Maturitas 75 (2013) 67–73

Contents lists available at SciVerse ScienceDirect

Maturitas

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

Bone turnover markers in statin users: A population-based analysis from the Camargo Cohort Study

José L. Hernández[a,*], José M. Olmos[a], Galo Romaña[b], Josefina Martinez[a], Jesús Castillo[b], Irina Yezerska[a], Carmen Ramos[b], Jesús González-Macías[a]

[a] Bone Metabolic Unit, Department of Internal Medicine, Hospital Universitario Marqués de Valdecilla, University of Cantabria-IFIMAV, RETICEF, Santander, Spain
[b] Centro de Salud Camargo, Santander, Spain

ARTICLE INFO

Article history:
Received 17 December 2012
Received in revised form 10 February 2013
Accepted 12 February 2013

Keywords:
Statins
Bone turnover markers
PINP
CTX
Bone metabolism

ABSTRACT

Objective: To analyze the effects of statin use on bone turnover markers (BTM), in participants from a large population-based cohort.
Subjects and methods: Cross-sectional study that included 2431 subjects (1401 women and 930 men) from the Camargo Cohort. We analyzed the differences in serum BTM between statin or non-statin users, by means of a generalized linear model, adjusted for a wide set of covariates and stratified by diabetes status. We also studied the effect of the type of statin, dose, pharmacokinetic properties, and length of treatment, on BTM.
Results: Five hundred subjects (21%) were taking statins (273 women and 227 men). Overall, they had lower levels of aminoterminal propeptide of type I collagen (PINP) and C-terminal telopeptide of type I collagen (CTX) than non-users ($p < 0.0001$). BTM levels were significantly lower in diabetic women using statins, than in female non-statin users with diabetes. In men, we found similar results, but only for CTX. All the statins users had lower levels of BTM than non-users, except subjects taking fluvastatin that showed slightly higher values. In the whole sample, no differences between dose or drug-potency were noted regarding BTM. When comparing with non-statin users, only subjects taking lipophilic statins had lower BTM levels ($p < 0.0001$). Serum CTX levels were lower in women using statins for more than 3 vs. 1–3 years ($p = 0.006$).
Conclusions: In a large population-based cohort, serum BTM were lower in participants taking statins than in non-users, and this effect was modulated by diabetes status. Overall, this decrease in BTM was more evident in subjects receiving the more lipophilic statins, especially when using for more than 3 years.

1. Introduction

The 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, or statins, are the most commonly prescribed drugs worldwide. In the last decades, many experimental reports have pointed out that the overall benefits observed with these drugs appear to be greater than what might be only expected from their lipid lowering effect [1,2]. As a matter of fact, a role for statins in bone metabolism was first proposed by Mundy et al. [3] when they proved, in vitro and in rodents, that lovastatin and simvastatin promoted new bone formation through up-regulation of bone morphogenetic protein-2 (BMP-2) expression.

Bone turnover markers (BTM) reflect whole body rates of bone resorption and bone formation, and provide a dynamic assessment of the skeleton which may complement the static information given by bone mineral density (BMD) measurement. Nevertheless, the effect of statins on bone turnover markers (BTM) has been reported in a few randomized controlled trials, with contradictory results, mainly based on its small sample size and shorter duration [4–6]. A recent systematic review concluded that only one out of the six trials included, found a small non-significant increase in bone alkaline phosphatase in the placebo group [7]. In any case, studies are difficult to compare due to several reasons, such as the type of statin, duration of use, dosage, and BTM considered. Concerning BTM, limitations variously include their biological variability and, in some cases, the multiple methodologies used for the same analyte [8]. Therefore, the International Osteoporosis Foundation (IOF) and the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) have recommended that a marker of bone formation (serum PINP) and a marker of bone resorption (serum CTX) are used as reference analytes for BTM in clinical studies [9].

* Corresponding author at: Bone Metabolism Unit, Department of Internal Medicine, Hospital Marqués de Valdecilla, 39008 Santander, Spain.
Tel.: +34 942 202655; fax: +34 942 202655.
E-mail address: hernandezjluis@gmail.com (J.L. Hernández).

0378-5122/$ – see front matter © 2013 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.maturitas.2013.02.003

Furthermore, there is growing evidence that pharmacokinetic characteristics of statins could influence their effect on bone. In particular, several observational studies have showed a positive effect of lipophilic statins on BTM, compared to a negative profile for hydrophilic statins, in hypercholesterolemic patients with or without type 2 diabetes mellitus [10–14].

The aim of the present study was to analyze the effects of statin use, type of agent, dosage, pharmacokinetic properties, and length of treatment, on bone formation (PINP) and resorption (CTX) markers, in participants from a large population-based cohort.

2. Subjects and methods

2.1. Study design and participants

The study population includes 2431 participants from the Camargo Cohort Study, recruited between February 2006 and February 2011. The study design has been previously detailed [15,16]. Briefly, this is a cross-sectional study nested in a prospective community-based study designed to evaluate the prevalence and incidence of metabolic bone diseases and disorders of mineral metabolism, osteoporotic fractures and risk factors for osteoporosis and fragility fractures. The cohort is composed by postmenopausal women and men older than 50 attending a primary care center in Northern Spain for medical reasons or for their regular health examination, whichever happened first. The study was approved by the Local Ethical Committee, and all patients gave written informed consent.

