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Deficient serum 25-hydroxyvitamin D is associated with an atherogenic lipid profile: The Very Large Database of Lipids (VLDL-3) study

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BACKGROUND: Cross-sectional studies have found an association between deficiencies in serum vitamin D, as measured by 25-hydroxyvitamin D (25[OH]D), and an atherogenic lipid profile. These studies have focused on a limited panel of lipid values including low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG).

OBJECTIVE: Our study examines the relationship between serum 25(OH)D and an extended lipid panel (Vertical Auto Profile) while controlling for age, gender, glycemic status, and kidney function.

METHODS: We used the Very Large Database of Lipids, which includes US adults clinically referred for analysis of their lipid profile from 2009 to 2011. Our study focused on 20,360 subjects who had data for lipids, 25(OH)D, age, gender, hemoglobin A1c, insulin, creatinine, and blood urea nitrogen. Subjects were split into groups based on serum 25(OH)D: deficient (<20 ng/mL), intermediate (≥20–30 ng/mL), and optimal (≥30 ng/mL). The deficient group was compared to the optimal group using multivariable linear regression.

RESULTS: In multivariable-adjusted linear regression, deficient serum 25(OH)D was associated with significantly lower serum HDL-C (−5.1%) and higher total cholesterol (+9.4%), non–HDL-C (+15.4%), directly measured LDL-C (+13.5%), intermediate-density lipoprotein cholesterol (+23.7%), very low–density lipoprotein cholesterol (+19.0%), remnant lipoprotein cholesterol (+18.4%), and TG (+26.4%) when compared with the optimal group.

CONCLUSION: Deficient serum 25(OH)D is associated with significantly lower HDL-C and higher directly measured LDL-C, intermediate-density lipoprotein cholesterol, very low–density lipoproteins cholesterol, remnant lipoprotein cholesterol, and TG. Future trials examining vitamin D supplementation and cardiovascular disease risk should consider using changes in an extended lipid panel as an additional outcome measurement.

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Introduction

Atherosclerotic cardiovascular disease (CVD) is the leading cause of death and disability-adjusted life years lost worldwide.[1] Elevated serum concentrations of low-density lipoprotein cholesterol (LDL-C) and triglycerides (TG) and low concentrations of high-density lipoprotein cholesterol (HDL-C) are known to be major risk factors for developing CVD.[2–5] A growing body of cross-sectional evidence indicates that blood levels of vitamin D, a fat-soluble vitamin, are inversely associated with an atherogenic lipid profile.[6–9] These studies have found that individuals with low serum 25-hydroxyvitamin D (25[OH]D) (defined as either <20 ng/mL,[6] <30 ng/mL,[7] or in the lowest quartile[8]) have higher LDL-C, higher TG, and lower HDL-C compared with those with higher levels of 25(OH)D (defined as ≥30 ng/mL[6,7] or higher quartiles[8]). Serum 25(OH)D is considered the best indicator for vitamin D status.[10] Lower serum levels of 25(OH)D are also independently associated with CVD events and mortality, even after adjusting for traditional risk factors including hyperlipidemia, diabetes, hypertension, smoking, body mass index (BMI), and prior history of myocardial infarction.[11–20] The impact of vitamin D supplementation on CVD risk reduction remains inconclusive and is a subject of much investigation and debate.[21]

Past studies examining the association between 25(OH)D and atherogenic lipid profiles used Friedewald-estimated LDL-C (LDL-C_f), which is less accurate than directly measured LDL-C (LDL-C_d), especially in the setting of low LDL-C and high TG.[22] LDL also consists of different densities, with small, dense LDL suggested as a more significant CVD risk factor than large, buoyant LDL particles.[23] The overall LDL particle density can be determined using the logarithmic LDL density ratio (LLDR), which is the ratio of dense-to-buoyant LDL subclasses (defined as $\ln[\{LDL_3\text{-C} + LDL_4\text{-C}\}/\{LDL_1\text{-C} + LDL_2\text{-C}\}]$).[24] Higher values of LLDR indicate denser LDL, which is potentially more atherogenic. No studies have examined associations between 25(OH)D and LDL-C_d or LDL density. Similarly, no studies have evaluated the relationship between 25(OH)D and remnant lipoprotein cholesterol (RLP-C). RLP-Cs are TG-rich lipoproteins consisting of intermediate-density lipoprotein cholesterol (IDL-C) and dense forms of very low–density lipoprotein cholesterol (VLDL-C). RLP-C has been independently associated with the development of CVD.[25–30]

Our study set out to examine the association of vitamin D deficiency, as defined by serum 25(OH)D < 20 ng/mL,[31] with an extended lipid panel (Vertical Auto Profile [VAP]) including HDL-C, total cholesterol (TC), non–HDL-C, LDL-C_f, LDL-C_d, IDL-C, VLDL-C, RLP-C, TG, and LLDR in a large cohort representative of the general US population. The inability of randomized controlled trials and cross-sectional studies to thus far agree on the associations between 25(OH)D and CVD risk may be due to confounders, such as glycemic status and kidney function that were not accounted for in prior cross-sectional studies. Current literature suggests there is an inverse association between 25(OH)D and incidence of type II diabetes,[32] insulin resistance,[33,34] and glycosylated hemoglobin.[35–37] Given the link between diabetes and CVD,[38] our study sought to control for glycemic status in our analysis. Previous research has also shown an association between 25(OH)D and kidney function,[39–41] necessitating controlling for kidney function in our study given the link between declining kidney function and increasing risk for CVD.[42,43] Our study also adjusted for age and gender in addition to glycemic status and kidney function. By using this database with directly measured lipid values and adjusting for clinical variables, we can further elucidate the relationship between 25(OH)D and lipids with greater power than prior studies. We hypothesized that 25(OH)D deficiency would be associated with a more atherogenic lipid profile.

Methods

Study population

Data in the Very Large Database of Lipids (VLDL) database were collected from 1,340,614 adults (≥18 years of age) in the United States who were clinically referred for VAP (Atherotech, Inc, Birmingham, AL) ultracentrifugation testing for lipid profiles from 2009 to 2011. The distribution of lipid values in this data set matches the distribution in the National Health and Nutrition Examination Survey 2007 to 2008.[44] For the primary analysis, we used a cohort of 20,360 individuals from the VLDL data set who had measurements of 25(OH)D, lipid fractions, age, gender, hemoglobin A1c (HbA1c), insulin, creatinine, and blood urea nitrogen (BUN). All laboratory measures were performed at Atherotech Diagnostics Laboratory in Birmingham, Alabama.

Lipid measurements

Direct measurements of LDL-C, IDL-C, VLDL-C, and HDL-C were conducted using inverted rate zonal, single vertical spin, and density gradient ultracentrifugation by the VAP technique. A high level of accuracy in VAP testing was confirmed through split sample comparisons conducted yearly (2007–2012) with beta quantification at Washington University's Core Laboratory for Clinical Studies reference laboratory for lipoprotein analysis, St. Louis, Missouri. TG were measured with the Abbott ARCHITECT c8000 system (Abbott Park, IL). Friedewald-estimated LDL-C was determined as described previously in individuals with TG < 400 mg/dL.[45] LLDR was calculated as described previously as $\ln([LDL_3\text{-C} + LDL_4\text{-C}]/[LDL_1\text{-C} + LDL_2\text{-C}])$.[24] RLP-C was calculated as described previously as VLDL3-C + IDL-C.[30,46] To convert lipoprotein values from mg/dL to mmol/L, multiply by 0.0259. To convert TG values from mg/dL to mmol/L, multiply by 0.0113.