ORIGINAL ARTICLE

Is prolactin serum level and coronary artery atherosclerosis correlated in postmenopausal women? A cross-sectional study

Postmenopozal kadınlarda serum prolaktin düzeyi ve koroner arter aterosklerozu arasında bir korelasyon var mı? Bir kesitsel çalışma

Alireza Amirzadegan, M.D., Elnaz Salimi, M.D., Ali Hosseinsabet, M.D.

Department of Cardiology, Tehran University of Medical Sciences, Tehran, Iran

ABSTRACT

Objective: Prolactin is correlated with some conditions that predispose individuals to atherosclerosis. Prolactin receptors have been found in atherosclerotic plaques. However, a correlation between the serum prolactin level and the extension and severity of coronary artery atherosclerosis has yet to be studied. This study was an examination of that relationship.

Methods: In total, 414 postmenopausal women with normal serum prolactin levels who were candidates for selective coronary angiography were enrolled. The patients' lipid profile and levels of serum prolactin, thyroid-stimulating hormone, C-reactive protein, urea, creatinine, and fasting blood sugar were measured. The Gensini score for each patient was calculated. The study population was divided into 3 groups according to the tertile of the serum prolactin level.

Results: There was no statistically significant difference in the Gensini score results between the 3 groups in the univariate analysis (p=0.075). The multivariable analysis showed that the serum prolactin level was not an independent determinant of the Gensini score (p=0.430), whereas age, hypertension, diabetes, and dyslipidemia were independent determinants of the Gensini score.

Conclusion: There was no statistically significant correlation between the serum prolactin level and coronary artery atherosclerosis expressed as the Gensini score in this sample of postmenopausal women.

ÖZET

Amaç: Prolaktin düzeyi, ateroskleroza eğilimi artıran çeşitli durumlarla ilişkilidir. Aterom plaklarında prolaktin reseptörleri bulunmuştur. Ancak serum prolaktin düzeyiyle koroner arter aterosklerozunun yaygınlık ve ciddiyeti arasında korelasyon henüz çalışılmamıştır. Bu çalışma bu ilişkiyi incelemektedir.

Yöntemler: Selektif koroner anjiyografi adayı olan, serum prolaktin düzeyleri normal 414 postmenopozal kadın çalışmaya alındı. Hastaların lipit profilleri, serum prolaktin, tiroit uyarıcı hormon, C-reaktif protein, üre, kreatinin ve açlık kan şekeri düzeyleri ölçüldü. Her bir hastanın Gensini skoru hesaplandı. Çalışma popülasyonu serum prolaktin düzeyinin üçte birlik dilimlerine göre 3 gruba ayrıldı.

Bulgular: Tek değişkenli analizde 3 grubun Gensini skorları arasında istatistiksel açıdan anlamlı herhangi bir farklılık yoktu (p=0.075). Çok değişkenli analizde, serum prolaktin düzeyinin Gensini skoru için bağımsız bir belirleyici olmadığı (p=0.430), buna karşılık yaş, hipertansiyon ve diyabetin bağımsız belirleyiciler olduğu saptandı.

Sonuç: Bu çalışmada, postmenopozal kadınlarda serum prolaktin düzeyiyle Gensini skoruyla ifade edilen koroner arter aterosklerozu arasında istatistiksel açıdan anlamlı bir korelasyon bulunmadı.

Prolactin is a peptide hormone secreted by the anterior pituitary gland.[1] Prolactin is associated with some conditions correlated with atherosclerosis, such as inflammation,[2] insulin resistance,[3] increased low-density lipoprotein,[4] decreased high-density lipoprotein,[5] hypertension,[6] increased body mass index,[7] endothelial dysfunction,[8] increased platelet aggregation,[9] increased fibrinogen level,[10] and smooth muscle proliferation.[11] Some of these associations have been demonstrated not only among patients with pro-

