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Vitamin D and omega-3 trial to prevent and treat diabetic kidney disease: Rationale, design, and baseline characteristics

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ABSTRACT

Diabetic kidney disease (DKD), defined as reduced glomerular filtration rate (GFR), elevated urine albumin excretion, or both that is clinically attributable to diabetes, is a common and morbid diabetes complication. Animal-experimental data, observational human studies, and short-term clinical trials suggest that vitamin D and omega-3 fatty acid supplements may be safe and inexpensive interventions to reduce the incidence and progression of DKD. The Vitamin D and Omega-3 Trial to Prevent and Treat DKD (VITAL-DKD) was designed as an ancillary study to the VITAL trial of 25,871 US adults. In a 2 × 2 factorial design, VITAL participants were randomly assigned to vitamin D_3 (cholecalciferol, 2000 IU daily) or placebo and to marine omega-3 fatty acids (eicospentaenoic acid and docosahexaenoic acid, 1 g/d) or placebo. VITAL-DKD enrolled a subset of 1326 VITAL participants with type 2 diabetes at baseline to test the effects of vitamin D and omega-3 fatty acids on changes in estimated GFR and urine albumin excretion. Over five years of follow-up, VITAL-DKD collected blood and urine samples to quantify changes in estimated GFR (the primary study outcome) and urine albumin excretion. At baseline, mean age of VITAL-DKD participants was 67.6 years, 46% were women, 30% were of racial or ethnic minority, and the prevalence of DKD (estimated GFR < 60 mL/min/1.73m^2 or urine albumin-creatinine ratio ≥ 30 mg/g) was 17%. In this type 2 diabetes population, VITAL-DKD will test the hypotheses that vitamin D and omega-3 fatty acids help prevent the development and progression of DKD.

1. Introduction

Diabetic kidney disease (DKD), defined as albuminuria, reduced glomerular filtration rate (GFR), or both that is clinically attributable to diabetes, is a large and growing public health burden [1]. Over the last 2–3 decades, the prevalence of DKD in the US has increased in direct proportion to the prevalence of diabetes itself, with an estimated 6.9 million people with DKD in 2005–2008 [2]. Intensive glucose control helps prevent DKD, and renin-angiotensin system (RAS) inhibitors help slow DKD progression [3–6]. However, residual risks of DKD development and progression are high, and few new treatments targeting DKD have successfully been introduced in the last two decades. As a result, approximately 50,000 patients now progress from DKD to end stage kidney disease (ESKD) in the US each year [7]. Moreover, patients with DKD are at markedly increased risk of cardiovascular disease and mortality [8]. To mitigate the growing public health burden of DKD, new approaches are needed to prevent DKD, its progression, and cardiovascular sequelae. Ideally, such approaches should be sufficiently accessible, inexpensive, safe, and effective to apply to the large at-risk diabetes population.

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Administration of vitamin D (cholecalciferol or ergocalciferol) is a promising therapeutic intervention for DKD prevention and treatment. While vitamin D has long been used to enhance bone health in selected populations, pleiotropic effects of vitamin D on other organ systems have more recently gained widespread attention [9,10]. Vitamin D may have particularly important effects on the kidney, an organ that plays a central role in vitamin D metabolism [11]. In animal-experimental models, 1,25-dihydroxyvitamin D (the active hormonal generated from cholecalciferol or ergocalciferol) prevents kidney damage by potently suppressing the RAS, reducing renal inflammation, and exerting direct pro-survival effects on podocytes [12]. These effects reduce albuminuria and glomerulosclerosis, in synergy with RAS inhibitors [12–14]. Human studies suggest that these effects may have clinical relevance. Lower circulating concentrations of 25-hydroxyvitamin D (used to assess vitamin D sufficiency) have been associated with increased risks of albuminuria and GFR loss in most (though not all) studies [15,16]. In short-term clinical trials of people with DKD, 1,25-dihydroxyvitamin D and its analogues significantly reduced albuminuria but also possibly decreased GFR [17]; whether this leads to progressive GFR loss over time or to long-term renoprotection, as with RAS inhibitors, is not known. Moreover, supplement forms of vitamin D (cholecalciferol and ergocalciferol) may be more appropriate for DKD prevention because they are less likely to cause hypercalcemia and are inexpensive, but effects of vitamin D supplements on human DKD are not known.

Omega-3 fatty acids, found naturally in high quantities in fatty fish, have vascular and anti-inflammatory properties that may help prevent and treat DKD [18]. In animal models of diabetes, omega-3 fatty acids reduced renal inflammation, mesangial expansion, tubulo-interstitial fibrosis, and glomerulosclerosis [18–20]. In epidemiologic studies, greater dietary fish intake was associated with decreased risks of albuminuria and reduced GFR, and higher plasma polyunsaturated omega-3 fatty acid concentrations were associated with slower loss of creatinine clearance [18]. Short-term clinical trials provide proof of concept for beneficial vascular and anti-inflammatory effects in humans: at least 7 intervention studies suggest that omega-3 fatty acids improve vasodilation and/or decrease markers of endothelial cell activation, important determinants of intraglomerular pressure and urinary albumin filtration, and at least 3 studies of persons with type 2 diabetes found that omega-3 fatty acids reduced measures of oxidative stress, which is closely linked with tissue inflammation and DKD progression. Moreover, a meta-analysis of 17 trials in DKD, IgA nephropathy, or other glomerular diseases reported that omega-3 fatty acids reduced albuminuria by 19% reduction (95% CI 4–34% reduction); the effect estimate was similar though not statistically significant restricted to trials of DKD [21]. Two subsequent trials provided additional supportive evidence that omega-3 fatty acids prevent loss of GFR [22,23].

