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BONE-FAT RELATIONSHIP IN POSTMENOPAUSAL WOMEN WITH HIP FRACTURES

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Abstract – Circulating adipokines, such as leptin and adiponectin, have been considered as having a major role in the bone-fat relationship. The present study was designed to determine the possible impact of adiponectin, leptin and LAR on hip fracture prediction in postmenopausal women hospitalized for fragility fracture.This monocentric, prospective study consisted of 104 postmenopausal women divided into two groups: Group 1 consisted of 49 subjects hospitalized due to the diagnosis of non traumatic hip fracture and Group 2 contained 55 postmenopausal women without history of hip fracture. LAR was significantly lower in postmenopausal women with hip fracture than women without fracture (p=0.011).In general linear model,significant by-group differences in terms of LAR persisted even after adjustment (p=0.016). We found that the leptin adiponectin ratio is an independent predictor of hip fracture in postmenopausal women hospitalized for fragility fracture.

Keywords:adiponectin ; leptin ; hip fracture

I. INTRODUCTION

Growing evidence suggests the presence of a complex interaction between bone and fat (1). Recently, circulating adipokines, such as leptin and adiponectin, specifically and highly expressed in human adipose cells, have been considered as having a major role in the bone-fat relationship (2,3). Low circulating adiponectinas well as high leptin levels are associated with obesity, type 2 diabetes, hypertension, metabolic syndrome,and coronary artery disease (4,5). However in bone metabolism, circulating adiponectin appears to exert a dominant negative effect on bone mass and to be an independent predictor of lower bone mass (6,7,8). Moreover, conflicting results have been reported by several studies examining the relationship between BMD and leptin in various cohorts (9,10), reflecting the complexity of the effects of these adipokines on bone biology in respect of to gender, bone compartment, skeletal region and disease severity. As the effect of leptin and adiponectin could paradoxically alter in people with advanced disease, the plasma leptin/adiponectin ratio (LAR) has been proposed as a preferential marker of susceptibility to different disorders (11), compared to leptin and adiponectin alone.The present study was designed to determine the possible impact of adiponectin, leptin and LAR on hip fracture prediction in postmenopausal women hospitalized for fragility fracture.

II. Methods

This monocentric, prospective study consisted of 104 postmenopausal women divided into two groups: Group 1 consisted of 49 subjects hospitalized from January 2008 through December 2012 in the Orthopedic department, Wolfson Medical Center due to the diagnosis of non traumatic hip fracture and Group 2 contained 55 postmenopausal women without history of hip fracture, recruited from the metabolic outpatient clinic at the Wolfson Medical Center. Patients with a history of unstable angina, MI, CVA or major surgery within the six months preceding entrance to the study were excluded. Patients with unbalanced endocrine disease including primary or secondary hyperthyroidism were excluded, as were patients with plasma creatinine > 2.5 mg/dl, elevation of liver enzymes to more than twice the upper normal limit, and calcium metabolism abnormalities.

The study was approved by the Institutional Review Board and the patients signed a full informed consent.

Biochemical parameters

Blood sampling for full chemistry, metabolic parameters and humoral factors including total cholesterol, HDL and LDL cholesterol, triglycerides, fasting glucose, HbA1C, fasting insulin, CRP, fibrinogen, calcium, phosphor, adiponectin and leptin was performed at baseline and at the end of the study. Plasma leptin was analyzed using Luminex xMAP technology (Linco Research Inc. St. Charles, MO, USA, Lincoplex panel B (HADK-2-61K-B). Adiponectin was determined by a commercial sandwich enzyme immunoassay technique, R&D Systems, Minneapolis, USA (catalog number DRP300).

Insulin resistance was defined by the homeostasis model assessment of insulin resistance (HOMA-IR).

Statistical analysis

Analysis of data was carried out using SPSS 9.0 statistical analysis software (SPSS Inc., Chicago, IL, USA, 1999). Distributions of continuous variables were assessed for normality using the Kolmogorov-Smirnov test (cutoff: $p < 0.01$). Normally distributed continuous variables were

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described using mean ± standard deviation. Variables with distributions significantly deviating from normal were described using median (minimum-maximum). Categorical variables such as sex, comorbidities and treatment prescriptions are presented as frequency (%). The General linear model (GLM) was developed by arriving at a model which explains the maximum amount of variability in the outcome variable, and inclusion of variables is this model was based on univariate results. For inclusion, the probability of F was set at 0.05, and at 0.10 for exclusion. Variables for inclusion were identified in univariate associations with the outcome of interest. Using a backward, stepwise approach was the method through which the most parsimonious model was developed. All tests were two-sided and considered significant at $p<0.05$.

III. RESULTS

Demographic and clinical characteristics of the study groups are presented in Table 1. As can be seen, Group 1 subjects were older, compared to Group 2. As expected, family history of fracture and history of the previous fracture differed significantly between groups, and were significantly higher in Group 1, as compared to Group 2. Prevalence of type 2 diabetes mellitus, as well as parameters of glucose metabolism, such as fasting glucose, HbA1C and HOMA-IR, did not differ significantly between groups. However, a marker of systemic inflammation (CRP) was significantly higher in Group 1, as compared to Group 2.

