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Association of Leptin: Adiponectin ratio and metabolic risk markers in postmenopausal women

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ABSTRACT

Leptin and adiponectin play an important role in the regulation of body weight and energy homeostasis. The purpose of the present study was to ascertain the relationship between leptin to adiponectin ratio (L:A) and metabolic risk factors in postmenopausal women.This is a cross sectional case-control study. A total of 523 postmenopausal women were recruited for the study 270 postmenopausal women with metabolic syndrome and 253 apparently healthy control postmenopausal women without metabolic syndrome. Biochemical and Anthropometrical parameters were measured. Leptin and adiponectin levels were determined by sandwich enzyme-linked immunosorbent assay, insulin resistance was determined by homeostasis model assessment for insulin resistance (HOMA-IR). Results of this study indicate that leptin (15.92 ± 10.50 *vs.*9.43 ± 4.39 pg/ml, $p < 0.001$), L:A ratio (1.08 ± 1.06 *vs.*0.42 ± 0.38 pg/ml, $p < 0.001$), HOMA-IR, the lipid profile, and other metabolic risk factors (waist circumference (WC), waist-to-hip ratio(WHR), body mass index((BMI)), fasting plasma glucose (FPG) level and fasting plasma insulin(FPI)) were significantly higher but HDL, HDL/LDL and adiponectin level (20.55 ± 10.76 *vs.*30.08 ± 13.08 pg/ml, $p < 0.001$)were significantly lower in postmenopausal women with metabolic syndrome than in women without the syndrome ($p < 0.001$). Further, in postmenopausal women with metabolic syndrome, L: A ratio was significantly positive ($p < 0.05$ or $p < 0.001$) correlated with WC, BMI, WHR, TG, FPG, TC/HDL, LDL/HDL, FPI and HOMA-IR ($p < 0.01$), and negatively correlated with HDL and HDL/LDL ($p < 0.001$). Conclusively L: A ratio was found to be significantly associated with central obesity and other metabolic risk factors so that high L:A ratio may act as a diagnostic marker for metabolic syndrome in postmenopausal women.

1. Introduction

Metabolic syndrome (MetS), a cluster of metabolic disorders such as obesity, hypertension, dyslipidemia, and hyperglyceridemia, increases the risk of developing atherosclerotic diseases such as cardiovascular disease (CVD) [1–3]. Therefore, MetS is a major public-health concern worldwide [4,5]. Recently, 2 adipocytokines, leptin and adiponectin recognized as key regulators of various metabolic disorders, and the serum/plasma leptin: adiponectin ratio (L: A) reported as a new surrogate marker for atherosclerosis in subjects with obesity and type 2 diabetes mellitus [6,7]. Leptin to adiponectin ratio has also been reported to be associated with insulin resistance, which is considered one of the pathophysiological conditions underlying MetS [8,9]. Paszkowski T et al., reported that, obesity is the most frequent disorder associated with women in their menopausal stage and occurs in approximately 65% of all women [13]. The development of central obesity, insulin resistance as well as the worsening of glucose and lipid metabolism has been associated with menopause, which results in an increased risk for metabolic syndrome and cardiovascular disease [14,15].

Leptin and adiponectin are mainly secreted by the adipose tissue. Their circulating concentrations increase and decrease respectively, in obese and/or diabetic subjects. Several experimental studies have shown that increased leptin may directly or indirectly through promoting insulin resistance exert multiple action at the cardiovascular level, [16] lack of adiponectin, like in knockout mice, results in accelerated metabolic syndrome and atherosclerotic progression. [17] More recently, the elevated leptin: adiponectin ratio (L: A) has suggested as an atherosclerotic index in patients with type 2 diabetes and a useful parameter to assess insulin resistance in patients with and without diabetes [8,9,18]. In obese type 2 diabetic patients who are susceptible to atherosclerosis, plasma concentrations of leptin increased, whereas those of adiponectin decreased. We therefore, hypothesize that the high leptin-to-adiponectin ratio serve as a potential diagnostic marker for development of Mets superior to leptin or

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adiponectin alone. Considering the above fact, the present study was designed to assess the potential of the leptin-to-adiponectin ratio as a biomarker for metabolic syndrome in postmenopausal women.

2. Materials and methods

A cross sectional case-control study was conducted with North Indian postmenopausal women ages 45–55 years. A total of 523 postmenopausal women were enrolled in this study and consisted of 270 women with metabolic syndrome (wMetS) according to NCEP-ATP III criteria and a control group of 253 age matched healthy women without metabolic syndrome (woMetS) who were non-alcoholic, non-diabetic, and who had no cardiac, respiratory, inflammatory, endocrine, or metabolic disease. Pregnant and lactating women with any gynecological or obstetrical problems and women receiving medication such as hormone replacement therapy were excluded from this study. A structured form was completed to collect information regarding subjects' medical, personal, family, dietary, and menstrual history. Ethical clearance has taken from the Institutional ethics committee of K.G. Medical University, Lucknow and "we certify that all applicable institutional and governmental regulations concerning the ethical use of human volunteers have followed during this research". Written informed consent was obtained from all the participants. This study was conducted under the principles of the declaration of Helsinki. Duration of study was three and half year.

