Association of vitamin D deficiency with incidence of type 2 diabetes in high-risk Asian subjects

Soo Lim, Min Joo Kim, Sung Hee Choi, Chan Soo Shin, Kyong Soo Park, Hak Chul Jang, Liana K Billings, and James B Meigs

ABSTRACT

Background: Recent studies suggest an association between 25-hydroxyvitamin D [25(OH)D] and type 2 diabetes (T2D) risk. However, prospective studies investigating the relation between vitamin D inadequacy and incidence of T2D incorporating obesity and dynamic measures of insulin resistance (IR) and pancreatic β cell function are limited.

Objective: We tested the hypothesis that baseline 25(OH)D is associated with the incidence of T2D in high-risk subjects for up to 5 y of follow-up, independently of obesity, baseline IR, and β cell function.

Design: We recruited 1080 nondiabetic Korean subjects [mean ± SD age: 49.5 ± 11.4 y] based on the presence of one or more risk factors for T2D, including obesity, hypertension, dyslipidemia, and/or family history of T2D. We measured anthropometric and biochemical indicators, HOMA2-IR, and the insulinogenic index (IGI; calculated as change in insulin at 30 min/change in glucose at 30 min) from a 75-g oral-glucose-tolerance test.

Results: Of the participants, 10.5% had a serum 25(OH)D deficiency (<10 ng/mL), 51.6% had an insufficiency (10.0–19.9 ng/mL), and 38.0% had a sufficiency (≥20 ng/mL), and the incidence of T2D at 32.3 ± 15.6 mo (±SD) declined accordingly: 15.9%, 10.2%, and 5.4%, respectively (P < 0.001). After adjustment for age, sex, blood pressure, lifestyles, family history, season, parathyroid hormone, and high-sensitivity C-reactive protein, the participants with 25(OH)D deficiency had an increased risk of T2D independently of BMI, HOMA2-IR, and IGI; the ORs were 2.06 (95% CI: 1.22, 3.49) for 25(OH)D 10–19.9 ng/mL compared with ≥20 ng/mL and 3.23 (95% CI: 1.66, 6.30) for 25(OH)D <10 ng/mL compared with ≥20 ng/mL.

Conclusion: The current prospective study suggests that vitamin D metabolism may play a role in T2D pathogenesis independently of known risk factors. This trial was registered at clinicaltrials.gov as NCT01508481.

INTRODUCTION

Cross-sectional studies have shown that 25-hydroxyvitamin D [25(OH)D] concentration, a commonly used marker for vitamin D status, is lower in individuals with type 2 diabetes (T2D) and impaired glucose tolerance than in those with normal glucose tolerance (1, 2). Prospective studies have shown a significant inverse association between baseline serum 25(OH)D and incident diabetes (3–11). In some studies, the association persisted after adjustment for T2D risk factors such as obesity, fasting glucose, and hypertension (3, 5, 6, 9, 11), whereas in other studies the association was attenuated or disappeared after adjustment for other T2D risk factors, such as BMI (7, 8, 10).

The mechanisms whereby low 25(OH)D concentrations increase T2D risk are not well understood. Cross-sectional studies have reported associations of 25(OH)D with insulin resistance (12, 13) and β cell function (14, 15), whereas others have not found an association (16, 17). The aforementioned prospective studies did not adjust for specific glycemic measures of insulin secretion or insulin sensitivity. A few prospective studies to date have shown an association between baseline 25(OH)D and future insulin resistance as measured on the basis of the HOMA-IR (4, 11, 18) and fasting insulin concentration (4). A most recent study by Kayaniyil et al (18), who examined the insulinogenic index (IGI) adjusted for insulin resistance, found that higher baseline 25(OH)D predicted better β cell function and decreased progression to T2D; however, this association was not significant after adjustment for BMI. Thus, the influence of vitamin D on diabetes risk after the effects of insulin secretion, insulin...
sensitivity, and overall adiposity are accounted for is not clearly understood.

Few studies have examined the association in high-risk populations, in whom preventive interventions are most likely to be targeted (7, 18). Asian populations are of special interest because vitamin D deficiency is common and the diabetes burden is increasing (19, 20). In this prospective study, we aimed to investigate the association between 25(OH)D status and T2D incidence, independent of obesity and specific baseline measures of insulin resistance and β cell function, in 1080 nondiabetic Korean subjects at high risk of diabetes development.

