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The association between chemerin and homeostasis assessment of insulin resistance at baseline and after weight reduction via lifestyle modifications in young obese adults

Mi Kyung Lee [a], Sang Hui Chu [b], Duk Chul Lee [c], Ki Yong An [a], Ji-Hye Park [a], Dong Il Kim [a], Jiyoung Kim [a], Jee Aee Im [d], Ji Won Lee [c,*], Justin Y. Jeon [a,**]

[a] Department of Sport and Leisure Studies, Sport Medicine Laboratory, Yonsei University, Republic of Korea
[b] Department of Clinical Nursing Science, Yonsei University College of Nursing, Nursing policy Research Institute, Biobehavioral Research Center, Republic of Korea
[c] Department of Family Medicine, Yonsei University College of Medicine, Republic of Korea
[d] Sport and Medicine Research Center, INTOTO Inc., Seoul, Republic of Korea

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ABSTRACT

Background: Chemerin is a recently discovered adipocytokine, associated with adiposity and insulin sensitivity. The current study investigated the effects of lifestyle intervention on circulating chemerin level and its association with insulin resistance and adiponectin in human.
Methods: Forty male and 20 female obese adults (mean age: 29.7 ± 5.7 y, mean BMI: 29.3 ± 4.5 kg/m^2) completed an 8-week lifestyle intervention program, which consisted of a home-based diet and exercise program. Anthropometric measurements and biomarkers were assessed at the baseline and at the end of the study.
Results: Eight weeks of lifestyle intervention reduced body weight, visceral fat and subcutaneous fat by 3.8%, 15.3% and 11.5%, respectively. The lifestyle intervention further reduced fasting insulin (10.9 ± 6.6 vs. 7.6 ± 5.3 μU/ml, $p < 0.001$) and homeostasis assessment of insulin resistance (HOMA-IR) (2.3 ± 1.5 vs. 1.6 ± 1.2, $p < 0.001$), chemerin (103.3 ± 20.7 vs. 96.5 ± 19.5 ng/ml, $p < 0.001$) and hs-CRP levels (1.3 ± 1.8 vs. 0.2 ± 0.2 mg/dl, $p < 0.001$) while it increased fasting pentraxin (PTX) 3 (0.6 ± 0.7 vs. 0.7 ± 0.4 ng/ml, $p = 0.049$) level. The Δ chemerin levels correlated with Δ insulin ($r = 0.349$, $p = 0.024$) and HOMA-IR ($r = 0.333$, $p = 0.36$) even after adjusting for age and gender.
Conclusion: The lifestyle intervention reduced circulating chemerin levels independent of visceral fat mass and adiponectin. Chemerin levels are associated with insulin resistance at the baseline and after the lifestyle intervention.

1. Introduction

Obesity is characterized by an excess accumulation of white adipose tissue (WAT) and is associated with various diseases including type 2 diabetes, cardiovascular disease and cancer [1–3]. Despite the clear link between obesity and these prevalent diseases, the mechanism responsible for linking obesity and these diseases remains unclear. WAT, in addition to serving an important metabolic role, is an active endocrine organ that secretes a number of peptides with diverse biological and physiological functions including regulation of satiety, carbohydrate and lipid metabolism, and insulin sensitivity [4]. The signaling molecules secreted from adipose tissue are collectively called 'adipocytokines'. Interestingly, obesity increases the production of pro-inflammatory adipocytokines that cause insulin resistance, but decreases the production of anti-inflammatory adipocytokines, which reduce insulin resistance [5,6].

Chemerin is a recently discovered adipocytokine that serves as a ligand for the G protein-coupled receptor CMK LR1 and plays a role in adaptive and innate immunity [7–9]. Chemerin is primarily produced in the liver and adipose tissue and is secreted as an 18 kDa inactive pro-protein that undergoes extracellular serine protease cleavage at the C-terminal portion to generate the 16-kDa active chemerin [7–9]. Chemerin is involved in adipogenesis and differentiation [10–12], and chemerin serum levels are also associated with obesity [13] and visceral adipose tissue [14,15]. Although several studies have identified an association between circulating chemerin levels and factors of metabolic syndrome [16,17], the role of chemerin in glucose homeostasis and insulin resistance is still controversial. Chemerin is reported to increase [18] insulin-stimulated glucose uptake in 3T3-L1 adipocytes as well as decrease insulin-stimulated glucose uptake in primary human skeletal muscle cells [19]. Recently 2 studies in chemerin-deficient [20] and

