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Changes in C-reactive protein during weight loss and the association with changes in anthropometric variables in men and women: LIFE Study

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Abstract

Objective—To investigate whether sex differences exist in the pattern of change in C-reactive protein (CRP) levels during weight loss, and whether the associations between weight change and CRP change differ by the types of anthropometric variables.

Design—Longitudinal, prospective analysis of subjects participating in an intentional weight loss trial (the Lose It For Ever: LIFE Study) followed-up for 30 months.

Subjects—212 healthy, obese men and women (age: 23–77y, BMI: 30–39kg/m²).

Measurements—Body mass index (BMI), waist and hip circumferences, and waist-to-hip ratio (WHR), CRP, and lifestyle variables repeatedly measured at baseline, 6, 12, 18, and 30-month follow-up.

Results—Weight change was J-shaped with a nadir at 12-months in both men and women (P for month² <0.0001). CRP level was consistently higher in women than in men, but the differences were less prominent and were not statistically significant at 12-month and 18-month follow-up. CRP changes between any two consecutive visits were significantly associated with changes in BMI during the same period in women. However, the associations between CRP changes and changes in waist or hip circumference were not as consistent, especially between 18- to 30-month

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Conflict of interest

The authors declare no conflict of interest.

follow-up when CRP significantly increased. The associations in men were generally similar among the different anthropometric measures. The association between changes in BMI and CRP were stronger in men than in women.

Conclusion—BMI change generally correlated well with CRP changes in both men and women in the course of follow-up. Significant sex-difference in CRP level at baseline diminished at 12- and 18-month follow-up, when both sexes had maintained the lost weight.

Keywords

C-reactive protein; anthropometric variables; weight change; longitudinal study; sex characteristics

Introduction

C-reactive protein (CRP) is a nonspecific marker of inflammation produced predominantly by the liver in response to interleukin 6.¹ Modest elevation of CRP can occur chronically,² and it has been associated with increased risk of cardiovascular disease, diabetes, or other adverse health outcomes.^{2–5} Obesity or excess adiposity is one of the determinants of CRP elevation,^{6, 7} and previous studies also showed a CRP decrease after surgical weight loss,⁸ as well as an increase following weight gain.⁹ Mild CRP elevation has been observed in individuals with greater long-term weight fluctuation.¹⁰ However, association between CRP and specific types of anthropometric measures is not well understood: CRP was positively associated with total and visceral fat in one recent study in older adults,¹¹ but they did not find significant association between CRP and subcutaneous fat. In addition, few studies have examined long-term longitudinal change in anthropometric measurements in relation to CRP change.^{12, 13, 14, 15}

Patterns of changes in the anthropometric variables during weight loss has been shown to vary by sex: During intentional weight loss, subcutaneous fat loss is more pronounced in women than in men, and men tend to lose more visceral fat and less subcutaneous fat.¹⁶ Since sex difference in the CRP level itself has also been observed,^{17, 18} and given the scarcity of available data regarding sex-specific CRP change during weight loss intervention, sex-specific analysis for the relationship between changes in several anthropometric variables and CRP changes is warranted to better understand determinants of mild CRP elevation.

In the present study we sought to determine whether sex differences exist in the pattern of change in CRP levels during weight loss. We also sought to evaluate whether the associations between weight change and CRP change differed by the types of anthropometric variables considered, including body mass index (BMI), waist and hip circumferences, and waist-to-hip ratio (WHR). The latter hypothesis was based on cross-sectional gender-specific associations of CRP with BMI in women and with waist circumference in men.⁷

MATERIALS AND METHODS

LIFE Study

The present analyses were done using data collected in a randomized trial (the Lose It For Ever: LIFE Study) that was designed to compare two weight loss strategies. The details of the trial have been described elsewhere.¹⁹ The primary goal of the trial was to evaluate the effectiveness of maintenance-tailored treatment (MTT) compared to standard behavioral treatment (SBT) in maintaining lost weight long term. Brief explanation of the intervention is given in Figure 1. Content for the SBT group was modeled after prior work of the investigators^{20–22} and closely resembled that used in many recent successful clinical trials, such as those by the Diabetes Prevention Program²³ and the Look AHEAD Research Group²⁴. MTT participants received the same number of sessions as did SBT participants but the therapy in the MTT group emphasized variety in both format and content in order to reduce habituation and boredom, and thus to increase behavioral adherence. The intervention lasted for 18 months, with repeated assessments at baseline, and 6, 12, 18 and 30 months. The study protocol was approved by the Institutional Review Board of the University of Minnesota.

