MAINTENANCE OF LONG-TERM ADEQUATE LEVELS OF VITAMIN D LOWERS HbA_{1C} IN AFRICAN AMERICAN PATIENTS WITH TYPE 2 DIABETES

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Objectives: We examined the long-term effects of enhanced Vitamin D (VitD) supplementation on parameters of type 2 diabetes mellitus (T2DM): serum hemoglobin A_{1c}, low density lipoprotein, high density lipoprotein, and triglyceride for the purpose of determining beneficial VitD levels in T2DM African Americans (AA).

Design and Methods: Following inclusion criteria, retrospective charts of patients aged ≥30 years were reviewed. VitD supplementation was given to patients as part of drug regimen over a three year continuum. Pearson correlations were used to assess the relationship between VitD levels and levels of each parameter. Repeated measure analysis of variance was conducted to identify difference in mean levels of each parameter between years with VitD included as part of therapy.

Results: Vitamin D supplementation was inversely associated with HbA_{1c} ($r = -.286$, $P=.031$). No correlation was found between levels of VitD and levels of LDL, HDL or TG. Hemoglobin A_{1c} levels were found to be significantly different under VitD treatment between year 1 (mean VitD 24.75 μg/mL, mean HbA_{1c} 9.15%, $P=.000$) and year 2 (mean VitD 33.84 μg/mL, mean HbA_{1c} 7.91%, $P=.000$) and between year 1 and year 3 (mean VitD 34.46 μg/mL, mean 7.98% HbA_{1c} $P=.000$).

Conclusion: In T2DM AA, significant improvements in HbA_{1c} are obtained with enhanced VitD supplementation as part of drug regimen over time. Our investigation provides the first known evidence of a relationship between enhanced VitD supplementation as part of a pre-existing medical regimen taken over long term and determinants of T2DM in a group of overweight and obese AA with T2DM. (*Ethn Dis*. 2014;24[3]:335–341)

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Key Words: Type 2 Diabetes, 25(OH)D, hypovitaminosis D, Vitamin D, African American, Vitamin D Supplementation, Hemoglobin A_{1c}

INTRODUCTION

Vitamin D Supplement and Standards of Dose

Supplements generically called vitamin D (VitD), ergocalciferol (vitamin D_2) and cholecalciferol (vitamin D_3) can help to ameliorate low VitD levels. For every 100 international units (IU) of VitD supplement ingested, circulating levels of serum 25-hydroxy-vitamin D (25[OH]D) increase by 1 ng/mL.[1–3] Accordingly, adults and children are advised an intake of 200 IU of VitD per day, and for those aged ≥51 years, 400–600 IU to maintain normal levels.[1] Young, healthy adults ingesting adequate VitD supplements over time can raise and maintain circulating 25(OH)D to levels suitable for overall good health. However these suggested doses become less discrete when clinical conditions that increase the risk of low VitD levels, hypovitaminosis D, become confounding factors.

Serum 25-Hydroxy-Vitamin D and Vitamin D Supplements

The best clinical indicator of VitD status is circulating 25(OH)D, which is the primary storage form of the metabolite.[4] Optimal blood levels of 25(OH)D are still a matter of current debate, however ≥30 ng/mL seems to be the accepted minimum after a study found that intestinal calcium absorption was increased significantly in women by raising circulating 25(OH)D levels from 20 to 30 ng/mL.[1,5] It has been established that VitD levels that fall within the range of 21 to 29 ng/mL are denoted insufficient, and levels <20 ng/mL denoted deficient.[1] With average circulating serum 25(OH)D levels between 18 and 25 ng/mL, most adults and children within the United States fall within a less than optimal range.[1]