* Correspondence to: J.W. Lee, Department of Family Medicine, Severance Hospital, Yonsei University College of Medicine 50,Yonsei-ro, Seodaemun-Gu, Seoul 120-752, Republic of Korea. Tel.: +82 2 2228 2338; fax: +82 2 362 2473.
** Correspondence to: J.Y. Jeon, Department of Sport and Leisure Studies, 134 Shinchon-dong, Seodaemoon-ku, Seoul 120-749, Republic of Korea. Tel.: +82 221236197; fax: +82 221238648.
E-mail addresses: indi5645@yuhs.ac (J.W. Lee), jjeon@yonsei.ac.kr (J.Y. Jeon).

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chemerin-receptor (CMKLR1)-deficient mice [21] showed systemic glucose intolerance with tissue specific effects of chemerin on insulin sensitivity and impaired insulin secretion.

Studies have reported strong association between circulating chemerin level and components of metabolic syndrome including adiposity [13,22–24]. Recently, we have found serum chemerin level was positively correlated with body fat, visceral adipose tissue [14], and serum triglycerides, and negatively correlated with adiponectin and high density lipoprotein cholesterol (HDL-C) [25]. The relationship between weight reduction and level of circulating chemerin level was further studied [26]. Chakaroun et al. [26] found that weight reduction via bariatric surgery, six months of a hypocaloric diet, and 12 weeks of aerobic exercise consistently reduce serum chemerin levels, as well as a chemerin expression in adipose tissue. They further reported that changes in chemerin levels were associated with a change in glucose infusion rates and high sensitive C-reactive protein (hs-CRP), independent of changes in BMI. These studies [25,26] suggest that chemerin levels increase with obesity and may cause dyslipidemia and insulin resistance, and that a reduction in adiposity via exercise or diet would reduce chemerin levels and insulin resistance. However, it is still unclear how a reduction in subcutaneous vs. visceral adipose tissue through lifestyle modifications would impact circulating chemerin levels in association with changes in insulin resistance.

Recent studies [27] have found that adiponectin up-regulates CMKLR1 mRNA expression and protein levels in primary human hepatocytes and significantly reduces CMKLR1 in the livers of adiponectin-deficient mice, suggesting that adiponectin is an inductor of CMKLR1 in vivo. A subgroup of subjects has recently been identified with high circulating chemerin and low adiponectin levels. This subgroup is 5.79 times more likely to have metabolic syndrome compared with subjects with low chemerin and high adiponectin levels [25], suggesting that there might be a meaningful interaction between chemerin and adiponectin in the development of metabolic syndrome and non-alcoholic fatty liver disease. Considering the notion that exercise may increase circulating adiponectin levels, of interest is the way in which lifestyle modifications including exercise might change chemerin levels in relation to changes in adiponectin and insulin resistance in obese non-diabetic adults. Therefore, the purposes of the current study are to test 1) whether lifestyle intervention change circulating chemerin levels, and 2) whether changes in chemerin levels after the lifestyle intervention are associated with insulin resistance, adiponectin levels and other anthropometric measures including visceral fat area.

2. Methods

2.1. Subjects and methods

The Shinchon Severance Hospital Research Review Committee approved this study. Written informed consent was obtained from all participants. The recruited subjects were either overweight or obese (BMI > 23 kg/m^2 or waist circumferences of >90 cm for men and >80 cm for women based on overweight criterion and metabolic syndrome criterion for WC for Asian [28–30]). Exclusion criteria include type 2 diabetes, a history of myocardial infarction and age of >60 y or <18 y. Subject characteristics are summarized in Table 1.

2.2. Intervention protocol

All subjects visited the clinic three times during the study period. The first visit consisted of an education session that explained the diet and exercise program for the first 4 weeks. In addition, subjects were provided with a diet and exercise diary as well as a pedometer. During the second visit, participants were educated about the diet and exercise program for weeks 5 to 8.

Table 1
Characteristics of participants.

