Bone Reports 5 (2016) 104–109

Contents lists available at ScienceDirect

Bone Reports

journal homepage: www.elsevier.com/locate/bonr

Smoking habits and parathyroid hormone concentrations in young adults: The CARDIA study

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ARTICLE INFO

Article history:
Received 29 December 2015
Received in revised form 29 March 2016
Accepted 27 April 2016
Available online 28 April 2016

Keywords:
Parathyroid hormone
Smoking
Young adults

ABSTRACT

Conflicting results have been reported concerning a relationship between smoking and serum PTH. Our study objective was to examine whether smoking was associated with serum PTH independent of correlates of PTH among young adults, and explore potential mechanisms.

This was a cross-sectional study of healthy individuals, 24–36 years old, examined during 1992 through 1993 in California, USA (a subset of Coronary Artery Risk Development in Young Adults study).

Linear regression was used to obtain adjusted means of PTH according to smoking habit (current, former, never). Biomarkers for calcium metabolism and bone turnover (including serum concentrations of osteocalcin, bone-specific alkaline phosphatase, and 24-hour urinary excretion of calcium) and bone mineral density were similarly compared by smoking.

376 participants were analyzed (171 women, 181 black). Over half reported never smoking. We observed lower PTH in current smokers compared to non-smokers and found no evidence of an interaction by race and sex. PTH was lowest in current smokers, intermediate in former smokers, and highest in never smokers (geometric mean PTH: 23.6, 26.7, 27.4 pg/mL, respectively: P for trend, 0.006) after adjusting for potential confounders including calcium intake. Among the biomarkers, serum osteocalcin concentration and 24-hour urinary excretion of calcium were lowest in current smokers. We observed no smoking-related difference in bone mineral density.

In this community-based sample of young adult men and women, smoking was associated with significantly lower PTH concentration. The mechanism and clinical implication of the finding, however, remains uncertain.

1. Introduction

Smoking is generally associated with lower concentration of vitamin D, lower bone mineral density and increased risk of fracture in the elderly. Therefore, a compensatory increase in parathyroid hormone (PTH) may be expected (Jorde et al., 2005). However, conflicting results have been reported in the literature on the relation between smoking and PTH. While some studies reported higher PTH among smokers (i.e. expected direction) (Rapuri et al., 2000; Szulc et al., 2002; Ortego-Centeno et al., 1997), others have reported lower PTH concentration among smokers (Mellstrom et al., 1993; Landin-Wilhelmsen et al., 1995; Brot et al., 1999; Need et al., 2002). One of the largest population-based observational studies documented this unexpected finding cross-sectionally (Jorde et al., 2005), yet the underlying mechanism and clinical implication of the finding remains to be elucidated.

In this study, we investigated a cross-sectional relationship between smoking habits and concentration of PTH using a population-based sample of men and women in the USA. The primary aim was to investigate whether PTH concentration differs among current, former and

Abbreviations: PTH, Parathyroid hormone; CARDIA, Coronary Artery Risk Development in Young Adults; BMI, Body mass index; 25OHD, 25-hydroxyvitamin D; $1,25(OH)_2D$, 1,25-dihydroxyvitamin D; BAP, Bone-specific alkaline phosphatase; U-PYDcr, 24-hour urinary excretion of pyridinoline standardized for urinary excretion of creatinine; BMD, Bone mineral density.

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http://dx.doi.org/10.1016/j.bonr.2016.04.003

never smokers after accounting for potential confounders. In light of inconsistencies in the literature, we did not have a hypothesis about the direction of the PTH and smoking association. The secondary aim was to explore potential mechanisms using biological markers related to calcium metabolism and bone turnover according to smoking habit.

2. Methods

2.1. Study population

We studied a subgroup of participants of the Coronary Artery Risk Development in Young Adults (CARDIA) study. A detailed description of CARDIA has been published elsewhere (Friedman et al., 1988). In brief, CARDIA is a cohort study of the evolution of cardiovascular risk among young adults, conducted since 1985. The participants for the present study were enrolled in the CARDIA study in the Oakland Clinical Center, California, who were returning for their fourth examination from June 1992 through May 1993 to participate in an ancillary study of bone mineral homeostasis (Bikle et al., 1999). All subjects, aged 24–36 years, were in good health and had a serum creatinine level <1.6 mg/dL and a serum calcium level ranging from 8.8 to 10.3 mg/dL. Within the year before the examination, all women menstruated regularly, were not taking oral contraceptive agents, and had not been pregnant ≥ 10 weeks or breastfeeding. Subjects with medical conditions or taking medications known to alter calcium homeostasis were excluded from the study (Bikle et al., 1999). The data were collected with written informed consent and with approval of the local Institutional Review Board. Of 402 ancillary study participants, we included those participants with no missing variables directly relevant to the primary aim (i.e. to examine association between smoking and PTH). We excluded those who gave unrealistic estimate of energy intake (800 or 8000 kcal/day in men; 600 or 6000 kcal/day in women), leaving 376 participants for analysis.

