5 µg/d	3 weeks	↑insulin secretion (IVGTT)
Lin (1994) ⁵⁹	15	2 µg thrice weekly	8 weeks	↑glucose tolerance, ↑insulin secretion (OGTT)
Kautzky-Willer (1995) ⁶⁰	10	Mean 1 µg thrice weekly*	12 weeks	↑insulin sensitivity (frequently sampled IVGTT)
Mak (1998) ⁶¹	8	1.5–2.5 µg thrice weekly*	4 weeks	↑glucose tolerance (OGTT), ↑insulin sensitivity (euglycemic clamp)
Khajehdehi (2003) ⁶²	48	0.030 µg/kg twice weekly	3 months	↓fasting glucose
Strozecki (2004) ⁶³	8	1–2 µg thrice weekly*	12 weeks	↓hemoglobin A1c, no change in fasting glucose or insulin

* Titrated dose. OGTT = oral glucose tolerance test, IVGTT = intravenous glucose tolerance test.