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Correspondence: Dr. Ali Hosseinsabet. Tehran Heart Center, Karegar Shomali, Tehran - Iran.
Tel: +982188967450 e-mail: ali_hosseinsabet@yahoo.com

lactinoma, but also among healthy individuals.[2–3,5–7] Prolactin receptors can be found in the macrophages of atherosclerotic plaques at the site of prominent inflammation, such as those near the lipid core and the shoulder region of atherosclerotic plaques,[12] monocytes, lymphocytes, and endothelial cells,[13,14] which are involved in the atherogenesis process. A significant elevation in the level of prolactin in patients with prolactinoma is associated with an increased intima-media thickness ratio in the carotid artery as a marker of atherosclerosis.[15,16] Similarly, the prolactin serum level rises not only among patients with acute myocardial infarction, in comparison with unstable angina sufferers and control groups, but also among patients with unstable angina, when compared with control groups.[17]

Abbreviations:

CAD	*Coronary artery disease*
CI	*Confidence interval*
ICC	*Intraclass correlation coefficient*

In the postmenopausal period, a low level of estrogen has been associated with accelerated atherosclerosis.[18] Previous research has demonstrated a correlation between the prolactin level and 10-year, all-cause mortality rates, and cardiovascular disease-specific mortality rates in women without a high prolactin level.[19] In contrast, no increase in the rate of mortality due to coronary artery disease (CAD) or a greater number of hospital admissions due to CAD in women with a prolactin measurement in the upper tertile of the normal range was detected in another study.[20]

In light of such evidence, the aim of this research was to test the hypothesis that the prolactin level might be correlated with the extension of CAD.

METHODS

Study population

The present cross-sectional study recruited 414 consecutive postmenopausal women who had no menstrual bleeding in the previous year and were admitted to our hospital for selective coronary angiography between April 2016 and April 2017. These symptomatic patients were candidates for selective coronary angiography at the discretion of their treating physicians based on positive noninvasive tests or a high-risk profile. Patients were excluded if they had a history of acute coronary syndrome or stroke in the previous 6 months, a prolactin serum level exceeding the upper limit of the normal range, or a history of liver disease, advanced renal disease, pituitary disease, hormone replacement therapy, antidepressant use, or thyroid disease.

Laboratory data

About a week prior to their admission, the patients underwent venous blood sampling for a cell blood count, biochemistry analysis, and lipid profile analysis. A clinical history was recorded after admission. Diabetes mellitus was defined as the use of insulin or oral antidiabetic agents or a fasting blood sugar level exceeding 126 mg/dL in 2 separate samples; hypertension was defined as the use of antihypertensive drugs, or a systolic blood pressure measurement of more than 140 mm Hg or a diastolic blood pressure value of more than 90 mm Hg in 2 separate visits; cigarette smoking was defined as current use or cessation of smoking during the prior 6 months; dyslipidemia was defined as the use of antilipidemic agents or a triglyceride level of more than 150 mg/dL, a high-density lipoprotein level of less than 50 mg/dL, a total cholesterol level of more than 200 mg/dL, a low-density lipoprotein level of more than 130 mg/dL in patients with 2 or more CAD risk factors, or more than 160 mg/dL in the presence of 1 or no risk factors; and a family history of CAD was defined as the presence of CAD in a first-degree relative (men ≤55 years and women ≤65 years).[21] The morning after undergoing coronary angiography, nonfasting venous sampling was performed between 8 am and 9 am to examine the level of prolactin (the prolactin level rises after a meal[22]), thyroid-stimulating hormone, and C-reactive protein. These serum samples were frozen at -80°C. The prolactin serum level was evaluated using a commercial kit (Roche Diagnostics, GmbH Mannheim, Germany) and examined via the electrochemiluminescent immunoassay method with an Elecsys 2010 analyzer (Roche Diagnostics, Risch-Rotkreuz, Switzerland). The normal range for this kit was 4.8 ng/mL to 23.3 ng/mL; accordingly, patients with a prolactin serum level of less than 23.3 ng/mL were selected.