Vitamin D Deficiency, Type 2 Diabetes and Vitamin D Supplementation

Ongoing studies have shown VitD deficiency and type 2 diabetes mellitus (T2DM) are linked. It has been recognized that calcium regulates insulin synthesis within pancreatic β-cells, and plasma calcium levels are mediated by VitD.[6–8] Insulin synthesis, secretion and resistance have therefore been associated with VitD deficiency.[6,9] One study showed that the prevalence of VitD deficiency was discovered to be higher in diabetic patients (24%, $P<.001$) than in controls (16%).[10] A study done with obese AA adolescents revealed low VitD levels correlated with insulin resistance.[11] Grant and Peiris' examination of disparity and mortality in association with VitD levels showed significant observational data that directly linked diabetes and chronic disease to hypovitaminosis D.[6] Vitamin D deficiency predicted higher fasting, postprandial blood glu-

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cose and diabetes mellitus as revealed in another investigation.[12]

Studies on VitD repletion by supplementation improved insulin secretion in VitD deficient and type 2 diabetes patients.[12–15] The synthesis of numerous proteins decrease during times of VitD deficiency, which are then restored by VitD supplements in the islets of Langerhans.[13] Supplementation with VitD has shown to reduce free fatty acids in patients with T2DM.[13] A New Zealand study on South Asian women found that insulin resistance improved noticeably after taking VitD supplements.[11] A cohort study showed that the intake of VitD supplements was inversely associated with the development of T2DM by analyzing serum 25(OH)D on subsequent T2DM incidence.[9] Two trials done in a study among patients with baseline glucose intolerance, revealed that VitD supplementation improved insulin resistance.[16]

Enhanced Vitamin D Supplementation

The efficacy of VitD supplementation is based on dose. Despite evidence of improvement to glucose homeostasis by VitD supplementation, few studies have specifically investigated the dosage necessary for significant response, particularly glucose control, to VitD replacement therapy on T2DM. It has been suggested that the optimal circulating 25(OH)D concentration for reducing insulin resistance is between 30 ng/mL and 48 ng/mL.[1] This recommendation provides evidence for an increase in recommended adequate levels in individuals with impaired glucose tolerance. Holick et al extend this enhanced dose approach in suggesting strategies to treat and prevent VitD deficiency (ie, megadose of 50,000 IU of D_2 once per week for 8 weeks, and administer the same dosage every 2 weeks to maintain blood levels between 40 and 50 ng/mL).[3,17] Alternatively suggested by Holick to correct VitD deficiency and maintain blood levels of 25(OH)D $\geq$30 ng/mL was 1000 IU or 2000 IU of vitamin D_3 treatment taken per day.[3] These numbers are specific to VitD deficient patients, since hypovitaminosis D has been found to correlate with T2DM patients, the dosage suggested by Holick are applicable to a T2DM disease state. A key clinical decision made by the scientific congress at the 14th Workshop on VitD, was to acknowledge the potential benefit of targeting higher VitD levels in preventing chronic disease such as T2DM.[6] However, research is still being developed to determine whether minimal standards for VitD intake should be increased for general health and in the prevention of disease.[6] The Office of Dietary Supplements (ODS), a part of the National Institutes of Health (NIH), has said levels >50 ng/mL of serum 25(OH)D accompany adverse effects.[18] However this report is not specific to VitD deficient individuals or to those in other disease states. Research has shown that doubling or tripling the standard VitD supplement doses (of 600 IU/day) would be safe.[19] Daily doses exceeding 10,000 IU appear to show signs of VitD toxicity, however this creates a broad safety margin for the VitD supplement,[19] enough to increase dose in a disease state such as T2DM. No toxicity has been reported using the enhanced dose treatment schedule suggested by Holick.[1]

African Americans (AA) are potentially at higher risk of VitD deficiency than other groups due to three factors: greater skin melanin, higher prevalence of obesity, and diet.[20]

