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RESEARCH ARTICLE

VITAMIN D DEFICIENCY AND CORONARY ARTERY CALCIFICATION IN SUBJECTS WITH TYPE 1 DIABETES

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Abstract

Objective The objective of this study is to examine the relationship among serum levels of 25 hydroxyvitamin D (25[OH] D), polymorphis ms in vitamin D-associated genes, and the presence and progression of coronary artery calcification (CAC) in adults with type 1 diabetes.

Introduction:-

Research Design and Methods:-

This prospective study included 374 non-Hispanic white individuals with type 1 diabetes (mean age 40 ± 9 years; 46% were male). CAC was measured at the baseline and 3- and 6-year follow-up visits were determined by electron beam computed tomography. Serum 25[OH]D levels were measured by liquid chromatography tandem mass spectrometry at the 3-year visit.

Results:-

Normal (>30 ng/mL), insufficient (20–30 ng/mL), and deficient (<20 ng/mL) 25-[OH]D levels were present in 65%, 25%, and 10% of the individuals with type 1 diabetes, respectively. 25[OH]D deficiency was associated with the presence of CAC at the 3-year visit, odds ratio (OR) = 3.3 (95% CI 1.6–7.0), adjusting for age, sex, and hours of daylight. In subjects free of CAC at the 3-year visit, 25[OH]D deficiency predicted the development of CAC over the next 3 years in those with the vitamin D receptor M1T CC genotype (OR = 6.5 [1.1–40.2], P = 0.04) than in those with the CT or TT genotype (OR = 1.6 [0.3–8.6], P = 0.57).

Conclusions:-

Vitamin D deficiency independently predicts prevalence and development of CAC, a marker of coronary artery plaque burden, in individuals with type 1 diabetes.Coronary artery disease (CAD) is the major cause of morbidity and mortality in patients with type 1 diabetes (1,2). Coronary artery calcification (CAC), a marker of coronary artery plaque burden, predicts coronary events in persons with type 1 diabetes (3). The presence and progression of CAC have become useful surrogate CAD end points in evaluating novel CAD risk factors (3,4).Vitamin D deficiency has been associated with increased risk of CAD (5–7) in people without diabetes, as well as cardiovascular mortality (8). Studies have also shown that vitamin D levels are lower in individuals with type 1 diabetes (9,10), although whether this relationship holds for different geographic populations is unclear (11). Vitamin D regulates calcium blood levels and affects vascular smooth muscle cell proliferation (12), inflammation (13), and the renin-angiotensin system (14), all of which have cardiovascular effects and could lead to coronary calcification. Serum level of 25-hydroxyvitamin D (25[OH]D) assesses vitamin D status best. 25[OH]D is the major circulating form of vitamin D and the precursor

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of the active form 1,25[OH]D. This active form binds in the circulation to vitamin D-binding protein (VDBP), to be transported to target organs where it mediates its biological effects by binding to the vitamin D receptor (VDR).
Cross-sectional studies of the relationship between 25[OH]D levels and CAC have been inconclusive. A study of 650 Amish subjects found no association (15); lower 25[OH]D levels were associated with carotid and aortal, but not with coronary artery, calcified plaques in 340 African Americans with type 2 diabetes (16). The Multi-Ethnic Study of Atherosclerosis (MESA) study (17) reported that lower 25[OH]D levels predicted development of CAC, but not progression of CAC. Our study examined the cross-sectional and longitudinal relationship between 25[OH]D levels and CAC in adults with type 1 diabetes. We also explored whether the potential relationship between 25[OH]D levels and CAC differed by polymorphisms in the VDBP and VDR genes.
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Research Design and Methods:-
The Coronary Artery Calcification in Type 1 Diabetes (CACTI) study population has been described previously (4). In brief, 652 men and women with type 1 diabetes and 764 nondiabetic control subjects aged 19–56 years, with no history of CAD, were enrolled in a prospective follow-up of the development and progression of CAC. Patients with type 1 diabetes had long-standing diabetes (mean duration 23 years, range 4–52 years) on enrollment. Control subjects had not been diagnosed with diabetes of any type, had fasting blood glucose in the normal range, and were generally spouses, friends, or neighbors of the patients. All subjects provided informed consent, and the study was approved by the Colorado Multiple Institutional Review Board.