Coronary angiography

Selective coronary angiography was performed according to the Judkins technique through the femoral artery. The contrast medium Visipaque (GE Healthcare, GE Healthcare Ireland, Cork, Ireland, was injected manually. A Siemens Axiom Artis (Siemens, AG, Munich, Germany) or a Philips AlluraClarity (Philips Healthcare, Inc., Best, the Netherlands) an-

giography system was used. The severity and extension of CAD was evaluated according to the method proposed by Gensini.[23] In brief, the score of 1, 2, 4, 8, 16, or 32 was correspondingly allocated to 25%, 50%, 75%, 90%, 99%, and 100% diameter stenosis. The score was multiplied by 5 for the left main; by 2.5 for the proximal portion of the left anterior descending artery and the left circumflex artery; by 1.5 for the mid-portion of the left anterior descending artery; by 1 for the distal portion of the left anterior descending artery, first diagonal, proximal, mid, and distal portions of the right coronary artery, posterior descending artery, distal portion of the left circumflex artery, and the obtuse marginal artery; and by 0.5 for the posterolateral branch and second diagonal arteries. A total score for each patient was computed. Each attending physician read the coronary angiography film of his/her patients. The presence of 50% or more stenosis in each coronary artery was assessed as considerable coronary artery stenosis and expressed as vessel disease (e.g., single-, double-, or triple-vessel disease). After the completion of the analysis, 44 (10%) coronary artery angiographies were selected randomly and read by 1 researcher and participating physicians for evaluation of inter- and intraobserver variability. Subsequently, these selected coronary artery angiographies were read by the patients' respective attending physicians once again. The research proposal was approved by the institutional review board, and written, informed consent was obtained from all of the members of the study group.

Statistical analysis

The study population was grouped according to prolactin serum level tertile. The categorical variables were shown as frequencies and percentages and were compared using the chi-square test or the likelihood ratio test, as appropriate. The continuous data were presented as means and standard deviations, if normally distributed, and were compared using one-way analysis of variance. The normal distribution of the data was evaluated using the Kolmogorov-Smirnov test, and the Levene test was applied to assess homogeneity among the variances. The Dunnett T3 method was employed due to the absence of variance homogeneity. The other continuous variables were presented as medians and interquartile ranges (25^{th}-75^{th} quartile) and were compared using a one-way Kruskal-Wallis test. A Bonferroni adjusted Mann-Whitney U-test was used to conduct post hoc analysis. The prolactin serum levels of the participants were also compared with respect to the presence of diabetes, hypertension, dyslipidemia, cigarette smoking, a family history of CAD, and considerable CAD using the Mann-Whitney U-test. The correlation coefficient was determined with the Pearson or Spearman's rank correlation coefficient, whichever was appropriate. The variables with a p value of less than 0.15 in this analysis and clinically important variables were included in a multivariable regression analysis to evaluate the correlation between the prolactin serum level and the Gensini score of the coronary artery. The establishment of multivariable linear regression model assumptions was reviewed and confirmed. Since the Gensini score results were not normally distributed, the score (Gensini score+1) was logarithmically transformed for normalization. The inter- and intraobserver variabilities were computed as intraclass correlation coefficients (ICCs). ICCs of more than 0.8 were considered acceptable. The statistical analyses were performed using IBM SPSS Statistics for Windows, Version 23.0 (IBM Corp., Armonk, NY, USA), and a p value of less than 0.05 was considered statistically significant. When a Bonferroni adjusted Mann-Whitney U-test was applied, a p value of less than 0.0167 was considered statistically significant.

RESULTS

The demographic and laboratory data of the study population are depicted according to the prolactin serum level tertile in Table 1. A histogram of the pro-

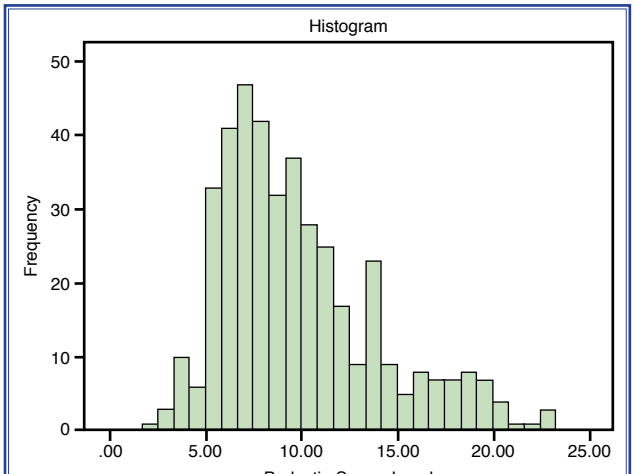

Figure 1. Histogram of prolactin serum level in the study population.

lactin serum level in the study population is presented in Figure 1. There were no statistically significant differences with respect to the demographic data; however, in the biochemical studies, there were significant differences in terms of creatinine (p=0.009) or the total cholesterol-to-high-density lipoprotein ratio (p=0.019). In all, 160 (36.3%) patients had considerable coronary artery stenosis. The presence of considerable CAD and the number of diseased vessels were not significantly different according to the serum prolactin level (Table 1).

