

Serum 25OHD concentration as a predictor of haemoglobin A1c among adults living in the USA: NHANES 2003 to 2010

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ABSTRACT

Background Vitamin D status influences glucose metabolism. Serum 25-hydroxyvitamin D (25OHD) concentrations have been inversely associated with type 2 diabetes risk. The optimal serum 25OHD level needed for adequate glycaemic control is unknown.

Objective To determine the relationship among serum 25OHD concentrations and degree of glucose regulation using percentage of haemoglobin A1c (HbA1c%).

Methods Data for adults ≥ 20 years from the National Health and Nutrition Examination Survey (NHANES) (2003–2010) were included. A binary logistic regression was used for serum 25OHD (nmol/L) as a continuous variable to determine the OR and 95% CI for HbA1c $> 6.5\%$, adjusting for sex, race and body mass index (BMI). Measures of serum 25OHD were grouped into quartiles and entered into a binary logistic regression model to determine the OR and 95% CI for HbA1c $> 6.5\%$ in an adjusted model.

Results Across all NHANES cycles, lower serum 25OHD was associated with greater odds of HbA1c $\geq 6.5\%$ when adjusting for sex, race, age and BMI (NHANES 2003–2004 (N=4402): OR 0.985, 95% CI 0.979 to 0.990; NHANES 2005–2006 (N=4409): OR 0.976, 95% CI 0.969 to 0.982; NHANES 2007–2008 (N=4525): OR 0.989, 95% CI 0.984 to 0.993; and NHANES 2009–2010 (N=5660): OR 0.988, 95% CI 0.984 to 0.991). In an adjusted model, the lowest quartile of serum 25OHD (0–41 nmol/L, N=4879) was associated with greater odds of HbA1c $\geq 6.5\%$ compared with the highest quartile (73–260 nmol/L, N=4472), OR 2.37, 95% CI 2.03 to 2.77. The odds of HbA1c $\geq 6.5\%$ were also greater for adults with serum 25OHD considered to be sufficient compared with the highest quartile, OR 1.68, 95% CI 1.56 to 1.61).

Conclusion Lower serum 25OHD concentrations are associated with poor glycaemic control (HbA1c $\geq 6.5\%$). Sufficient serum 25OHD levels were also associated with poorer blood glucose control. Further research is needed to investigate an optimal serum concentration or threshold to support adequate blood glucose control.

INTRODUCTION

In 2010, the Centers for Disease Control and Prevention estimated ~25 million individuals in the USA are living with diagnosed diabetes, and another ~7 million people have undiagnosed diabetes.¹ There is expected to be a

What this paper adds

- ▶ Vitamin D is involved in glucose metabolism.
- ▶ Reduce serum vitamin D concentrations are associated with the risk of Type 2 diabetes mellitus.
- ▶ Serum vitamin D concentrations considered to be sufficient are associated with the risk of Type 2 diabetes mellitus

70% increase among adults living with type 2 diabetes mellitus (T2DM) between the years 2010 and 2030.² This exponential rise in prevalence of T2DM poses a public health crisis considering the strain of healthcare costs, burden of disease complications and reduction in quality of life. The ability to identify all potential influences on this looming crisis continues to be vital.

T2DM is a metabolic disorder related to a signalling defect leading to insulin resistance that prevents glucose from entering into the cell.³ The pathophysiology of T2DM differs from type 1 diabetes mellitus (T1DM) in many ways with the primary characteristic of T2DM being insulin resistance, whereas beta cell destruction is the main cause of T1DM.⁴ Glycosylated haemoglobin A1c (HbA1c), reported as a percentage, is an estimation of blood glucose control and considered an acceptable diagnostic method by the American Diabetes Association.⁵ A HbA1c of 6.5% has been established as a threshold value for a diagnosis of T2DM. While many factors influence blood glucose control, the association between poor blood glucose control and micronutrient deficiencies needs to be considered.^{6–8}

Vitamin D has a functional role in maintaining blood glucose homeostasis, although this mechanism is not fully understood.^{9–13} Once metabolised into its active form, vitamin D is involved in several biochemical processes including insulin function and



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cellular glucose uptake.^{3 14 15} Vitamin D receptors have been identified in pancreatic tissue including beta cells, although its specific functional role within the pancreas is not clear.^{3 14-17}

Classifying optimal serum 25-hydroxyvitamin D (25OHD) concentrations as the biomarker for vitamin D status continues to be debated. Concentrations of 25 nmol/L (10 ng/mL) or less of calcidiol (25OHD) have been associated with calcium malabsorption increasing the risk of bone disorders and muscle dysfunction, whereas concentrations greater than or equal to 75 nmol/L (30 ng/mL) have been associated with normal function.^{14 17} Inconsistency in 25OHD concentrations used to define deficiency in previous research studies creates a challenge in determining the threshold value for evaluating an association between vitamin D status and risk for T2DM. Few research studies have been designed to assess the relationship among varying levels of serum 25OHD concentrations and measures of blood glucose control among adults in the USA.^{10 13 18 19} Therefore, the primary aim of this study is to describe the relationship between serum 25OHD concentrations and measures of HbA1c percentage in a large cross-sectional sample of adults in the USA, using National Health and Nutrition Examination Survey (NHANES) data from 2003 to 2010. The second aim of this study is to determine whether lower 25OHD concentrations are associated with greater odds of having a HbA1c greater than or equal to 6.5%.