Vitamin D Deficiency and African Americans

African Americans are potentially at higher risk of VitD deficiency than other groups due to three factors: greater skin melanin, higher prevalence of obesity, and diet.[20] Parent VitD is obtained from sun exposure and diet, then converted in the liver to 25(OH)D.[4] Pigments in dark skin reduce sun exposure, which lowers the levels of circulating 25(OH)D.[4] Under normal conditions at any latitude in North America, at any time of the year, young, healthy Blacks do not achieve optimal 25(OH)D levels.[4] African Americans need longer exposure to the sun and ultraviolet (UV) B rays in order to increase epidermal synthesis of previtamin D_3.[20] This evidence is not only shown in AA, but other ethnic groups with high melanin in the skin, including Indian and Pakistani immigrants to Great Britain.[20–23] Low dietary intake of VitD is also a contributing factor to VitD deficiency among AA.[6] Many experts believe that an intake of 1000 IU of VitD supplements or more may be needed for most people to achieve optimal circulating 25(OH)D levels.[4] Reports have indicated a relationship between lower VitD concentrations and increased body weight among AA.[20] Adipose tissue has been shown to act as a major storage reservoir for VitD in both rats and humans.[20] High adiposity in AA is an independent predictor of hypovitaminosis D, after a current study showed that an increase in body mass index (BMI) had an 8% increase risk of VitD deficiency.[20] African Americans with BMI of >35 kg/m^2 had a 50% greater prevalence of having hypovitaminosis D vs their White counterparts.[20] Holick suggests weight-based calculation methods to determine the amount of VitD needed, taking body size into account when determining the appropriate replacement.[24]

Parameters under Study

Hemoglobin A_{1c} (HbA_{1c}) is a marker used in the diagnosis and monitoring of blood glucose levels in T2DM. Reports have shown a strong association between HbA_{1c} levels and VitD status. One study observed an inverse relationship ($P=.0045$) between VitD status and HbA_{1c} levels in a sample of US participants, aged 35–74 years, who did not report a history of diabetes.[25]

Vitamin D and its effects on dyslipidemia have been recently studied in patients with T2DM. Lipid panel (low density lipoprotein [LDL], high density lipoprotein [HDL], and triglyceride [TG]) have been associated with cardiovascular disease among patients with T2DM.[26] Short-term studies have shown that correcting for VitD deficiency does not improve lipid profile. Some research has indicated that long-term VitD supplementation of patients with T2DM showed a significant decrease in LDL and total cholesterol.[26]

Suggestions for prescribed Vitamin D amounts have been established for certain conditions such as T2DM, insulin deficiency, obesity and VitD insufficiency and deficiency, [26] however no study, to our knowledge, has offered suggestions on dosage for populations facing these pathologies concurrently, in particular AA. Our study is a preliminary investigation of VitD dosage ranges that would be a beneficial addition to the drug regimen for AA T2DM patients presenting at the Howard University Hospital Diabetes Treatment Center (HUH DTC).

MATERIALS AND METHODS

Patients and Protocol

A patient chart review from April 2007 to January 2012 was conducted for 840 male and female T2DM Black adults. Participants were being treated at HUH DTC. Fasting blood samples for glucose, lipids and 25(OH)D were obtained from all participants. A fasting plasma glucose of ≥7.8 mmol/L (126 mg/dL) or a 2 hour glucose level of ≥11.1 mmol/L (200 mg/dL) following a 75 g oral glucose load or a HbA1c levels of ≥6.5% was defined as diabetic.[11] Circulating 25(OH)D levels of ≥20 ng/mL were considered adequate according to ODS. All diagnosed T2DM patients were given 50,000 IU of ergocalciferol, Vitamin D_2 supplement per week for eight weeks, followed by 2,000 IU supplement per day for maintenance as part of the drug regimen. Patients were excluded from study if they: 1) were a patient for <3 years or if they had discontinuous records, (ie, did not have a continuum of at least three years of chart records for VitD and HbA_{1c}); 2) had a mean VitD level of <20 ng/mL by the second calendar year of chart review; 3) had a mean HbA_{1c} level of ≤7.0% in the first calendar year of chart review; or were age ≤29 years of age by the first year of chart review. Cutoff levels of VitD adequacy of ≥20 ng/mL by the second year of chart review would indicate that patient's 25(OH)D levels were increased over time, and patient was compliant in taking VitD supplements. Cutoff level of HbA_{1c} >7% in the first year of chart review were done according to common $HbA1_c$ treatment targets for T2DM set by Mayo Clinic and NIH.[27,28] Clinicians at DTC determined an HbA_{1c} level >7% out of treatment target levels based on clinical history of its patients. After preliminary review of all patient charts and applying our inclusion criteria, 43 patients were eligible for study. This study has been approved by the Institution Review Board of Howard University for human studies.

