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Original article

Parathyroid hormone is associated with incident diabetes in white, but not black adults: The Atherosclerosis Risk in Communities (ARIC) Study

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Abstract

Objective. – Accumulating evidence has linked elevated parathyroid hormone (PTH) with insulin resistance, beta cell dysfunction and dysglycaemia, however, its role in the development of diabetes is largely unclear, particularly among non-whites. We sought to examine the association of PTH with the incidence of diabetes.

Methods. – We studied 8066 white and 2034 black adults aged 46–70 years at baseline (1990–92) from the ARIC Study with follow-up for incident diabetes ascertained during study visits conducted in 1993–95 and 1996–98. Hazard ratios (HR) and their 95% CIs for diabetes adjusted for demographics, lifestyle, and 25-hydroxyvitamin D were estimated according to PTH measured at baseline.

Results. – PTH was higher among blacks than whites (median [IQR], 43.8 [35.0–55.8] vs. 37.9 [30.4–47.3] pg/mL; $P < 0.001$). During a median follow-up of 6 years, 498 white and 167 black participants developed diabetes. The association of PTH with diabetes varied significantly by race (P-interaction 0.02). PTH was not associated with risk for diabetes among black adults. Among whites, HRs according to quintiles of PTH were 1 (referent), 0.95 (0.71, 1.29), 0.95 (0.70, 1.28), 1.12 (0.84, 1.51), and 1.31 (0.98, 1.76) (P-trend 0.03). When a clinical cut-point for PTH was applied ($\geq$ 65 pg/mL; 5.7% of whites), the HR for diabetes among whites was 1.38 (1.01, 1.88). Results were similar when restricted to participants with normal baseline kidney function.

Conclusion. – In this large, population-based study, elevated PTH was independently associated with risk for diabetes among white, but not black adults. Further studies are needed to elucidate the mechanisms that may underlie this differential association of PTH with diabetes across race groups.
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Keywords: Diabetes; Parathyroid hormone; Prospective study; Race

1. Introduction

Parathyroid hormone (PTH) helps to regulate circulating calcium concentrations by promoting bone resorption, suppressing urinary calcium loss, and enhancing the formation of calcitriol, the active metabolite of vitamin D. PTH levels are elevated in primary hyperparathyroidism and secondarily in vitamin D deficiency, chronic kidney disease, and other conditions.

Recent evidence has linked elevated PTH concentrations with insulin resistance, beta cell dysfunction, and dysglycaemia [1–5], which may eventually lead to the development of diabetes. Indeed, studies of patients with primary hyperparathyroidism have shown a higher prevalence of diabetes compared to control populations [6–9]. While this evidence has suggested a role for PTH in the development of diabetes, these studies have primarily included small numbers of patients recruited from medical clinics. In addition, these studies have almost exclusively included only white adults. Blacks are known to have a higher prevalence

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and incidence of diabetes [10,11], higher concentrations of PTH [12], and differences in PTH-calcium metabolism compared to whites [13–15].

The objective of the current study was to examine the association of PTH with the incidence of diabetes in the Atherosclerosis Risk in Communities (ARIC) study, a population-based cohort of white and black adults. We hypothesized that elevated PTH would be associated with greater risk of incident diabetes and that this association would vary significantly according to race group (black vs. white).

2. Materials and methods

2.1. Participants

The ARIC Study is a prospective cohort of 15,792 middle-aged adults from four U.S. communities: Forsyth County, NC; Jackson MS; Minneapolis, MN, and Washington County, MD. Only blacks were recruited in Jackson, MS, while participants in the other centres reflected the source population (mostly white). The first examination of participants (visit 1) took place from 1987 to 1989, with the first three follow-up visits (visits 2–4), each occurring approximately every 3 years. All participants provided written informed consent at each examination, and institutional review boards from each centre approved the study annually.