METHODS

Data were obtained using publicly available information from NHANES for 2003 to 2010 (<https://www.cdc.gov/nchs/nhanes/index.htm>). Information regarding laboratory and interview protocols for NHANES data collection has been published elsewhere.²⁰ Participants in this study

included adult men and non-pregnant women 20 years of age and older. The sample was further restricted to include participants with a measured HbA1c% and serum 25OHD concentrations.

Results from previously published research indicate decreased bioavailability of vitamin D among obese individuals.²¹ Significant reduction of serum 25OHD concentrations have been observed with increasing body mass index (BMI); however, this relationship does not appear to be reciprocated (ie, no influence on body fat accumulation).^{22 23} Increased adipose tissue is involved in endocrine disruption of vitamin D disposition resulting in lower circulating 25OHD.^{23 24} Given the strong relationship between obesity and serum 25OHD, we included BMI as a control variable in our analyses. Additionally, we controlled for demographic variables including age, sex and race.

Statistical methods

Continuous variables were reported as mean (SD) and categorical variables as frequency (percentage). Our primary aim was to determine whether 25OHD measures are predictors of HbA1c >6.5%. We conducted binary logistic regression using SPSS V.24, using the continuous variables for serum 25OHD to determine the OR and 95% CI for HbA1c >6.5% while adjusting for sex, race and BMI. Observing a consistent significant association between measures of serum 25OHD and HcA1c across the NHANES cycles, measures of serum 25OHD were grouped into quartiles in order to determine which serum 25OHD measures were at greater odds of having a HbA1c >6.5% compared with greater measures of 25OHD. Quartiles of 25OHD were entered into a binary logistic regression model to determine the OR and 95% CI for HbA1c >6.5% while adjusting for age, sex, race and

Table 1 Descriptive information NHANES 2003 to 2010

| Variables | 2003 to 2004 | 2005 to 2006 | 2007 to 2008 | 2009 to 2010 |
|----------------------------------|--------------|--------------|--------------|--------------|
| Sex N (%) | | | | |
| Male | 2130 (48.4) | 2112 (49.9) | 2206 (48.8) | 2729 (48.2) |
| Female | 2272 (51.6) | 2297 (52.1) | 2318 (51.2) | 2931 (51.8) |
| Race N (%) | | | | |
| Mexican American | 881 (20) | 901 (20.4) | 792 (17.5) | 1049 (18.5) |
| Hispanic | 134 (3) | 136 (3.1) | 515 (11.4) | 577 (10.2) |
| Non-Hispanic white | 2359 (53.6) | 2228 (50.5) | 2209 (48.8) | 2751 (48.6) |
| Non-Hispanic black | 836 (19) | 975 (22.1) | 833 (18.4) | 968 (17.1) |
| Other | 192 (4.4) | 169 (3.8) | 175 (3.9) | 315 (5.6) |
| Age (years) M (±SD) | 50.4 (19.4) | 48.1 (18.7) | 50.9 (17.8) | 49.3 (17.7) |
| 25OHD (nmol/L) M (±SD) | 58.7 (24.0) | 57.1 (21.0) | 57.5 (24.4) | 60.1 (25.8) |
| HbA1c (%) M (±SD) | 5.6 (0.96) | 5.6 (1.0) | 5.8 (1.0) | 5.7 (1.0) |
| BMI (kg/m ²) M (±SD) | 28.4 (6.3) | 28.8 (6.8) | 29.0 (6.6) | 29.2 (6.8) |

BMI, body mass index; HbA1c, haemoglobin A1c; NHANES, National Health and Nutrition Examination Survey; 25OHD, 25-hydroxyvitamin D.

Table 2 Binary logistic regression model predictors HbA1c >6.5% NHANES 2003 to 2010

| Variable | 2003 to 2004 exp (B), 95% CI | 2005 to 2006 exp (B), 95% CI | 2007 to 2008 exp (B), 95% CI | 2009 to 2010 exp (B), 95% CI |
|----------|--------------------------------------------------------------------------------|-------------------------------------------------------------------------------|-------------------------------------------------------------------------------|-------------------------------------------------------------------------------|
| 25OHD | 0.983 (0.978 to 0.987)* 0.980 (0.975 to 0.985)† 0.985 (0.979 to 0.990)‡ | 0.974 (0.968 to 0.980)* 0.970 (0.964 to 0.976)† 0.976 (0.969 to 0.982)‡ | 0.986 (0.982 to 0.990)* 0.984 (0.980 to 0.988)† 0.989 (0.984 to 0.993)‡ | 0.988 (0.985 to 0.992)* 0.984 (0.980 to 0.987)† 0.988 (0.984 to 0.991)‡ |
| BMI | 1.069 (1.054 to 1.084)* 1.091 (1.074 to 1.109) † 1.078 (1.061 to 1.096)‡ | 1.073 (1.059 to 1.088)* 1.092 (1.076 to 1.109)† 1.079 (1.063 to 1.096)‡ | 1.078 (1.065 to 1.092)* 1.097 (1.083 to 1.112)† 1.089 (1.074 to 1.105)‡ | 1.078 (1.066 to 1.090)* 1.095 (1.082 to 1.109)† 1.088 (1.074 to 1.101)‡ |

p<0.0001.