2.1. Criteria for metabolic syndrome

The NCEP-ATP III criteria for metabolic syndrome are based on simple clinical and biochemical parameters. The current subjects were classified as having metabolic syndrome if they had three or more risk factors, which included any 3 of the following: 1) waist circumference (WC) > 88 cm (35 in); 2) triglycerides (TG) ≥ 150 mg/dL (1.69 mM); 3) highdensity lipoprotein cholesterol (HDL-C) < 50 mg/dL (1.29 mM); 4) systolic blood pressure (SBP) ≥ 130 mmHg or diastolic blood pressure (DBP) ≥ 85 mmHg; and 5) fasting plasma glucose (FPG) ≥ 110 mg/dL (6.1 mM). For Asian Indian women, the cut-off point for waist circumference was > 80 cm and that for body mass index (BMI) was > 23 kg/m2 (modified with various components of NCEP-ATP III).

2.2. Anthropometric measurements

BMI, WC, and hip circumference (HC) were evaluated in all subjects. The waist-to-hip ratio (WHR) was calculated from the WC and HC. The WHR is an indicator for measuring central/visceral obesity (WC was measured at the narrowest point superior to the hip and was divided by the circumference of the hips measured at their greatest gluteal protuberance). BMI was calculated as the ratio of body weight to body height squared and was expressed in kg/m^2. Using an appropriate cuff size, a physician measured blood pressure on the right arm in a sitting position after 5 min of rest. The first and fourth Korotkoff sounds were recorded as systolic and diastolic BP. Blood pressure was measured again after 5 min of rest and the average was used in analysis.

2.3. Biochemical measurements

Blood samples for measuring serum biochemical parameters were obtained from all women in the morning after 12 h of fasting. Serum and plasma were separated out from a total sample of 4.0 mL blood. Blood plasma glucose and the serum lipid profile were estimated using a glucose oxidase-peroxidase and enzymatic method, respectively (Randox Laboratories Ltd., Antrim, UK). Fasting plasma insulin (FPI) was estimated using an immuno-radiometric assay (Immunotech Radiova, Prague, Czech Republic). Insulin resistance, which indicates proneness to developing metabolic syndrome,was evaluated using the HOMA-IR method (*21*) was determined using the formula: [FPG (mM) × fasting insulin (μU/mL)]/22.5.

2.4. Detection of serum leptin and Adiponectin levels

In a total of 523 women, Leptin and Adiponectin levels were determined by a solid phase sandwich enzyme-linked immunosorbent assay (ELISA) method (Quantikine Leptin and Adiponectin, R&D system Oxford, UK).

2.5. Statistical analysis

Statistical analysis was carried out using the STATISTICA version 6.0. Quantitative variables are presented as the mean ± standard deviation. Comparisons of continuous data between two independent groups were done by Student unpaired *t*-test. A two-tailed ($\alpha = 2$) Welch corrected probability $p < 0.05$ was considered statistically significant.

3. Results

Out of a total of 523 postmenopausal women (age 45–55 yrs), 253 did not have metabolic syndrome (control group: woMetS) and 270 had metabolic syndrome (study group: wMetS).

3.1. Demographic and biochemical characteristics in postmenopausal women wMetS and woMetS

Differences between postmenopausal women wMetS and woMetS (Table 1) in terms of biochemical and anthropometric parameters, *i.e.*, BMI (27.92 ± 5.12 *vs.* 22.55 ± 3.81), WHR (0.87 ± 0.05 *vs.* 0.82 ± 0.04), FPI (11.79 ± 8.90 *vs.* 8.73 ± 5.89), and HOMAIR (3.32 ± 2.70 *vs.* 1.98 ± 1.42), were highly significant ($p < 0.001$ Further comparison of postmenopausalwomen with and without metabolic syndrome revealed that serum leptin (15.92 ± 10.50 *vs.* 9.43 ± 4.39), leptin adiponectin ratio (1.08 ± 1.06 *vs.*0.42 ± 0.38) concentrations increased and adiponectin (20.55 ± 10.76 *vs.* 30.08 ± 13.08) concentration decreased significantly with metabolic syndrome $p < 0.001$)

3.2. Metabolic risk factors in postmenopausal women wMetS and woMetS

Comparison of metabolic risk factors revealed significant differences between postmenopausal women wMetS and woMetS (Table 2) in terms of WC (88.30 ± 14.05 *vs.* 72. 29 ± 8.71, $p < 0.001$), SBP (131.88 ± 12.04 *vs.* 117.67 ± 8.01, $p < 0.001$), DBP (87.94 ± 7.87 *vs.* 79.84 ± 5.97, $p < 0.001$), high TG (155.07 ± 44.29 *vs.* 103.49 ± 20.67, $p < 0.001$), low HDL (41.15 ± 4.90 vs.

Table 1
Demographic characteristics and biochemical parameters in postmenopausal women with and without metabolic syndrome.

S. no.	Variables	Postmenopausal women with metabolic syndrome	Postmenopausal women without metabolic syndrome	P-value
1.	BMI	27.92 ± 5.12	22.55 ± 3.81	< 0.001
2.	WHR	0.87 ± 0.05	0.82 ± 0.04	< 0.001
3.	FP Insulin	11.79 ± 8.90	8.73 ± 5.89	< 0.001
4.	HOMA-IR	3.32 ± 2.70	1.98 ± 1.42	< 0.001
5.	Leptin (pg/ml)	15.92 ± 10.50	9.43 ± 4.39	< 0.001
6.	Adiponectin (pg/ml)	20.55 ± 10.76	30.08 ± 13.08	< 0.001
7.	L: A Ratio	1.08 ± 1.06	0.42 ± 0.38	< 0.001

Data are shown as mean ± S.D. *$p < 0.01$. Abbreviations: BMI, body mass index; WHR, waist-to-hip ratio; FPI, fasting plasma insulin; IR, insulin resistance.