Serum PTH levels were measured in samples collected at visit 2 (1990–1992; baseline for this analysis), which was attended by 14,348 participants. Excluded from the analysis were participants who self-identified as neither black nor white ($n = 42$) and blacks from the Minnesota and Maryland centres ($n = 49$), due to small numbers; those who had at visit 2 fasting glucose $\geq$ 126 mg/dL, non-fasting glucose $\geq$ 200 mg/dL, a self-report of physician diagnosed diabetes or use of diabetes medications ($n = 2{,}146$), a glycated haemoglobin (HbA_{1c}) $\geq$ 6.5% ($n = 178$); an unknown diabetes status at visit 2 or during follow-up ($n = 217$); those who did not attend visits 3 or 4 ($n = 982$); those missing specimens for measurement of PTH at visit 2 ($n = 629$), and those with extreme PTH values (> 200 pg/mL, $n = 5$). For the primary analysis, our final analytic sample included 10,100 participants (8066 whites; 2034 blacks).

2.2. Clinical measurements

Standard protocols for data collection were used across study centres and examinations. Participants were asked to fast for at least 12 h before each examination and to avoid smoking or engaging in heavy physical activity for at least 2 h.

2.3. Serum PTH levels

Intact PTH was measured in previously unthawed serum on the Roche Elecsys 2010 analyser using a second-generation electrochemiluminescence immunoassay that uses a biotinylated monoclonal antibody (Roche Diagnostics, Indianapolis, Indiana, USA) in 2012–2013 at the Advanced Research and Diagnostic Laboratory, University of Minnesota, Minneapolis, Minnesota. Serum PTH by the Elecsys method has shown excellent long-term stability at −80 °C [16]. Using split samples collected at visit 2 and stored, we estimated the coefficient of variation to be 9.7% for PTH. In a sample of participants ($n = 1330$), we had a second measurement of PTH taken 3 years later and measured in the same laboratory with the same method. The 3-year Spearman correlation was 0.64.

2.4. Incident diabetes

Among those without prevalent diabetes at baseline (visit 2), we classified individuals as having incident diabetes if they met any of the following criteria: fasting glucose level of at least 126 mg/dL; non-fasting glucose level of at least 200 mg/dL; reported current use of glucose lowering medication; or a positive response to the question, "Has a doctor ever told you that you had diabetes (sugar in the blood)?" Serum glucose was available for all participants at visit 2 and nearly all participants at visits 3 and 4 (97% and 89%, respectively). Among whites, 99% fasted for at least 8 hours at each visit, and for blacks, 97%, 96%, and 95% were fasted at visits 2–4, respectively.

2.5. Other variables

Information on age, race, educational level, usual alcohol intake, and parental history of diabetes was based on self-report. Participants were asked to bring to each visit all medications taken in the 2 weeks before the examination; all medication names were transcribed and coded. Physical activity was measured with the Baecke questionnaire at visit 1, but not at visit 2, so values from visit 1 were carried forward [17]. Height and weight were measured, and body mass index (BMI) at visit 2 was calculated as weight in kilograms divided by height in meters squared. Waist circumference was measured in centimetres at the level of the umbilicus. Sitting blood pressure was measured in triplicate with a random-zero sphygmomanometer; the mean of the last two measurements was used.

Serum 25-hydroxyvitamin D [25(OH)D], calcium, and phosphorous were also measured in 2012–13 in stored specimens from visit 2. 25(OH)D was measured using LC/MS/MS instrumentation (coefficient of variation 10.9%). Calcium, albumin, and phosphorous were measured on the Roche Modular P Chemistry Analyser (Roche Diagnostics) using colorimetric methods. The coefficient of variation was 2.4% for calcium and 3.0% for phosphorous. Calcium levels corrected for albumin were calculated. Serum glucose level was measured by a modified hexokinase-glucose-6-phosphate dehydrogenase procedure at each visit. Insulin was measured by radioimmunoassay at visit 2. HbA_{1c} was measured in frozen whole-blood samples from visit 2 using high performance liquid chromatography (Tosoh 2.2 Plus in 2002–04 and the Tosoh G7 in 2007–08; Tosoh Corporation, Tokyo, Japan) [18]. Serum creatinine was measured at visit 2 using a modified Jaffe reaction. Cystatin C was measured in 2012–2013 from stored samples collected at visit 2 using the Gentian cystatin C assay on the Roche Modular P Chemistry analyser. Plasma triglycerides were determined by enzymatic