Education was provided to all patients of the HUH DTC about T2DM, and their specific drug regimen; patients were put on drug regimens to control their T2DM. All patients were either on intensified insulin therapy and/or antidiabetic medications including statin and antihypertensive agents. Vitamin D therapy was the only additional supplement provided in the regimen of controlling diabetes.

Levels of each parameter were recorded every 90 days (± 90 days). Means were calculated for each patient VitD record level over one calendar year; this average would represent year 1 (Y1) of a patient's overall VitD level in that year. The same procedure was conducted to calculate year 2 (Y2) and year 3 (Y3) of VD levels for each patient. A summated mean was calculated for all 43 patients for Y1, Y2, and Y3. Mean VitD levels for all patients for Y1, Y2, and Y3 of chart review was 24.75 ng/mL (± 11.65), 33.84 ng/mL (± 12.32), and 34.46 ng/mL (± 10.43), respectively. Mean HbA_{1c} levels were calculated using the same method. Mean HbA_{1c} levels were 9.16% (± 1.64) in Y1, 7.91% (± 1.18) in Y2 and 7.98% (± 1.51) in Y3 (Table 1). Patients' charts were reviewed from January 2008 to October 2012 in three year continuums.

Body mass index was measured according to formula (weight [kg]/height [m^2]). The BMI range was determined using the Centers for Disease Control table for calculating BMI values for selected height and weight. Patient's age was calculated using patients' date of birth (Table 1).

Statistical Analysis

All analyses were performed using Statistical Software for the Social Sciences (SPSS) version 20 software. A natural log transformation was used to reduce skewness in distribution of HbA_{1c}, 25(OH)D, LDL, HDL, and TG. Log-transformation values were used for repeated measure analysis of variance (ANOVA) and pairwise comparison was used to identify significant differences between years. A Pearson correlation was performed on VitD levels and levels of all parameters. Missing data was filled using mean values for all participants in the corresponding calendar year. Significance level for all tests was set at $P\leq.05$.

Table 1. Characteristics of all T2DM patients in year 1, year 2, and year 3 of vitamin D treatment

	Year 1	Year 2	Year 3	*P*
N	43	43	43	
Male/female, *n*	14/29	14/29	14/29	
BMI, N/OW/O, *n*	32/8/3	32/8/3	32/8/3	
Age, years	60.91 ± 12.14	61.91 ± 12.14	62.91 ± 12.14	
Vitamin D, ng/mL	24.75 ± 11.65	33.84 ± 12.32	34.46 ± 10.43	.000[a]
HbA1c, %	9.16 ± 1.64	7.91 ± 1.18	7.98 ± 1.51	.000[a]
LDL, mg/dL	91.17 ± 28.06	86.47 ± 27.89	79.27 ± 28.37	.020[a]
HDL, mg/dL	50.86 ± 14.10	51.35 ± 15.58	52.89 ± 16.45	.414
Triglyceride, mg/dL	131.71 ± 100.49	107.04 ± 52.96	109.59 ± 50.86	.234

Data presented as mean ± SD unless noted otherwise.
BMI: N, normal; OW, overweight; O, obese.
[a] $P<.05$.