For the purpose of this paper, participants were excluded if they had a coexisting medical disorder that might affect bone metabolism or were on medications with effect on bone health (corticosteroids, bisphosphonates, calcitonin, strontium ranelate, parathyroid hormone, selective estrogen receptor modulators, hormone replacement therapy, and calcium or vitamin D supplements). Also excluded were subjects on anticonvulsivants, glitazones, or lipid-lowering medications other than statins. Physical activity was recorded as high (moving, walking and working energetically and participating in vigorous exercise), moderate (walks reasonable distances, does light housework shopping or equivalent, normal activities of day-to-day living but no appreciable exercise), and sedentary (little walking outside home, or sits in a chair or lies in bed most of the time). Smoking habits were assessed by asking if the participant was currently smoking, has never smoked or was an ex-smoker. Regarding alcohol consumption, subjects with an intake $\geq$20 g/d were considered as current drinkers. Dairy calcium intake was assessed by a food frequency questionnaire [17]. Height was measured using a standard stadiometer with the participant wearing no shoes, and it was recorded to the nearest centimeter. Weight was measured using an electronic scale that was calibrated periodically, and it was recorded to the nearest 100 g. During weighing, the participants wore light clothes and no shoes. We calculated body mass index (BMI) as weight in kilograms divided by height in meters squared.

2.1.1. Working definitions

Current statin use was defined as use of any HMG-CoA reductase inhibitor. All the patients were on a stable statin dose for al least 12 weeks. Duration of use was divided in three categories (<1 year, 1–3 years or >3 years). Statins were further grouped into two strata according to their lipid-lowering potency: low potency (pravastatin, lovastatin and fluvastatin), and high potency (simvastatin and atorvastatin). Moreover, statins were dichotomized according to their biochemical properties, into hydrophilic (pravastatin) and lipophilic (lovastatin, fluvastatin, simvastatin and atorvastatin). Finally, these agents were categorized into two groups according the dose necessary to reduce LDL cholesterol by 30% or more (high vs. low-dose statins) [18]. Subjects with fasting glucose $\geq$ 126 mg/dl (7 mmol/l) or using regular antidiabetic medications were defined as diabetic ones [19].

2.1.2. Laboratory measurements

Blood samples were obtained, only once at baseline, from an antecubital vein in the morning after a requested 12-h overnight fast. Serum was divided into 0.5-ml aliquots and stored at −40 °C. Routine biochemical parameters were measured by standard automated methods in a Technicon Dax autoanalyser (Technicon Instruments, Co., USA). Total calcium measurements were corrected for albumin concentration in accordance with a previously published formula [20]. Glomerular filtration rate (GFR) was calculated using the four-variable MDRD formula and expressed in ml/min/1.73 m^2 [21].

Serum concentrations of aminoterminal propeptide of type I collagen (PINP), C-terminal telopeptide of type I collagen (CTX), 25-hydroxyvitamin D (25OHD), and intact parathyroid hormone (PTH) were determined by a fully automated electrochemiluminiscence system (Elecsys 2010, Roche Diagnostics, GmbH, Mannheim, Germany). The PINP limit of detection was 5 ng/ml (reference range between 20 and 76 ng/ml), and its intraassay and interassay coefficients of variation (CV) 3.1% and 3.5% respectively [22–24]. The detection limit of serum CTX was 0.010 ng/ml, its intra-assay and inter-assay CV 4.2% and 4.7% respectively, and its reference range 0.100–1.000 ng/ml [21,22]. The detection limit of serum 25OHD was 4 ng/ml. The intraassay CV was 5% and interassay was 8.5%. Regarding intact PTH, the detection limit was 6 pg/ml (reference range, 15–65 pg/ml). Intra and interassay CV were 5.4% and 5.9%, respectively.

2.1.3. Bone mineral density assessment

BMD was measured by DXA (Hologic QDR 4500, Bedford, MA, USA) at the lumbar spine (L2–L4), femoral neck (FN), and total hip (TH). Results were expressed in grams per square centimeter. In vivo precision was 0.4–1.5% at the different measurement sites. Quality control was performed according to the usual standards [25].

2.1.4. Statistical analysis

Results were expressed as mean ± SD or percentages, as appropriate. Unpaired Student's t test or Mann–Whitney U-test, and one-way ANOVA were used to determine the differences between groups for continuous variables, and χ^2-test for categorical variables. Variables non-normally distributed were log-transformed before analyses. We adjusted for differences in BTM between groups using a general linear regression model. Because we found a significant interaction between diabetes status and serum BTM, we split the group into two, according to the presence or absence of type 2 diabetes mellitus, and regression analyses were performed separately. Regression models were initially age and BMI adjusted, and then adjusted for age, BMI, years since menopause (in the case of women), GFR, calcium intake, family history of fractures, smoking and alcohol intake (Model 1). A value of $p < 0.05$ was considered statistically significant in all the calculations. All analyses were conducted using SPSS 15.0 (Chicago, IL, USA).

3. Results

3.1. Baseline characteristics of the study sample and general results

The study included 2431 participants (1401 women and 930 men). Statins were currently taken at baseline by 500 subjects