LIFE Study participants

The LIFE Study consisted of 213 obese men and women aged 18 years or older with a body mass index (BMI) of 30 to 39 kg/m² in 2004 and 2005 who did not meet the following exclusion criteria: current use of weight-loss medications or participation in another organized weight loss program; history or presence of cancer, cardiovascular disease, diabetes, chronic fatigue, arthritis, or fibromyalgia; inability to walk at least 10 minutes without stopping; current pharmacologic or behavioral treatment for a major psychological disorder; and current use of a thyroid hormone. In addition, women were excluded if they were pregnant, < 6 months postpartum, breastfeeding, or planning to become pregnant in the ensuing 30 months. We did not exclude participants with high CRP levels (≥ 10 mg/L) at any visits since the present study included only apparently healthy obese individuals, and CRP increase can be considered as an attribute of obesity.

Anthropometric and laboratory examination

Participants had BMI, other anthropometric measures and high sensitive CRP (referred as CRP hereafter) assessed at baseline, 6-, 12-, 18- and 30-months during the study. BMI (kg/m²) was calculated from weight (kg) and height (cm) measured in light clothing, without shoes (Tanita BWB 800, Tanita corp., Arlington Heights, IL). Waist circumference (cm) was measured at a point equidistant from the iliac crest and the twelfth rib, and hip circumference (cm) was measured at the level of the greater trochanter with a steel measuring tape. Waist-to-hip ratio (WHR) was calculated as a measure of central adiposity. CRP level (mg/dl) was measured by Fairview Diagnostics Laboratory using fasting blood samples drawn by a certified phlebotomist at each visit and stored at minus 70 °C until study completion. The test was performed on the Roche Modular P chemistry analyzer (Roche Diagnostics Corporation) using the CRP (Latex) HS kit (Roche Diagnostics, Indianapolis, IN). The laboratory CV for low concentration sample (mean 1.05 mg/L) was 1.6%, and high concentration sample (mean 2.43 mg/L) was 2.6%.

Questionnaire-based assessment

Questionnaires were used at baseline to assess educational level; employment and marital status; cigarette smoking; medical history; and previous participation in a formal dieting program. Usual nutritional and alcohol intake of the participants in the previous six months were assessed at baseline and at each successive visit using a 62-item Block Food Frequency Questionnaire (FFQ).^{25, 26} We calculated daily total energy intake (kcal), alcohol intake (g), and intakes of total fat, carbohydrates and sweets as percentages of total energy (%E). The Paffenbarger Activity Questionnaire was used to estimate weekly energy expenditure (kcal).²⁷

Statistical analyses

Of 213 participants in the trial, one without waist and hip circumference measurements, dietary and physical activity assessment at baseline was excluded, leaving 212 subjects (112 women and 100 men) for the present analyses. Although the time pattern of weight change differed significantly between MTT and SBT as previously reported¹⁹, associations between changes in anthropometric variables and CRP were not significantly different by groups (interaction $p > 0.10$ for all follow-up intervals: baseline to 6-month, 6- to 12-month, 12- to 18-month, and 18- to 30-month). Therefore, the data were collapsed across assigned treatment conditions for the present analyses.