2.2. Measurement

Demographic information was obtained using standardized questionnaires. Weight was measured on a balance beam scale. Height was measured using a vertically mounted metal centimeter ruler. Body mass index (BMI) was computed as weight (kg) divided by square of height (m). At examination, fasting blood including creatinine, phosphate and calcium (collected between 8:00 and 11:00 AM) and 24-hour urine samples were obtained for analysis using routine laboratory procedures and an automated chemistry analyzer (Bikle et al., 1999).

PTH and other biomarkers were measured on stored samples 3 years after study completion (Bikle et al., 1999; Ettinger et al., 1997). PTH was measured using a 2-site immunoradiometric assay that detects only intact PTH (i.e. biologically active 84-amino-acid peptide) (Nussbaum et al., 1987). Serum 25-hydroxyvitamin D (25OHD) was measured by RIA in the Calciotropic Hormone Reference Laboratory, University of California, San Francisco. Serum 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) was measured by a competitive protein-binding assay using the vitamin D receptor present in calf thymus cytosol (Bikle et al., 1999). Osteocalcin was measured using a mid-molecule–specific RIA for human osteocalcin (Taylor et al., 1988). Bone-specific alkaline phosphatase (BAP) was measured spectrophotometrically after heat inactivation (Farley et al., 1981). Free pyridinoline cross-links in urine were measured using an ELISA developed by Metra Biosystems (Seyedin et al., 1993). The results of this method were compared with that of direct assessment after HPLC purification (Black et al., 1988) for 20 subjects in each race and gender group to verify the comparability of this method with that using HPLC ($r > 0.9$ for all groups) before adopting this method for use in assessing all subjects (Bikle et al., 1999). 24-hour urinary excretion of pyridinoline was standardized for urinary excretion of creatinine (U-PYDcr) for analysis.

2.3. Assessment of lifestyle information

The usual diet was assessed by a diet history interview (CARDIA dietary history) in which food models and measuring cups and spoons were used to estimate portion size. The previous month was used as a frame of reference for estimating the usual intake. Intake of dietary calories and calcium were estimated according to the nutrient data base developed by the Nutrition Coordinating Center at the University of Minnesota. The estimate of calcium intake included supplemental sources. Validity and reliability of the CARDIA dietary history has been published elsewhere (Liu et al., 1994). Sun exposure time was assessed by query for weekday and weekend separately and then calculated as hours per week. The CARDIA physical activity history questionnaire was used to quantify physical activity level, and scored accordingly (physical activity score). The amount of time per week spent in leisure, occupational, and household physical activity over the previous 12 months was assessed. We estimated total physical activity expressed in exercise units as a product of intensity and frequency. The validity and reliability of the questionnaire was published elsewhere (Jacobs et al., 1989).

Additionally, we examined bone mineral density (BMD) at various sites according to smoking habit. Dual-energy x-ray absorptiometry measurement of BMD for the whole body, total hip, left and right total arms, and lumbar spine was obtained by using a Hologic QDR 2000 densitometer (Hologic, Inc.) in the array scanning mode, separately for each area of the body (total hip, lumbar spine, and whole body). The total arm was assessed using the whole-body scan (Fujiyoshi et al., 2013). In vivo precision for BMD, based on repeated scans of 20 volunteers done 1 to 6 weeks apart and expressed as a coefficient of variation, was 0.9% for whole-body BMD.

2.4. Statistical analysis

We used linear regression models to obtain adjusted PTH concentrations according to smoking habits (Current, Former, and Never). Due to skewed distributions, we log-transformed the following variables in our statistical models: PTH, 25OHD, BAP, U-PYDcr and calcium intake in density. When any of these variables was used as a dependent variable, we back-transformed the results to present the adjusted geometric means for ease of interpretation. For the main analyses, we constructed the following models: Model 1 adjusted for age (years), race (Black, White), sex, and education (up to 15 years, 16 years or greater). Model 2 adjusted additionally for calcium intake in density (mg/1000 kcal/day, supplements included, log-transformed), serum concentrations of 25OHD (ng/mL, log-transformed), creatinine (mg/dL), and season (Jan–Mar, Apr–Jun, July–Sep, and Oct–Dec) of blood draw. Model 3 further adjusted for physical activity score and sun-exposure time (hours/week). Model 4 further adjusted for body mass index (kg/m^2).

For each sex and race/ethnicity group, we observed that PTH concentrations tended to be high in never smokers, and low in current smokers, then we tested interaction by sex or race/ethnicity on the association of smoking and PTH by inserting a product term in the models. All the interaction terms were non-significant throughout the models. Therefore, we presented sex- and race-combined results. We tested linear trend of PTH across the smoking habits by using an ordinal variable ($0 =$ never, $1 =$ former, and $2 =$ current smoker). As sensitivity analyses, we repeated the main analyses replacing calcium density in the models with either a) calcium density excluding supplemental source (i.e. dietary source of calcium only) or, b) absolute amount of calcium intake (mg/day) or, c) serum calcium concentration (mg/dL).

For the secondary aim, we estimated the adjusted means of the following biological markers: serum phosphate [mmol/L], serum $1,25(OH)_2D$ [nmol/L], 24-hour urinary calcium [mmol/day], fractional excretion of calcium (FEca, also known as calcium/creatinine clearance