SUBJECTS AND METHODS

Study population

More than 10,000 people underwent a routine physical check at our institution, the Seoul National University Bundang Hospital (SNUBH), Seongnam, Korea, in 2006. Of them, we consecutively included 1487 men and women aged 30–69 y who had cardiometabolic risk factors and gave their informed consent to the Biomarkers on Glucose Metabolism and Cardiovascular Risk study. The study participants in this study were from all over South Korea: the approximate geographic coordinates of South Korea are 33° to 38° North and 124° to 131° East. The goal of the Biomarkers on Glucose Metabolism and Cardiovascular Risk Study was to investigate associations between biomarkers and incidence rates of T2D in subjects at high risk of T2D.

After 257 participants with T2D diagnosed on the basis of glycated hemoglobin (Hb A1c) ≥ 6.5% were excluded, non-diabetic participants with one or more risk factors for diabetes—including overweight [defined as a BMI (in kg/m²) ≥ 25; 55.0% of all recruited participants], hypertension [defined on the basis of the Joint National Committee 7 report (21) as ≥ 140 (systolic blood pressure)/90 (diastolic blood pressure) mm Hg or the use of antihypertensive medications; 19.5% of all recruited participants], dyslipidemia [defined by high triglycerides (> 150 mg/dL) or low HDL cholesterol (< 40 mg/dL in men and < 50 mg/dL in women) or lipid-lowering-medication use; 21.1% of all recruited participants], a family history of diabetes (6.8% of all recruited participants), and/or prediabetes (defined as Hb A1c ranging from 6.0 to 6.4%; 2.1% of all recruited participants)—were included. At baseline and follow-up, we used Hb A1c instead of fasting plasma glucose or postprandial 2-h glucose to diagnosis diabetes, because the variability of Hb A1c is less than that of fasting plasma glucose or 2-h plasma glucose (22).

In this cohort, 14.2% of participants were taking antihypertensive medications: 89 (8.2%) were taking calcium channel blockers, 59 (5.5%) angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, 28 (2.6%) β-blockers, 24 (2.2%) diuretics, and 6 (0.6%) other drugs. For lipid control, 10.9% of participants were taking lipid-lowering medications: 97 (9.0%) were taking statins, 19 (1.8%) fibrates, 3 (0.3%) niacin, 4 (0.4%) omega-3 (n-3) fatty acids, and 2 (0.2%) other medications. Totals of 4.9% and 0.7% of participants were taking more than one antihypertensive medication (n = 53) or lipid-lowering medication (n = 8), respectively; 8.4% of participants (n = 91) were taking both antihypertensive and lipid-lowering medications.

In addition, 150 participants were excluded because they were taking vitamin D supplements. Finally, 1080 participants were enrolled at baseline. Participants were assessed at 6-mo intervals for up to 5 y (from 1 January 2007 to 31 December 2011) to collect data on development of T2D and fasting plasma glucose, Hb A1c, and lipid concentrations. Use of vitamin D supplements was also checked at every 6-mo visit. This study was approved by the SNUBH’s institutional review board. Written informed consent was obtained from every participant.

Primary endpoint

The primary endpoint was the development of T2D, which was defined as Hb A1c ≥ 6.5% based on one of the American Diabetes Association’s diagnosis criteria for diabetes (22). Hb A1c was measured with a Bio-Rad Variant II Turbo HPLC analyzer in SNUBH—a National Glycohemoglobin Standardization Program level II–certified laboratory. We excluded 5 participants with type 1 diabetes by measuring glutamic acid decarboxylase antibody (> 1 unit/mL) for cases who had typical symptoms, including extreme thirst, increased hunger, frequent urination, and unexplained weight loss and fatigue with sudden onset.