Blood CRP levels were obtained in 212, 196, 178, 157, and 162 individuals at 0, 6, 12, 18, and 30 months, respectively. Missing values for CRP as well as those for other repeated-measure variables due to drop out were imputed using multiple imputation,²⁸ a strategy which replaces each missing value with a random sample of plausible values that represent the uncertainty about the right value to impute, instead of estimating each missing value through simulated values.²⁹ The method also known as multivariate normal imputation was recently validated by others.³⁰ Imputed variables in this analysis include both anthropometric (BMI, and waist and hip circumferences) and behavioral variables (nutritional and alcohol intake, and physical activity). The multiple imputation procedure was carried out under the assumption that missing data were missing at random. Nevertheless, participants with missing CRP for at least one visit ($n=76$) were younger (44.6 vs. 50.7 years, $p < 0.001$), and less likely to be white race (43.9 vs. 77.6%, $p < 0.001$) and married (56.1 vs. 70.1%, $p = 0.046$) than those with complete data ($n=146$). Sex, BMI, anthropometric variables, medical history and CRP level did not differ between two groups. As a sensitivity analysis, we performed completer analysis restricted to those with all CRP measurements.

Prior to the imputation and the following analysis, variables with skewed distributions (CRP, total energy and alcohol intake, % energy from sweets, and weekly energy expenditure) were logarithmically transformed to approximately normalize the distributions.³⁰ For these variables, geometric means are presented along with the 95% confidence intervals. Anthropometric variables were divided by the standard deviation at baseline to be examined for the associations with CRP change.

The patterns and significance of CRP changes over time were examined using random coefficient models with both linear and quadratic slopes (i.e., month and month-squared), adjusted for baseline levels of age (continuous), race (white, black, others), education (graduate degree, college graduate, others), job (professional, clerical, blue collar/other job, not employed), marital status (married, others), medical history (heart disease, hypertension, high cholesterol), smoking status (never, past, current), previous participation in a formal dieting program (yes, no) and treatment assignment (MTT, SBT). Similarly, patterns and significance of changes in anthropometric variables (BMI, waist and hip circumference) were also examined in random growth models allowing random intercept and slopes for month and month-squared.

Associations between change in CRP and changes in the anthropometric variables were examined separately for each follow-up interval (baseline to 6-month, 6- to 12-month, 12- to 18-month, and 18- to 30-month) using mixed effects model. Subsequent multivariate models were adjusted for baseline levels of age, race, education, job, marital status, medical history, smoking status, previous participation of formal dieting program and treatment assignment as well as repeated measurements on total energy and alcohol intake, % energy from fat, carbohydrates, and sweet, and weekly energy expenditure (all continuous). Since anthropometric measures are correlated with one another, we examined a model that simultaneously included waist and hip circumferences, waist circumference and BMI, and waist and hip circumferences and BMI.

All the analyses were conducted separately for men and women using SAS 9.2 for Windows,²⁹ and all reported P values are two-sided. PROC MI was used for Multiple imputation of missing values. Random growth models and mixed models were carried out by PROC MIXED. Summary estimates were derived by combining the results of analyses carried out on the five imputed datasets with PROC MIANALYZE.

RESULTS

The mean age of female subjects was younger than that of men (47.2 years vs. 50.4, $P<0.001$, Table 1). The proportion of women who had been in previous formal dieting programs was significantly higher than that in men (78.6% vs. 31.0%, $P<0.001$). Prevalence of current smoking was also higher in women than in men (8.9% vs. 2.0%, $P=0.013$).

Mean BMIs at baseline were 34.8 kg/m² in women and 35.0 kg/m² in men (Table 2, PFigure 2 upper panel). At baseline, men had significantly greater waist circumference than women (117.2 cm vs. 104.2 cm, <0.001 , Figure 2 lower panel), and significantly smaller hip circumference than women (118.4 cm vs. 123.0 cm, $P<0.001$). On average, weight decreased significantly and reached a nadir at 12-months. Weight increased thereafter in both men and women (P for month² <0.0001). Overall patterns and significance of changes in BMI, waist and hip circumference were similar in both men and women; however, hip circumference changes during weight regain period significantly differed by sex (P for interaction=0.020, Figure 3). Specifically, hip circumference in men did not increase as much as in women from 18- to 30-month follow-up (0.9 vs. 2.6 cm). Due to similar

changing pattern of waist and hip circumferences in women, WHR remained relatively constant ($P=0.052$).