	Male (N = 40)	Female (N = 20)	Total (N = 60)
Age	30.7 ± 5.5	27.7 ± 5.5	29.7 ± 5.7
Anthropometric measure			
BMI (kg/m^2)	29.8 ± 4.5	28.2 ± 4.2	29.3 ± 4.5
Weight (kg)	90.6 ± 15.0	74.3 ± 12.2	85.2 ± 16.1
WC (cm)	101.0 ± 9.5	92.6 ± 8.7	98.2 ± 10.0*
WHR	0.9 ± 0.04	0.9 ± 0.04	0.9 ± 0.05
Fat mass (kg)	27.4 ± 9.3	28.4 ± 8.8	27.7 ± 3.0
Muscle mass (kg)	35.9 ± 4.6	24.7 ± 3.3	32.2 ± 6.8*
VFA (cm^2)	145.5 ± 41.5	87.4 ± 33.4	126.1 ± 47.5*
SFA (cm^2)	210.2 ± 96.7	230.2 ± 102.4	216.8 ± 98.2
Blood pressure			
SBP (mm Hg)	137.6 ± 16.3	124.6 ± 16.1	133.2 ± 17.3
DBP (mm Hg)	89.1 ± 13.9	74.7 ± 13.8	84.3 ± 15.4
Glucose metabolism			
Glucose (mg/dl)	83.9 ± 9.6	87.9 ± 6.1	85.2 ± 8.8
Insulin (μU/ml)	10.6 ± 6.7	11.3 ± 6.5	10.9 ± 6.6
HOMA-IR	2.2 ± 1.5	2.5 ± 1.5	2.3 ± 1.5
Lipid profile			
TC (mg/dl)	201.3 ± 40.6	197.2 ± 29.9	199.9 ± 37.2
HDL-C (mg/dl)	48.3 ± 9.3	56.5 ± 12.4	51.0 ± 11.0*
TG (mg/dl)	129.1 ± 84.4	81.0 ± 51.3	113.1 ± 77.9*
Others			
Chemerin (ng/ml)	107.1 ± 19.9	95.49 ± 20.0	103.2 ± 20.5*
Adiponectin (μg/ml)	3.9 ± 1.4	5.5 ± 1.4	4.4 ± 1.5*
Pentraxin-3(ng/dl)	0.6 ± 0.6	0.6 ± 0.9	0.6 ± 0.7
hs-CRP (mg/dl)	0.9 ± 1.1	2.0 ± 2.5	1.3 ± 1.8*

Data are the mean ± standard deviation, BMI: body mass index, WC: waist circumference, WHR: waist–hip ratio, VFA: visceral fat area, SFA: subcutaneous fat area, SBP: systolic blood pressure, DBP: diastolic blood pressure, HOMA-IR: homeostasis model assessment-insulin resistance, TC: total cholesterol, HDL-C: high density lipoprotein–cholesterol, TG: triglycerides, hs-CRP: high sensitivity C-reactive protein.
* $p < 0.05$ between genders.

Home-based exercise protocol: All participants were encouraged to walk >10,000 steps/day. Of these 10,000 steps, participants were asked to complete 3000 steps as exercise that increased their heart rate up to 65% of their age-predicted maximum heart rate. In addition to walking, participants were asked to complete one of two different types of resistance exercise programs, which were explained to them at weeks 0 and 4 of the study. Each resistance exercise program included ten different exercises using their own body weight and participants were asked to complete 2 sets of each exercise.

Dietary intervention protocol: Subjects were asked to reduce their daily calorie intake to 1200 kcal/day (55–60% carbohydrates, 20–25% fat and 15–20% protein). To help participants limit their rice intake, a rice bowl that could only hold 200 kcal of cooked rice was provided to all participants. Information on healthy eating was provided during the education sessions at weeks 0 and 4 of the study. Participants were asked to submit their diet and exercise diary weekly, which was followed by a phone call from a nutritionist and exercise therapist.

2.3. Adherence

To increase adherence to the study protocol, subjects completed questionnaires about their history of physical activity and exercise limitations. Based on these questionnaires, telephone-based counseling was provided during the first week of intervention by an exercise therapist and medical doctor. All subjects were asked to create an online blog (club.cyworld.com/getfit) and were instructed to upload their exercise and diet diary weekly. If a subject did not post their exercise and diet diary on time, then a text message reminder was sent to him or her. If a subject still did not post their exercise and diet diary, then they received a telephone call from an exercise specialist who provided encouragement. In addition, subjects received telephone calls twice a month by a physician or an exercise. An online forum was also created where subjects could ask questions about the diet and exercise program and receive a response within 12 h.

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