25(OH)D Concentration as a primary exposure

To assess vitamin D status (23), serum 25(OH)D was measured by using Diels–Alder derivatization and ultraperformance liquid chromatography–tandem mass spectrometry (Waters)—a gold standard for evaluating 25(OH)D concentration (24). Total 25(OH)D was summed from 25(OH)D3 and 25(OH)D2. Calibration with standard reference material 972 from the National Institute of Standards and Technology was done, and the intra- and inter assay CVs were 4.0% and 7.7% at 29.0 ng/mL, respectively. We also recorded dates of 25(OH)D measurement and categorized them into 4 seasons: spring (March–May), summer (June–August), fall (September–November), and winter (December–February). In the current study, 20 ng/mL 25(OH)D was used as a cutoff for vitamin D sufficiency according to the recommendation from the WHO and more recently the Institute of Medicine (25, 26).

Confounding clinical and biochemical exposures

Height, body weight, waist circumference, and BMI were measured by using standard methods. Blood pressure measurements were made after participants were seated for 10 min. Measurements were made twice, with a 5-min rest period between measurements, and the mean value of measurements was used.

Smoking status was divided into 3 categories: current smokers (if the subjects smoked currently for ≥ 1 y), nonsmokers (if the subjects never smoked), and ex-smokers (if the subjects had quit). Alcohol intake was assessed by questioning patients about how often they usually drank beer, spirits, sake, or wine during the most recent 12 mo, quantified according to the following categories: 1) almost every day, 2) 3–4 d/wk, 3) once or twice a week, 4) once or twice a month, or 5) never in the past year. Patients were also asked how much they usually drank on a drinking day (reported in mL). Alcohol intake (in g alcohol/wk) was determined by multiplying the weekly intake of each
alcoholic beverage by its ethanol content (beer 5%, spirits 40%, sake 12%, and wine 12%), which was categorized into 3 categories: abstinent (<20.0 g/wk), mild to moderate (20.0–199.9 g/wk), or heavy (≥200 g/wk) drinker.

Participants’ involvement in leisure and sport activities (eg, walking, jogging, running, aerobics, dancing, yoga, cycling, hiking, climbing, skating, swimming, table tennis, badminton, tennis, basketball, soccer, and golf) were surveyed for physical activity, which was classified into 3 categories: none, irregular (1–2 times/wk), and regular (≥3 times/wk) exercise or used as a continuous variable. One bout of exercise was defined as exercising for ≥30 min.

In a 12-h fasting state, a 75-g oral-glucose-tolerance test (OGTT) was done at baseline. Fasting and postglucose load at 30 min and 2-h glucose and fasting and postglucose load at 30 min insulin concentrations were measured. Plasma glucose concentrations were measured with a Hitachi 747 chemistry analyzer, and plasma insulin concentrations were measured by radioimmunoassay (Linco). The fasting concentrations of triglycerides and HDL were measured by using the Hitachi 747 chemistry analyzer. High-sensitivity C-reactive protein (hsCRP) concentrations were measured by immunonephelometry (Dade Behring). Circulating concentrations of intact parathyroid hormone (iPTH) were measured by using an electrochemiluminescence immunoassay on the Modular Analytics E170 platform (Roche).

Mediating physiologic exposures

To evaluate insulin resistance, HOMA2-IR was calculated from fasting glucose and insulin concentrations as reported previously (27). Pancreatic β cell function was evaluated by taking the IGI, which was calculated by the ratio of 30-min insulin minus fasting insulin to 30-min glucose minus fasting glucose (Δinsulin30/Δglucose30) (28) and has been validated against the gold standard measures of insulin secretion (first-phase insulin secretion on intravenous glucose tolerance testing) (29).

Statistical analysis

All data are presented as means ± SDs and were analyzed by using SPSS Windows version 17.0 (SPSS Inc). Triglyceride and hsCRP concentrations were normalized by logarithmic transformation. The differences in continuous variables between 25(OH)D classifications were tested by using ANOVA followed by Tukey’s multiple-comparison test. Categorical variables were compared by the linear-by-linear association analysis. Correlations between variables were analyzed by using Pearson correlation. The HRs of 25(OH)D on T2D risk were determined by using the Cox proportional hazard model, with T2D incidence as the dependent variable. The following variables were included as independent variables in model 1: age, sex, systolic blood pressure, physical activity, family history of T2D, smoking status, alcohol consumption, antihypertensive medication use, lipid-lowering-medication use, season at 25(OH)D measurement, Hb A1c, log-transformed triglycerides, HDL cholesterol, iPTH, and log-transformed hsCRP. In model 2, BMI was additionally adjusted for. In model 3, HOMA2-IR and IGI were additionally adjusted to the model 2. Significance was defined as 2-sided P < 0.05.