Circulating adiponectin and leptin levels were significantly higher in Group 1 than in Group 2 ($p=0.005$ and $p=0.044$, respectively). LAR was significantly lower in postmenopausal women with hip fracture than women without fracture ($p=0.011$).

Univariate GLM analysis for leptin, adiponectin and LAR (carried out to control for variables) differed significantly by groups (Table 2). In the GLM model for adiponectin and leptin, these parameters were not significantly associated with group, meaning that after controlling for variables, there was no between-group difference in circulating leptin as well as adiponectin. Nevertheless, significant by-group differences in terms of LAR persisted even after adjustment ($p=0.016$).

IV. DISCUSSION

The present study found that the leptin adiponectin ratio is an independent predictor of hip fracture in postmenopausal women hospitalized for fragility fracture. The results of the present study are consistent with those of studies reporting that the LAR is a preferential independent marker in different disorders, compared to leptin and adiponectin alone. The potential explanation for these findings is the concept of "reverse epidemiology", whereby the association between a predictor and disease in the general population is inverted in patients with established disease. The concept of "reverse epidemiology" has been described in the association between adipokines and cardiovascular disease (12), and is the reason that the plasma leptin adiponectin ratio has been proposed as a preferential marker of atherosclerosis, compared to leptin and adiponectin alone in patients with advanced renal failure, diabetes mellitus and coronary arteries disease (13,14,15). Despite potential roles of human adipose cells in bone metabolism, the relationships between adipokines and different osteoporosis-related phenotypes have not been evaluated. To the best of our knowledge, the present study is the first to examine the relationship between the LAR and hip fracture in postmenopausal women hospitalized in an orthopedic department for non traumatic fracture.

Consistent with previous findings, we observed increased levels of circulating adiponectin as well as leptin in postmenopausal women with hip fracture, compared to postmenopausal non osteoporotic women without hip fracture. The potential involvement of adipokines in the regulation of bone metabolism is suggested by clinical studies reporting its association with BMD. However, positive, negative and no relationship between adiponectin as well as leptin and total body BMD has been reported, reflecting the complexity of the effects of these adipokines on bone biology, in respect to gender, menopausal status, bone compartment and skeletal region.

In conclusion, our findings suggest that the Leptin adiponectin ratio appears to be an independent predictor of hip fracture and preferential marker, compared to leptin and adiponectin alone. Future research should focus on the clinical impact of the LAR level and its ability to predict fragility fractures in postmenopausal women, as well as in the general population.

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Table 1: Baseline characteristics of the study groups:

Variables	**Postmenopausal women with hip fractures (49)**	**Postmenopausal women without hip fractures (55)**	**p-value**
Age (years)	78.4 +/-8.9	59.6+/-10.0	0.0001
BMI (kg/m^2)	26.4+/-4.3	32.2+/-5.9	0.0001
Previous fracture (%)	12 (25%)	0	0.0001
Cardiovascular risk factors:			
Diabetes mellitus (%)	16(33%)	18(33%)	ns
IHD (%)	4(8%)	0	0.0001
Smokers (%)	7(14%)	2(4%)	ns
Hypertension (%)	25(44%)	10(18%)	0.002
Concomitant medications:			
Statins (%)	22s(45%)	27(49%)	ns
B-blockers (%)	15(31%)	20(36%)	ns
Diuretics (%)	11(22%)	7(13%)	ns
Antidiabetic medications (%)	15(31%)	13(24%)	ns
Hormone Replacement therapy (%)	3(6%)	0	0.0001
Creatinine (mg/dl)	0.7±0.2	0.9±0.1	0.030
Urea (mg/dl)	38.8±18.2	33.5±9.9	ns
CRP(mg/l)	7.2 ± 6.5	0.6 ± 0.6	0.0001
Glucose(mg/dl)	135.8±55.2	125.3±49.4	ns
HgA1C (%)	5.8 ± 1.1	6.1 ± 0.6	ns
Insulin (IU/ml)	20.6±21.2	22.0±36.0	ns
Triglycerides (mg/dl)	131.3±62.9	132.6±60.6	ns
LDL Cholesterol (mg/dl)	97.1±33.0	113.6±34.5	0.049
HDL Cholesterol (mg/dl)	44.4±14.3	52.0±11.8	0.009
HOMA-IR	7.7±0.4	8.2±8.9	0.024
Adiponectin (ng/ml)	13816.5±8233.3	9360.6±5972.1	0.005
Leptin (ng/ml)	14794.7±8557.0	6720.7±8873.8	0.044
LAR	2.1±2.2	4.0±4.5	0.011

Table 2: Multiple linear regression analysis

Variables	Adiponectin		Leaptin		LAR	
	F value	P valaue	F value	P value	F value	P value
Corrected Model	4.622	0.002	2.233	0.028	2.792	0.038
Age	1.643	0.204	0.999	0.321	2.239	0.142
HOMA-IR	6.256	0.015	0.043	3.327	2.716	0.106
HDL cholesterol	0.386	0.537	-	-	0.515	0.477
Group	1.847	0.179	3.896	0.053	6.237	0.016