RESULTS

Yearly Treatment Comparisons

Results for parameters of T2DM over three calendar years are summarized in Table 1 and Figure 1. There was a significant improvement in serum VitD concentration after supplementation from Y1 to Y2 (24.75 ng/mL ± 11.65 vs 33.84 ng/mL ± 12.32, respectively, P=.000), and between Y2 and Y3 (33.84 ng/mL ± 12.32 vs 34.46 ng/mL, respectively, P=.000). There was no significant difference in VitD serum concentrations between Y2 and Y3 under maintained supplementation, which indicated that these levels remained statistically unchanged (Table 1). Hemoglobin A_{1c} levels improved significantly between Y1 and Y2 (9.16% ± 1.64 vs 7.91% ± 1.18, respectively,) P=.000) , and Y1 and Y3 (9.16% ± 1.64 vs 7.98% ± 1.51, respectively, P=.000) (Table 1). Low density lipoprotein also showed significant improvement between Y2 and Y3 (86.47 mg/dL ± 27.89 vs 79.27 mg/dL ± 28.37, respectively, P=.02) and between Y1 and Y3 (91.17 mg/dL ± 28.06 vs 79.27 mg/dL ± 28.37, respectively, P=.02). Figure 1 represents the relationship between circulating 25(OH)D and HbA_{1c} serum concentration at Y1, Y2 and Y3 of chart review for 43 participants. Trending of increased 25(OH)D levels and decreased serum HbA_{1c} was observed.

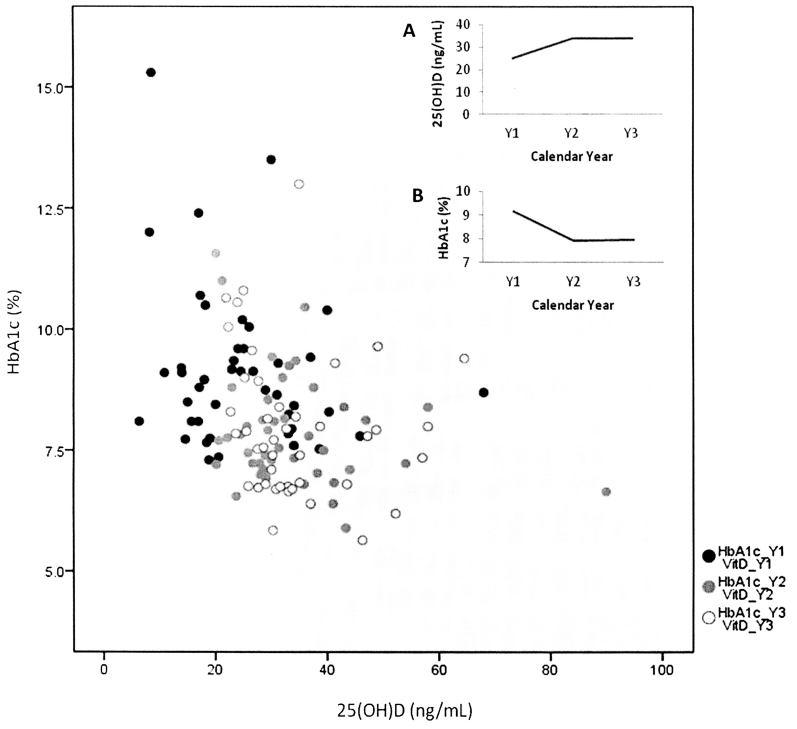

Fig 1. Relationship between serum 25hydroxyvitamin D [25(OH)D] and HbA_{1c} serum concentration at year 1(Y1), year 2(Y2), and year 3(Y3) of chart review for 43 subjects. Shapes represent intersection of each subject's blood 25(OH)D level and HbA_{1c} level in year. Inlay graphs A and B represent the mean increase in 25(OH)D and HbA_{1c} over three year period

Effects of Vitamin D Treatment

Pearson correlation between overall 25(OH)D levels and HbA_{1c} showed a significant negative correlation with 25(OH)D serum concentrations ($r=-0.286$, P=.031), with VitD accounting for about 8% of the variation in HbA_{1c} over three year period of its supplementation (Table 2).