RESULTS

Comparison of variables at baseline according to 25(OH)D categories

The current study participants were aged 49.5 ± 11.4 y, and 46.2% were men. The concentration of 25(OH)D was 19.6 ± 9.3 ng/mL. The 25(OH)D concentrations measured in winter were similar to those measured in other seasons: 19.1 ± 8.4 ng/mL in winter, 19.4 ± 9.1 ng/mL in spring, 20.0 ± 9.9 ng/mL in summer, and 20.1 ± 9.9 ng/mL in fall.

In Table 1, the clinical characteristics and biochemical variables are compared according to 25(OH)D categories: ≥20.0 ng/mL (50 nmol/L; sufficient) compared with 10.0–19.9 ng/mL (25–50 nmol/L; insufficient) compared with <10.0 ng/mL (25 nmol/L; deficient). These cutoff values were suggested by the WHO and Institute of Medicine (25, 26). No significant differences in Hb A1c and fasting glucose and insulin concentrations obtained during the OGTT were found between the 3 groups. Postglucose load 30-min insulin concentrations were higher in participants with 25(OH)D sufficiency than in those with 25(OH)D insufficiency or deficiency. The participants in the 25(OH)D sufficient group had a higher IGI and a lower HOMA2-IR than did those in the 25(OH)D-insufficient or -deficient groups.

The correlation analysis showed that the serum 25(OH)D concentration correlated negatively with fasting and postload 30-min insulin concentrations, HOMA2-IR, iPTH, and hsCRP and positively with serum calcium and IGI (all P < 0.05) (see Supplementary Table 1 under “Supplemental data” in the online issue).

Primary outcome: incidence of T2D

Of the 1080 participants, 97 (9.0%) developed T2D over 32.3 ± 15.6 mo of observation. The incidence rates of T2D, defined as Hb A1c ≥ 6.5%, were 15.9%, 10.2%, and 5.4% in the 25(OH)D-deficient, -insufficient, and -sufficient groups, respectively (P < 0.01). Kaplan-Meier analysis showed a higher probability of developing T2D in participants in the 25(OH)D-deficient group than in those in the 25(OH)D-insufficient or 25(OH)D-sufficient group (P < 0.01) (Figure 1).

Using the Cox proportional hazard model, we further investigated the independent role of 25(OH)D concentration in T2D development during the 5-y follow-up period (Table 2). No subject died before T2D development. In model 1, participants with 25(OH)D insufficiency and deficiency had a higher incidence of T2D than both those with 25(OH)D sufficiency: the HRs were 1.85 and 3.40, respectively. In model 2, in which BMI was additionally adjusted for, the significant associations between 25(OH)D concentration and incidence of T2D were maintained: HRs for the 25(OH)D-insufficient and -deficient group (P < 0.01) (Figure 2).

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also significantly associated with the incidence of T2D ($P = 0.001–0.033$).

On the basis of the 75-g OGTT result at baseline, 48.7% and 20.5% of participants in this study were classified as IFG (fasting glucose concentration = 100–125 mg/dL) and IGT (postload 2-h glucose concentration = 140–199 mg/dL), respectively. When quartiles of 25(OH)D concentrations were used instead of current 25(OH)D categories, a similar but attenuated trend was found between 25(OH)D status and incidence of T2D (HR of lowest quartile compared with highest quartile: 2.41; 95% CI: 1.21, 5.75). The fact that the highest-quartile 25(OH)D group (24.5–60.4 ng/mL) overlapped with our defined 25(OH)D-insufficient group may explain the slightly attenuated findings. When 56 participants who had taken vitamin D supplements for 3 mo during the follow-up period were excluded in the hazard models, similar results were obtained.

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### Discussion

In this study of an Asian population at high risk of T2D, we showed that the participants with 25(OH)D deficiency had an incidence of T2D development 3.4 times that in those with sufficient levels, even after adjustment for obesity, dynamic measure of insulin resistance and pancreatic $\beta$ cell function, and other known risk factors for T2D.