There was no statistically significant difference in terms of the Gensini score between the 3 groups in the univariate analysis (p=0.075). In the univariate analysis, age, diabetes, hypertension, and a history of dys-

Table 1. Demographic and laboratory data of the study participants

Variable	Groups			*p*
	First Tertile (prolactin <7.5 ng/mL) n=137	Second Tertile (prolactin >7.5 ng/mL and <10.8 ng/mL) n=140	Third Tertile (prolactin >10.8 ng/mL) n=137	
Age (years)	62.2±6.7	63.3±7.6	64.5±7.9	0.101
Body mass index (kg/m^2)	29.7±5.3	30.1±5.2	29.7±5.1	0.774
Cigarette smoking (%)	3 (2.2)	2 (1.4)	4 (2.9)	0.691
Hypertension (%)	91 (66.4)	89 (63.6)	78 (56.9)	0.251
Diabetes (%)	74 (54)	64 (45.7)	55 (40.1)	0.068
Dyslipidemia (%)	85 (62)	73 (52.1)	70 (51.1)	0.132
Family history of coronary artery disease (%)	31 (22.6)	31 (22.1)	26 (19)	0.725
Hematocrit (%)	39.9±3.4	40.0±3.2	39.4±3.2	0.217
White blood cell count (µL)	7189.0±1995.0	7517.0±1865.0	251854.0±72421.0	0.320
Platelet count (µL)	253289.0±58686.0	248345.0±58500.0	251854.0±72421.0	0.800
Fasting blood sugar (mg/dL)	116.0 (99.0–158.5)	108.5 (95.0–140.8)	105.0 (95.0–122.5)	0.008*
Urea (mg/dL)	29.4 (24.8–37.5)	31.5 (24.0–37.7)	31.9 (26.0–38.0)	0.428
Creatinine (mg/dL)	0.79±0.16	0.78±0.15	0.84±0.18	0.008**
Total cholesterol (mg/dL)	172.2±43.0	164.5±43.6	160.3±35.4	0.051
Triglyceride (mg/dL)	132.0 (109.0–179.5)	127.5 (89.0–169.0)	127.0 (96.5–164.5)	0.070
LDL (mg/dL)	101.0 (79.5–130.5)	92.5 (72.3–121.8)	93.0 (71.6–120.0)	0.050
HDL (mg/dL)	45.7±10.5	47.8±11.3	45.3±10.8	0.108
Total cholesterol/HDL ratio	3.7 (3.0–4.7)	3.2 (2.8–4.3)	3.4 (3.0–4.4)	0.019***
CRP (mg/dL)	0.3 (0.2–0.5)	0.3 (0.2–0.6)	0.4 (0.2–0.7)	0.346
TSH (IU/mL)	1.1 (0.6–1.8)	1.2 (0.6–1.7)	1.4 (0.7–2.2)	0.284
Considerable coronary artery disease (%)	49 (35.8)	62 (44.3)	49 (35.8)	0.243
Single-vessel disease (%)	25 (18.2)	21 (15)	22 (16.1)	0.759
Double-vessel disease (%)	9 (6.6)	15 (10.7)	10 (7.3)	0.406
Triple-vessel disease (%)	15 (10.9)	26 (18.6)	17 (12.4)	0.151
Gensini score	3.5 (0.0–17.8)	8.0 (0.3–34.9)	5.5 (0.0–27.0)	0.075

LDL: Low-density lipoprotein; HDL: High-density lipoprotein; CRP: C-reactive protein; TSH: Thyroid-stimulating hormone.
*First tertile vs. third tertile (p=0.003); **First tertile vs. third tertile (p=0.014), Second tertile vs. third tertile (p=0.004); ***First tertile vs. second tertile (p=0.005).

lipidemia, as well as the level of fasting blood sugar, urea, and creatinine were statistically significantly correlated with the Gensini score (Table 2).