In summary, abundant data point to potential renal benefits of both vitamin D and omega-3 fatty acids, but existing evidence is inadequate to recommend routine vitamin D or omega-3 supplementation for the prevention or treatment of DKD. Therefore, we designed the Vitamin D and Omega-3 Trial to Prevent and Treat DKD (VITAL-DKD) to assess the efficacy and safety of vitamin D and omega-3 fatty acids for the prevention and treatment of DKD. Because both vitamin D and omega-3 fatty acid supplements may have beneficial effects that reduce cardiovascular morbidity and mortality among people with diabetes and DKD [11,18], secondary outcomes of VITAL-DKD will assess the effects of these interventions on cardiovascular risk.

2. Materials and methods

2.1. Study design

This study was designed as an ancillary study to the Vitamin D and Omega-3 Trial (VITAL), a randomized, double-blind, placebo-controlled trial of the benefits and risks of vitamin D and marine omega-3 fatty acids in the primary prevention of CVD and cancer (NCT01169259) [24]. The parent VITAL trial is a large study (N = 25,871) that is conducted primarily by mail. The parent VITAL trial collected baseline blood samples on a subset of participants (N = 16,954), but follow-up blood samples and urine samples were collected only among a subset of generally healthy participants. The VITAL-DKD trial was built into the parent VITAL trial. Specifically, a subset of VITAL participants with type 2 diabetes at baseline was identified, recruited, and enrolled into VITAL-DKD. Each VITAL-DKD participant was randomly assigned by the parent VITAL trial to vitamin D or placebo and omega-3 fatty acids or placebo. The VITAL-DKD trial collected baseline and follow-up outcome and covariate data specific to DKD to assess effects of study interventions on estimated GFR and albuminuria. The VITAL-DKD trial was approved by the Partners Human Research Committees, the Institutional Review Board of Brigham and Women's Hospital, and registered with clinicaltrials.gov prior to enrolling participants (NCT01684722).

2.2. Study population

The parent VITAL trial is restricted to older individuals (men ages ≥50 years, women ages ≥55 years) because rates of chronic disease (including cardiovascular diseases, cancer, and kidney disease) increase substantially with age [24]. VITAL excluded persons with clinically apparent cardiovascular disease or cancer (except non-melanoma skin cancer) because it is a trial for the primary prevention of these conditions. For the VITAL-DKD trial, we recruited a subset of VITAL participants with prevalent type 2 diabetes. Specifically, we targeted parent VITAL trial participants who reported a physician diagnosis of diabetes at screening and agreed to donate a blood sample to the VITAL study, From this group, we excluded (a) persons who reported a diagnosis of diabetes only during pregnancy (presumed gestational diabetes), and (b) persons who reported diabetes diagnosis prior to age 30 and first treated with insulin (likely type 1 diabetes). We also excluded participants with a known cause of kidney disease other than diabetes (Table 1).

2.3. Enrollment

Potentially eligible individuals were identified during the parent VITAL trial placebo run-in period. Consecutive potentially eligible individuals were contacted for VITAL-DKD until the enrollment goal of 1320 participants was met. Potentially eligible individuals were mailed a VITAL-DKD kit that included a separate ancillary study consent form, an ancillary study-specific questionnaire, and urine collection materials. Participants entered the VITAL-DKD ancillary study if they: [1] returned complete and valid DKD ancillary study materials; [2] returned a blood sample as part of the parent VITAL trial; [3] met all parent VITAL trial and DKD ancillary study eligibility criteria; and [4] were randomized into the parent VITAL trial.

Table 1
Eligibility criteria for the Vitamin D and Omega-3 Trial to Prevent and Treat Diabetic Kidney Disease (VITAL-DKD).

Inclusion criteria
Age ≥ 50 years (men), ≥ 55 years (women) (P)
Self-reported physician diagnosis of diabetes (DKD)
Blood and urine samples returned during placebo run-in (DKD)
Exclusion criteria
Prevalent cardiovascular disease or cancer (except non-melanoma skin cancer) (P)
Dialysis (P) or kidney transplant (DKD)
Hypercalcemia, hypo- or hyper-parathyroidism (P)
Severe liver disease (cirrhosis) or granulomatous disease (P)
Diagnosis of diabetes only during pregnancy (DKD)
Diabetes diagnosis prior to age 30 & first treated with insulin (DKD)

(P) = parent VITAL trial criterion; (DKD) = criterion specific to VITALDKD.