DISCUSSION

With enhanced intake of VitD, annual improvements in HbA_{1c} levels in AA with T2DM were revealed. To our knowledge, our investigation provides the first evidence of a relationship between enhanced VitD supplementa-

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Table 2. Overall Pearson correlations for 25(OH)D and all study parameters over three year continuum

		HbA1c	LDL	HDL	TG
N		43	43	43	43
25(OH)D	*r*	−0.286[a]	−0.092	0.142	−0.034
	P	0.031	0.278	0.182	0.415

[a] $P<.05$.

tion as part of a pre-existing medical regimen taken over long term and determinants of T2DM in a group of overweight and obese AA with T2DM.

Mean circulating Vitamin D levels for all T2DM patients at the beginning of the study (Y1) was shown to be 24.75 ng/mL (± 11.65 SD) (Table 1). Although this average exceeds the 20 ng/mL levels established by ODS as sufficient for general health, serum 25(OH)D levels >30 ng/mL have been deemed optimal for health.[1] A possible explanation for the significant improvement in both HbA_{1c} and LDL in T2DM patients by Y2 of the study was the significant increase in serum 25(OH)D levels during supplementation to optimal levels of 33.84 ng/mL by Y2 and 34.46 ng/mL by Y3 (Table 1, Figure 1, Figure 2). This study not only supports Holick's discussion on healthy levels for serum 25(OH)D in general populations, but lays the foundation for possible higher targeting levels of serum 25(OH)D necessary to combat chronic disease such as T2DM in particular AAs.[1,3,17]

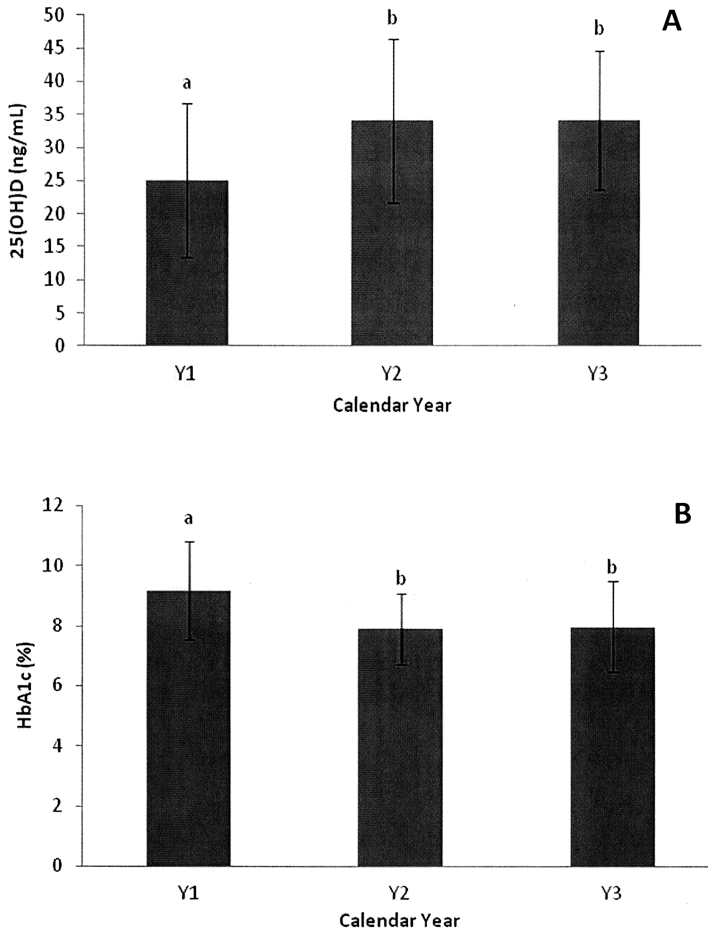

Fig 2. Graphs A and B represent the mean increase in 25(OH)D and HbA_{1c} over three year period. Data presented as mean ± SE. Means with the same letter are not significantly different from each other

Data revealed that several patients of this study were VitD deficient and many VitD insufficient in Y1. With all patients being of color and nearly 75% obese in this study, increasing standard levels of VitD supplementation needed to be increased for any visible health benefits in these AA patients.