The serum prolactin level was not an independent

Table 2. Univariate analysis of the Gensini score and the possible confounding continuous variables

Variable	Description	Correlation Coefficient	*p*
Age (years)	63.5±7.5	0.225	<0.001
Body mass index (kg/m^2)	29.8±5.2	-0.044	0.377
Fasting blood sugar (mg/dL)	109.0 (97.0–141.3)	0.266	<0.001
Cholesterol (mg/dL)	165.7±41.1	0.077	0.117
Triglyceride (mg/dL)	128.0 (97.0–170.0)	0.039	0.426
Low-density lipoprotein (mg/dL)	95.0 (75.0–123.0)	0.095	0.053
High-density lipoprotein (mg/dL)	46.3±10.9	-0.055	0.266
Total cholesterol/ HDL ratio	3.5 (2.9–4.5)	0.068	0.165
Urea (mg/dL)	30.7 (24.7–37.8)	0.110	0.025
Creatinine (mg/dL)	0.8±0.2	0.101	0.040
White blood cell count (x µL)	7394±1954	0.089	0.069
Platelet count (x µL)	251142±63382	0.033	0.498
Hematocrit (%)	39.8±3.3	-0.095	0.054
Prolactin (ng/mL)	9.0 (6.8–11.9)	-0.026	0.597
C-reactive protein (mg/dL)	0.3 (0.2–0.6)	0.052	0.287
Thyroid-stimulating hormone (IU/mL)	1.2 (0.7–2.0)	<0.001	0.995
Gensini score	5.5 (0–25.1)	–	–

Continuous data are presented as means and standard deviations or medians and interquartile ranges, whichever is appropriate, and the categorical data are presented as frequencies and percentages. HDL: High-density lipoprotein.

Table 3. Univariate analysis of the Gensini score and the possible confounding categorical variables

Variable	Categorical variables		Mann-Whitney U	*p*
	Diabetes (–)	Diabetes (+)		
	(n=221)	(n=193)		
Gensini score	3.5 (0.0–15.3)	11.5 (1.0–36.3)	16400.5	<0.001
	Hypertension (–)	Hypertension (+)		
	(n=156)	(n=258)		
Gensini score	3.0 (0.0–13.5)	8.5 (1.0–31.8)	15628.0	<0.001
	Dyslipidemia (–)	Dyslipidemia (+)		
	(n=186)	(n=228)		
Gensini score	3.8 (0.0–20.4)	7.5 (1.0–28.3)	18317.0	0.016
	Cigarette smoking (–)	Cigarette smoking (+)		
	(n=405)	(n=9)		
Gensini score	5.5 (0.0–29.3)	2.0 (0.0–5.5)	1234.0	0.094
	Family history of CAD (–)	Family history of CAD (+)		
	(n=326)	(n=88)		
Gensini score	5.5 (0.0–24.6)	5.5 (0.0–26.8)	14180.5	0.868

CAD: Coronary artery disease.

Table 4. Multivariable regression analysis for the evaluation of the correlation between the prolactin serum level and the log (Gensini score +1)

Variable	β	95% confidence interval		*p*
		Lower bound	Upper bound	
Age (years)	0.320	0.021	0.038	<0.001
Diabetes (%)	0.120	0.035	0.296	0.013
Hypertension (%)	0.107	0.021	0.285	0.023
Dyslipidemia (%)	0.105	0.022	0.270	0.021
Cigarette smoking (%)	-0.050	-0.657	0.182	0.266
Family history of coronary artery disease (%)	0.048	-0.069	0.230	0.288
High-density lipoprotein (mg/dL)	-0.069	-0.010	0.001	0.144
Urea (mg/dL)	0.029	-0.004	0.008	0.547
Creatinine (mg/dL)	0.090	-0.012	.756	0.057
White blood cell count (x µL)	0.076	<0.001	<0.001	0.108
Hematocrit (%)	-0.083	-0.037	0.002	0.081
C-reactive protein (mg/dL)	0.036	-0.054	0.126	0.436
Prolactin (ng/mL)	-0.036	-0.021	0.009	0.430