*Univariate model.

†Controlled for age, sex and race.

‡Multivariate model controlled for age, sex, race and BMI.

BMI, body mass index; HbA1c, haemoglobin A1c; NHANES, National Health and Nutrition Examination Survey; 25OHD, 25-hydroxyvitamin D.

BMI. For all analyses, p value <0.05 was considered statistically significant.

RESULTS

Results for descriptive characteristics for each NHANES cycle are presented in table 1. Using binary logistic regression analyses, the odds of having a HbA1c measure of 6.5% or greater was associated with having a greater BMI and lower measure of 25OHD (table 2). This was consistent for each NHANES cycle. When all variables were added into the full model, including sex, race, BMI and 25OHD, the BMI and 25OHD were associated with greater odds of having a HbA1c of 6.5% or greater. Adults with a 25OHD in the lowest quartile have greater odds of having a HbA1c of 6.5% or greater when compared with those in the highest quartile (table 3). Furthermore, the odds of having a HbA1c percentage of 6.5% or greater remained statistically significant for each quartile of 25OHD below the reference.

DISCUSSION

The aim of this study was to describe the relationship between serum concentrations of 25OHD and HbA1c. We observed that lower measures of serum 25OHD were associated with greater HbA1c. Additionally, adults with serum 25OHD concentrations within the lowest quartile had significantly greater odds of having a higher HbA1c% compared with adults with concentrations in the highest quartile. Furthermore, we found that adults with serum 25OHD concentrations within the acceptable or recommended ‘sufficient’ range of serum 25OHD (30–50 nmol/L) had greater odds of having a HbA1c >6.5%.

The results from the present study coincide with similar studies where greater risk of T2DM was associated with lower serum 25OHD concentrations.^{10 13 25} In

a cross-sectional study of adults 18 years of age and older, an inverse relationship was observed between HbA1c levels and serum 25OHD concentrations.²⁶ Authors of a longitudinal study from Finland reported lower incidence of T2DM among men and women in the highest serum 25OHD quartile compared with the lowest quartile.²⁷ A

Table 3 Quartiles of serum 25OHD in multivariate logistic regression model predictor HbA1c >6.5%

| Quartiles serum 25OHD (N, %) | OR (95% CI) |
|---------------------------------------------------|---------------------------------------------------------------------------------------------------|
| Q1: 0 to 41 nmol/L N=4879 (26.4) | 2.60 (2.26 to 3.01)* 3.08 (2.65 to 3.59)† 2.37 (2.03 to 2.77)‡* |
| Q2: 42 to 56 nmol/L N=4879 (26.4) | 1.85 (1.58 to 2.16) ^A * 1.97 (1.68 to 2.31) ^B † 1.68 (1.56 to 1.61)‡* |
| Q3: 57 to 72 nmol/L N=4430 (24) | 1.48 (1.26 to 1.74)* 1.49 (1.27 to 1.75)† 1.37 (1.16 to 1.61)‡ |
| Q4 (reference): 73 to 260 nmol/L N=4472 (24.2) | 1 |

p<0.0001.

*Univariate model.

†Controlled for age, sex and race.

‡Multivariate model controlled for age, sex, race and BMI.

BMI, body mass index; HbA1c, haemoglobin A1c; 25OHD, 25-hydroxyvitamin D.

strength of our study is the large sample size of adults over the age of 20 years living in the USA. Although NHANES is designed to represent individuals living in the USA, it is cross-sectional data including measurements from one time point limiting the generalisability to all populations. We did not account for use of medications to treat diabetes due to a large percentage of missing data. Approximately 2% or less of the sample size for each NHANES cycle reported use of insulin to control their blood glucose. Additionally, >90% of responses regarding use of oral medication for diabetes was missing. We were unable to consider the time of year in which blood samples were collected and analysed due to lack of availability. Neither was supplemental dietary vitamin D.

In conclusion, lower serum 25OHD is associated with poor glycaemic control among adults 20 years and older. Since adults with serum 25OHD levels considered to be sufficient had greater odds of having a HbA1c >6.5%, additional research is needed to determine appropriate threshold serum 25OHD concentrations associated with optimal glucose metabolism.

Contributors MN analysed the data and wrote the manuscript. JIB contributed to manuscript editing, the study design and manuscript revisions. All authors contributed to the critical interpretation of the results, reviewed the manuscript for important intellectual content and approved the final version of the manuscript. MN is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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