Vitamin D is a multifunctional hormone that can affect many essential biological functions, ranging from immune regulation to...
mineral ion metabolism. Although the major function of vitamin D is to maintain calcium and phosphate homeostasis and to promote bone mineralization, many extraskeletal roles for vitamin D have been identified (32). We recently found that vitamin D inadequacy is associated with significant coronary artery stenosis in a community-based elderly cohort (33). Other investigators have shown that low vitamin D status is associated with an increased risk of various diseases, such as cancer, hypertension, and cardiovascular disease (32).

To date, a significant inverse association has been found between serum 25(OH)D and T2D or impaired glucose metabolism in both cross-sectional studies (1, 2) and longitudinal studies (3, 4, 11, 18). These studies have found that BMI is the key confounding factor, because obesity is correlated with low vitamin D and high T2D risk (7, 8, 10). In our study, obesity was accounted for explicitly by adjusting for BMI or waist circumference in the regression models, which did not attenuate the association between vitamin D and T2D risk. Most recently, a meta-analysis provided evidence of a strong inverse association between circulating 25(OH)D concentrations and risk of incident T2D (5). This association remained in a new analysis of the European Prospective Investigation into Cancer and Nutrition–Norfolk study after adjustment for relevant confounding factors (5).

Of note, the previous studies that investigated the association between vitamin D and T2D did not adjust for dynamic baseline glycemic measures of insulin secretory function or insulin sensitivity (3, 4, 11). In contrast, our study highlights the influence of 25(OH)D concentration on T2D incidence, independent of baseline measures of insulin secretion and sensitivity—potential risk factors for T2D development. We examined the independent contribution of 25(OH)D concentration to T2D risk after adjusting for HOMA2-IR, IGI, and obesity. These data suggest that 25(OH)D is an independent predictor of T2D risk beyond BMI, body weight, and specific measures of insulin resistance and β cell function—measures for which abnormalities may predispose to T2D.

There is ample evidence in vitro and in vivo studies showing that vitamin D activity is essential for pancreatic β cell function (34–36). In our study, the circulating concentration of 25(OH)D was positively associated with IGI, which reflects acute phase insulin secretion; however, the correlation was weak ($r = 0.077$, $P < 0.05$). Insulin resistance has also been reported to be associated with vitamin D insufficiency (4, 12, 37). Vitamin D may have a direct effect on insulin sensitivity through stimulation of insulin receptor expression (38). The 25(OH)D concentration in this study was negatively correlated with HOMA2-IR, but the correlation between these 2 was also modest ($r = -0.107$, $P < 0.05$). Thus, although vitamin D may be involved in pancreatic β cell function and insulin sensitivity, the association with IR or β cell function cannot fully explain how vitamin D affects the development of T2D.

Several putative mechanisms whereby vitamin D status influences T2D risk can be postulated (32). A modest but significant correlation between 25(OH)D and serum calcium concentrations was shown in our study. Recent in vivo and in vitro studies reported that VDR gene suppression resulted in a decrease in intracellular Ca$^{2+}$ concentrations (39) and 1,25-dihydroxy-vitamin D$_3$ and calcium regulated transcription of calcium transporter genes (40). Thus, vitamin D deficiency might be associated with T2D development by calcium balance, which is essential for insulin secretion in pancreatic β cells (37).

The concentration of 25(OH)D was negatively correlated with hsCRP in the current study. A study in humans showed that the serum 25(OH)D status was inversely related to the tumor necrosis

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**TABLE 2**

Independent role of 25(OH)D for incidence of T2D

<table>
<thead>
<tr>
<th>25(OH)D groups</th>
<th>Sufficient ($n = 410$)</th>
<th>Insufficient ($n = 557$)</th>
<th>Deficient ($n = 113$)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1: MV</td>
<td>1.00</td>
<td>1.84 (1.11, 3.05)</td>
<td>3.22 (1.66, 6.26)</td>
<td>0.002</td>
</tr>
<tr>
<td>Model 2: MV + BMI</td>
<td>1.00</td>
<td>1.80 (1.08, 2.99)</td>
<td>3.25 (1.67, 6.31)</td>
<td>0.002</td>
</tr>
<tr>
<td>Model 3: MV + BMI + HOMA2-IR + IGI$^2$</td>
<td>1.00</td>
<td>2.06 (1.22, 3.49)</td>
<td>3.23 (1.66, 6.30)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

