Similar to Adiponectin, Serum Levels of Osteocalcin are Associated with Mammographic Breast Density in Postmenopausal Women

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Abstract

Objective: Breast cancer is the most common type of cancer in Canadian women and worldwide. Mammographic density is a well-established breast cancer risk. Recent evidence suggested inverse correlations among adiponectin, osteocalcin, and the risk developing breast cancer. The objective of the study was to evaluate the relationship between breast density and adiponectin and osteocalcin concentrations.

Methods: A cross-sectional study was performed in 239 women, age range 40 to 60. Mammographic density, serum adiponectin, and osteocalcin levels were measured. According to the Wolfe method, participants were divided into those with low-risk and high-risk pattern mammograms.

Results: The study population included 107 premenopausal and 132 postmenopausal women. Parameters were no different between women with low-risk and high-risk patterns. In obese postmenopausal women, the high-risk pattern mammogram group had significantly higher values of adiponectin and osteocalcin compared with the low-risk pattern group. Multiple linear regression analyses showed that adiponectin and osteocalcin levels were associated with high-risk pattern mammograms.

Conclusion: Adiponectin and osteocalcin levels were directly associated with high-risk pattern mammograms in obese postmenopausal women. These results do not support the use of adipokines as biomarkers; nevertheless, the most important factor is to assess the risk through breast density.

Key Words: Menopause, obesity, mammographic breast density, osteocalcin, adiponectin

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INTRODUCTION

Epidemiological studies have stressed the fact that obesity represents a significant risk factor for the development of cancer, although the exact mechanism of this relationship remains to be determined.[1] Possible mechanisms that relate obesity to cancer risk include insulin resistance, increased production of insulin-like growth factors, and increased bioavailability of steroid hormones.[2] Research also suggests that this association may be explained by adipocytokines secreted from adipose tissue, such as leptin, resistin, and adiponectin.[3]

Low serum adiponectin levels are associated with an increased risk for breast cancer, particularly in postmenopausal women. In vitro assays have indicated that the addition of adiponectin to the human MDA-MB-231 breast cancer cell line–induced growth arrest and promoted apoptosis.[4,5] However, other studies have shown different results.[6,7] Another observation is that adiponectin has an antiangiogenesis effect in non–breast cancer cell lines.[8] Consequently, adiponectin may act as a molecular mediator linking adipose tissue and carcinogenesis.[9]

Breast cancer is the most common type of cancer in Canadian women and worldwide.[10] In women 50 to 74, screening by means of x-ray mammography is effective in reducing the rate of breast cancer mortality.[11] Nevertheless, there are limited data regarding the relationship of mammographic density, one of the strongest predictors of breast cancer risk, and adiponectin levels. Woolcott et al.[12]

found that adiponectin levels were directly associated with mammographic density, independent of overall body weight, whereas another study found no such association.[13]

Other hormones, such as osteocalcin, which is classically considered a marker of bone formation, are suspected to be involved in the regulation of glucose and fat metabolism.[14] It has been demonstrated that osteocalcin can stimulate insulin secretion, by acting directly on proliferation and secretion of the pancreatic cells.[14,15] Furthermore, it has been shown that osteocalcin can increase insulin sensitivity, probably by inducing the expression of adiponectin in adipocytes. In addition, it has been shown that osteocalcin is produced by adipose tissue.[15] It has been shown that osteocalcin levels are directly related to adiponectin, but it is still unknown whether the levels of osteocalcin correlate to mammographic density.

The objective of this study was to examine the association between plasma adiponectin and osteocalcin concentrations with mammographic density.

METHODS

Study Design

This cross-sectional study was conducted with 239 women, who consecutively attended the Medical Research Unit in Endocrine Diseases of the National Medical Center, Mexican Social Security Institute, Mexico City. The Hospital Research Ethics Committee approved the protocol, and all participants gave written informed consent. Women with arterial hypertension, renal disease, liver disease, thyroid disorders or other endocrine disorders, breast cancer history, or chronic diseases were excluded. Anthropometric measurements of height and weight were obtained using a medical scale, and a physical examination, including measurement of blood pressure, and obstetrical and medical information were obtained. BMI was calculated as body weight in kilograms divided by the square of height in meters.

Laboratory Measurements

Venous blood samples for biochemical analysis were obtained in the morning after an overnight fast from an antecubital vein between 7:30 and 8:30 AM using vacuum tubes. The samples were centrifuged at 400 g for 15 minutes, and aliquots were obtained and stored at −70°C until assayed in a single run. Plasma glucose, triglycerides, total cholesterol, and HDL cholesterol were measured by enzymatic assays with a Roche Cobas analyzer using commercial kits (Stanbio Laboratory, Boerne, TX). Adiponectin concentrations were determined by radioimmunoassay using commercial kits from Millipore Co. (Billerica, MA), sensitivity was 1 ng/mL, and intra-assay and inter-assay coefficients of variation were 3.9% and 8.5%. Serum 17-β estradiol levels were measured by a solid-phase radioimmunoassay with a kit from Diagnostic Products Corporation (Los Angeles, CA). The intra-assay and inter-assay coefficients of variation were 4.0% and 8.6%, respectively; the sensitivity of this assay was 10 pg/mL. Osteocalcin was measured by chemiluminescent immunoassay (Immulite Analyzer, Siemens Medical Solutions USA, Malvern, PA) sensitivity was 0.55 ng/mL, and coefficients of variation were 2.8% and 7.2%.

Mammographic Breast Density

Digital mammography was determined using the GE Healthcare Senographe 2000 D (GE Healthcare, Chicago, IL). Mammographic densities were measured clinically from all four views of the mammogram, the cranio-caudal and mediolateral oblique views of the right and left breasts. Wolfe's parenchymal pattern was used to classify MBD into four parenchymal patterns on the basis of the extent and type of density: N1—non-dense, no ducts visible; P1—ductal prominence occupying less than one fourth of the breast; P2—prominent ductal pattern occupying more than one fourth of the breast; and DY—homogenous plaque-like areas of extreme density.[16] These patterns were again dichotomized into low-risk (N1 and P1) and high-risk (P2 and DY) patterns.[16,17] A single experienced radiologist read all mammograms in a blinded manner.

This measure of mammographic density has been used in multiple previous studies and consistently has shown to be associated with breast cancer risk.[18,19]

Statistical Analysis

The Kolmogorov-Smirnov statistical test was used to assess the normality of the distributions, and a non-parametric statistical analysis was performed. To compare differences among groups, the Friedman and Kruskal-Wallis tests were used. The Spearman test was used to evaluate correlation values, and a multivariate analysis was performed to adjust for age and BMI. Statistical analyses were carried out using Statistica version 8 (StatSoft, Tulsa, OK). Significance was achieved at $P < 0.05$.

The analyses were repeated after participants were divided into normal-weight (BMI <25 kg/m^2) and overweight or obese (BMI >25 kg/m^2) groups according to the WHO criterion in the premenopausal and postmenopausal women, respectively.

RESULTS

The study population included 107 premenopausal and 132 postmenopausal women who did not use hormone therapy