Vitamin D deficiency has been linked to the pathogenesis of T2DM by its direct or indirect relation to impairments in insulin secretion and insulin synthesis.[6,13] Our study aimed to measure the long-term effects of VitD supplementation on the biomarker HbA_{1c}, an indicator of glycemic control in these patients. Hemoglobin A_{1c} blood serum levels significantly improved by Y2 of supplement from 9.17% to 7.91% in Y2 and remained fairly stable in Y3 (7.98%) in Y3.

After adjusting for known environmental risk factors such as socioeconomic status, the risk of T2DM is estimated to be twice as high in African Americans vs their European American counterparts, therefore genetic factors may explain some of the differences in the disease risk within certain populations.[29] A study concluded that genetic ancestry had a significant association with T2DM, however, no single gene was sufficient to explain observed ethnic differences in T2DM risk.[29] Another study found that variations within the intron of transcription factor TCF7L2 gene was very strongly associated with development of T2DM.[30] Furthermore, the risk associated with two intronic single nucleotide polymorphisms within the TCF7L2 gene in individuals of Indian Asian and Afro-Caribbean origin were studied and found that the risk allele was associated with a higher rate of T2DM.[30]

A study analyzed ethnic differences in T2DM risk among 78,419 apparently healthy middle-aged women and found that the risk of T2DM was significantly higher among Asians, Hispanics and Blacks than among Whites before and after accounting for BMI.[31] It was concluded that T2DM is primarily determined by obesity and lifestyle factors such as diet and exercise.[31] Obesity being a risk factor for T2DM in AAs is an important criterion of our study in analyzing the effects that high adiposity has on VitD availability in AA populations.

Genome wide association approaches have been recently used to examine T2DM in African Americans. A Genome Wide Association Study (GWAS) using 965 AA cases with T2DM and end-stage renal disease, and 1,029 population-based controls identified novel single nucleotide polymorphism (SNP) T2DM-susceptibility loci between genes RND3 and RBM43 in the AA population.[32] This suggests that multiple loci underlie T2DM susceptibility in AA populations and that these loci are distinguished from those identified in other ethnic populations.[30,32] Another investigation evaluated 29 genetic risk variants of T2DM as identified by GWAS in a cohort of 4,288 AAs.[33] Seven of the 29 SNPs examined were found to be associated with T2DM risk.[33] Having only conducted the study with an AA population, the results extend some of the recent GWAS findings to AAs and could be used to guide future efforts in identifying causal variants for T2DM.[33] A different GWAS study observed traits related to glucose homeostasis and identified variants in a lipid biosynthesis gene, SC4MOL, and TCERG1L, a modulator of adiponectin, which is associated with fasting insulin and insulin resistance in AAs.[30] Another study conducted looked at racial differences in T2DM that conferred genetic variation and found that risk alleles decreased in frequency from Sub-Saharan Africa through Europe to East Asia.[30] These findings could explain higher risk for T2DM in individuals of African descent than of East Asian descent.[30]

CONCLUSION

Our study indicates that enhanced VitD dosage may be required to combat T2DM in overweight and obese T2DM AA. Our study showed that a high dosage regiment of VitD significantly improved HbA_{1c} levels over long term.

Restoring Vitamin D may prove to be associated with improving insulin response and better glucose control, and may be of effective therapeutic importance in T2DM and pre-diabetic state.[34]

Vitamin D treatment was used as the only supplement along with insulin therapy and or antidiabetic medications. The confounding effects of these drugs on VitD supplements requires further investigation. Further randomized controlled trials are necessary to clarify the effectiveness of VitD supplementation in improving T2DM parameters in obese and overweight AA.

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