$^1$ All values are RRs (95% CIs). A Cox proportional hazards model was used for incidence of type 2 diabetes after adjustment for age, sex, systolic blood pressure, physical activity, family history of type 2 diabetes, smoking status, alcohol consumption, antihypertensive medication use, lipid-lowering medication use, season at 25(OH)D measurement, glycated hemoglobin, log-transformed triglycerides, HDL cholesterol, intact parathyroid hormone, and log-transformed high-sensitivity C-reactive protein. Sufficient, insufficient, and deficient 25(OH)D concentrations were defined as ≥20.0, 10–19.9, and <10 ng/mL, respectively. IGI, insulinogenic index; MV, multivariate; 25(OH)D, 25-hydroxyvitamin D.

$^2$ Calculated as change in insulin at 30 min/change in glucose at 30 min.
factor-α concentration (41). Another experimental study suggested that a low 25(OH)D concentration influences the activity or expression of macrophages and lymphocytes (42). These data suggest a close link between 25(OH)D concentration and inflammatory process and could suggest a potential mechanism by which vitamin D may be involved in T2D development.

In the current study, we used 20 ng/mL 25(OH)D as a cutoff for vitamin D sufficiency because the WHO and, more recently, the Institute of Medicine have suggested the use of 20 ng/mL as an adequate cutoff value (25, 26). Recent studies have adopted this value more (43, 44). Indeed, a recent study found that 20 ng/mL 25(OH)D was associated with an increased risk of relevant clinical diseases, including hip fracture, myocardial infarction, and death (45).

This study had several strengths. First, we assessed IGI, a dynamic estimate of first-phase insulin secretion, which has been validated from healthy subjects to diverse phenotypes (46, 47). Second, the serum 25(OH)D concentration was measured by ultraperformance liquid chromatography–tandem mass spectrometry, which was calibrated at the National Institute of Standards and Technology. Third, the iPTH concentration, which is important but not commonly measured, was adjusted. Inadequate vitamin D usually leads to increased iPTH, which in turn is inversely associated with insulin sensitivity (48). Last, this study was performed in high-risk subjects of Asian ethnicity. Most previous studies were done in healthy subjects (6, 8–11), and the study subjects consisted of predominantly white populations. Indeed, vitamin D insufficiency was 62% (85%) when 30 ng/mL was used as the cutoff in the current study, similar to that in other Asian countries, which indicated that up to 70% of the general population had vitamin D insufficiency, defined as 30 ng/mL 25(OH)D (19). This may represent a public health problem, considering the numerous complications and diseases associated with vitamin D deficiency (49).

Our study also had limitations. Although a sophisticated function to assess β cell function, such as IGI, was used, the gold standard technique (ie, a clamp study) was not used. We had no data on β cell function or insulin resistance at follow-up. Data on sun exposure time, use of sunscreen, and dietary habits were not captured. Last, there was a possibility of unmeasured confounding underlying the association between vitamin D and diabetes, which precluded conclusions about causality.

In conclusion, our data illustrate an independent association between 25(OH)D and T2D incidence in the prospective study of the relation between vitamin D status, T2D, and dynamic glycemic traits. Evaluation of vitamin D deficiency and its potential health effects is particularly important because 25(OH)D concentrations are lower than recommended in many countries whose diabetes burden is also highly prevalent (20, 49).

Although vitamin D deficiency is increasing, screening and treating the condition is relatively simple and inexpensive. Additional interventional trials are needed to assess whether increasing vitamin D concentrations through vitamin D–fortified diets or supplementation may prevent or mitigate the consequences of vitamin D deficiency on T2D risk.

The authors’ responsibilities were as follows—SL: guarantor of this work, had full access to all the data, and takes full responsibility for the integrity of the data and the accuracy of data analysis; SL, MJK, and HCJ: conducted the data research, contributed to the discussion, and wrote, reviewed, and edited the manuscript; and SHC, CSS, KSP, LKB, and JBM: reviewed and edited the manuscript and contributed to the discussion. None of the authors declared a conflict of interest. The sponsors played no part in the study design; the collection, analysis, or interpretation of the data; the writing of the report; or the decision to submit the manuscript for publication.

REFERENCES