determinant of the log (Gensini score+1) (p=0.430). Multivariable regression analysis in the presence of possible confounders revealed that age, hypertension, diabetes, and dyslipidemia were independent determinants of the log (Gensini score+1) (Table 3). In the subgroup of patients with considerable CAD, the Gensini score was not statistically significantly different between groups arranged according to tertiles of the serum prolactin level (p=0.208). Furthermore, the difference in the prolactin level between the patients with considerable CAD and those without considerable CAD failed to reach statistical significance (9.0 ng/mL [interquartile range: 7.1–11.5 ng/mL] vs. 8.9 ng/mL [interquartile range: 6.5–12.2 ng/mL]; p=0.921). The inter- and intraobserver variability for the Gensini score ICCs was 0.96 (95% confidence interval [CI]: 0.93 to 0.98) and 0.98 (95% CI: 0.97 to 0.99), respectively.

DISCUSSION

In the present cross-sectional study, we examined the correlation between normal prolactin serum levels and the extension and severity of CAD expressed as the Gensini score in postmenopausal women and found no statistically significant association. To the best of our knowledge, our study is the first of its kind to evaluate this association.

Arslan et al.[15] compared the carotid intima–media thickness of patients with prolactinoma and control subjects and found that the intima–media thickness was greater in the former group. In a similar study, Jiang et al.[16] reported the same finding. These studies compared patients with an elevated serum level of prolactin with individuals who had a normal serum prolactin level using ultrasonography, whereas we evaluated coronary artery atherosclerosis in subjects with a normal serum prolactin level.

Previous research has indicated that in postmenopausal women with a normal serum prolactin level, there was no correlation between the value of the intima-media thickness in the carotid artery and the prolactin serum level.[24] These findings have been confirmed in patients with chronic kidney disease and are aligned with our findings.[25]

Raaz et al.[17] reported that the serum prolactin level was not statistically significant in a comparison of stable angina patients with documented CAD and controls. In another study of subjects with a normal serum prolactin level (male and female, 45–79 years), the risk of the incidence of CAD was not different in terms of the serum prolactin level;[20] nevertheless, in a small study of postmenopausal women, the serum prolactin level was associated with the European Society of Cardiology HeartScore, a composite

index that predicts 10-year cardiovascular mortality.[23] Elsewhere, Haring et al.[19] reported a correlation between cardiovascular mortality and the level of prolactin in women.

Prolactin receptors have been detected in advanced atherosclerotic plaques of the coronary artery.[20] One of the proposed hypotheses is that the inflammatory environment of atherosclerotic plaques leads to the expression of prolactin receptors in advanced atherosclerotic plaques. Moreover, the auto/paracrine role of prolactin in atherosclerotic plaques has been proposed as a mechanism.[21] Atherosclerosis progression can be promoted in the presence of a high serum level of prolactin, as is the case in patients with prolactinoma; however, a normal serum prolactin level does not appear to play a significant role in the progression of atherosclerosis. Given the presence of prolactin receptors in advanced atherosclerotic plaques, it may be postulated that the prolactin may lead to the progression of atherosclerotic plaques in the advanced stage, while it may exert no significant effect on the progression of less advanced atherosclerotic plaques. These hypotheses should be evaluated in well-designed future studies.

It is also deserving of note that the Gensini score in our study is lower than that cited in the other available studies of postmenopausal women,[26,27] probably because only a minority of our study participants (36.2%) had considerable CAD. However, our comparison of the prolactin level between those with and without CAD yielded no difference of statistical significance.

Study limitations

The cross-sectional design of the present study presents a limitation inherent in this type of research. The fact that our study is a single-center study limited to postmenopausal women and that the majority of our study population did not have considerable CAD are other notable drawbacks. Moreover, we were not able to precisely assess age at menopause in our study sample because many of them could not recall the date with precision. We were not able to use the high-sensitive method to evaluate C-reactive protein, nor could we utilize intravascular ultrasonography or optical coherence tomography to assess coronary artery atherosclerosis.

Conclusion

Our findings demonstrated no statistically significant correlation between coronary artery atherosclerosis expressed as the Gensini score and serum prolactin level in postmenopausal women with a normal prolactin serum level.

Ethics Committee Approval: The research proposal was approved by the institutional review board (Approval date: 15-May-2015, Approval number: IR.TUMS.MEDICINE.REC.1395.1086).

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Conflict-of-interest: None.

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