Participants were examined at a baseline visit in 2000–2002. Data used in these analyses are from the second (3-year) and third (6-year) follow-up visits, both conducted approximately 2.5 ± 0.4 years after each prior visit. For these analyses, all subjects with type 1 diabetes who had complete data at the 3-year visit were included. A total of 374 non-Hispanic white subjects with type 1 diabetes were analyzed. Anthropometric measurements were obtained, including height, weight, minimal waist circumference, and hip circumference. BMI was calculated in kilograms/meters squared. Resting systolic blood pressure and fifth-phase diastolic blood pressure were measured three times while the patients were seated after a 5-min rest, and the second and third measurements were averaged. Hypertension was defined as a blood pressure ≥140/90 mmHg or participant receiving current antihypertensive treatment. Current medication, tobacco use, and family medical history were obtained by standardized questionnaire. Vitamin D and calcium intake were obtained by a validated food frequency questionnaire (Harvard 1988) and included the use of supplements.

Laboratory measures:-
Total, HDL-cholesterol, and triglycerides were measured by standard enzymatic methods, and LDL-cholesterol was calculated by the Friedewald formula. Albumin excretion rate (AER) was calculated from urinary albumin measured in two timed overnight urine samples, and the results from the two nights were averaged. 25[OH]D levels were measured by liquid chromatography tandem mass spectrometry by Quest Diagnostics on samples collected at the 3-year visit. Season of blood draw was classified as fall/winter for blood drawn during the months of October to March and spring/summer as April to September, and the number of hours of average daylight over the 2 weeks before the study visit was calculated on the basis of study date and latitude of the study visit (Denver, CO, latitude 39° 45’ N). Individuals were categorized as vitamin D sufficient (25[OH]D >30 ng/mL), insufficient (20–30 ng/mL), or deficient (<20 ng/mL), according to current clinical guidelines (18).Genomic DNA was extracted from leukocytes by the salting out method. Vitamin D-binding protein (VDP) gene polymorphisms 420 (C/A) and 416 (T/G) and vitamin D receptor (VDR) gene polymorphism M1T (T/C) and Bsm1 (G/A) were genotyped in a multiplex dot-blot sequence-specific oligonucleotide polymerase chain reaction (SSO-PCR) assay (Roche Molecular Systems, Pleasanton, CA).

Coronary artery calcification:-
Two sets of high-resolution noncontrast contiguous 3-mm tomographic images were acquired at 0.1-s exposure on an Imatron C-150XLP electron-beam CT scanner (Imatron, San Francisco, CA) as described previously (4). The two sets of scans were acquired within 5 min, and CAC scores were averaged. Calcium volume scores (CVS) were square root transformed, and the difference in square root transformed CVS between the 3- and 6-year examinations was calculated. Progression of CAC was defined as a change in square root transformed CVS of ≥2.5 (19).

Statistical analyses:-

All statistical analyses were conducted in the SAS 9.2 system (SAS Institute, Cary, NC). Statistical significance was defined as $P < 0.05$. The association of 25[OH]D level with genotype was determined after adjustment for age, sex, hours of daylight, AER, vitamin D intake, and calcium intake. The association of vitamin D deficiency with the presence of CAC at the 3-year follow-up visit was examined in a multiple logistic regression model initially adjusted for age, sex, and hours of daylight. Additional models were run adjusting for BMI, HDL-cholesterol, LDL-cholesterol, and triglycerides. Models adjusted for factors that may affect vitamin D levels (AER, total vitamin D intake, and total calcium intake) were also run to examine the precision of our estimates. Genotypic data were added to these models.

The effect of vitamin D deficiency on progression of CAC from the 3- to 6-year visit was examined in a multiple logistic regression model adjusted for age, sex, hours of daylight, presence of CAC at the 3-year visit, AER, total vitamin D intake, and total calcium intake. An interaction term for vitamin D deficiency and presence of CAC at the 3-year visit was included to examine incident compared with prevalent CAC. In addition, an interaction term for vitamin D deficiency and the VDR genotype M1T was included to explore a possibility of gene–environment interaction on CAC progression.

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Result:-

Characteristics of study participants at the 3-year visit are summarized in Table 1. Age- and sex-adjusted mean 25[OH]D levels for type 1 diabetes subjects were 35.4 ± 0.7 ng/mL. Normal (>30 ng/mL), insufficient (20–30 ng/mL), and deficient (<20 ng/mL) 25-[OH]D levels were present in 65%, 25%, and 10% of the patients with diabetes, respectively.