CRP level was higher in women than in men at all time points, but the absolute differences in CRP levels were statistically significant only at baseline and at the 6-month and 30-month follow-up (Figure 4). CRP decreased in both sexes until 18-month follow-up. Increase in CRP levels from 18- to 30-month follow-up was more pronounced in women ($P=0.010$) than in men ($P=0.066$). Consequently, CRP level at 30-month follow-up in women was not statistically significantly different from that at baseline (4.5 vs. 3.7 mg/l, $P=0.065$), while that in men was still statistically significantly lower than baseline (2.7 vs. 2.0 mg/l, $P=0.018$) although absolute difference was similar between sexes (0.8 vs. 0.7 mg/l).

In women, CRP changes between any two consecutive visits were significantly associated with changes in BMI during the same period (Table 4). The associations between CRP changes and changes in waist or hip circumference were not as consistent, especially between 18- to 30-month follow-up when CRP significantly increased (but neither the associations between CRP changes and changes in waist or hip circumference were statistically significant). The associations in men were generally similar among the different anthropometric measures. The association between changes in CRP and hip circumference appeared weaker compared to those with BMI. Generally, the association between changes in BMI and CRP were stronger in men than in women.

In a model that simultaneously included waist and hip circumferences, changes in waist circumference between any proximal visits were significantly associated with CRP change independent of hip circumference change only in men (data not shown in table). On the contrary, BMI changes were significantly (from 6- to 12-month and 12- to 18-month) or borderline significantly (baseline to 6-month and 18- to 30-month) associated with CRP change independent of waist circumference change in women.

Discussion

In the present study, we found significant CRP changes during a period of intentional weight-loss in both men and women. Associations between several anthropometric measurements and CRP were generally similar to those with BMI. Between 18- to 30-month follow-up, during which significant weight regain in the aggregate occurred, CRP correlated only with BMI in women, and with BMI, waist circumference and WHR in men. CRP level was higher in women than in men at baseline, but this significant sex-difference disappeared at 12- and 18-month follow-up and then appeared again at 30-month follow-up after weight regain.

There are several issues to be discussed. First, the finding in men that hip circumference did not regain as in women suggests that regained weight in men may have been preferentially deposited as abdominal fat. Although the underlying mechanism for this is unknown, there is now evidence from several longitudinal studies that support this speculation: weight regain tended to occur as fat regain;^{31, 32} there was greater mobility of abdominal fat than subcutaneous fat in men compared to women.¹⁶

Second, CRP change generally correlated well with BMI change in both men and women. The present finding is consistent with previous studies that found both weight loss and gain to be positively associated with CRP changes,^{8, 9} fat mass decrease during weight loss was associated with CRP change,¹⁵ or another trial that observed significant decrease in CRP in the obese subgroup of exercise intervention, and in those who decreased body fat, weight, or waist circumference¹⁴; however, this study is the first to provide detailed data on long-term longitudinal associations between CRP and different anthropometric variables by sex. During the initial weight-losing period, the association seemed stronger for waist circumference in men and for hip circumference in women. It is possible that a greater proportion of abdominal fat was preferentially lost in men, and vice versa in women.¹⁶ Since hip circumference may also represent amount of lean body mass,³³ and an inverse association between lean body mass and CRP has been previously reported,³⁴ hip association with CRP may be expected to be different from that of waist circumference. Our finding in women that only BMI change was associated with CRP change between 18- to 30-month follow-up may suggest that weight regain in women would not have been restricted to fat in waist or hip.

Third, we found significantly higher CRP level in women compared to men at baseline. This finding is consistent with two US population-based multiethnic studies,^{17, 18} The sex-difference, however, diminished at 12- and 18-month follow-up, and became significant again at 30-month follow-up, implying that the sex-difference including those observed in previous studies may not be due to some invariable biological trait related to sex, but might rather due to a characteristic of individuals (obese in the present sample, or general contemporary US population in the previous studies) included in the analysis. Indeed, a study in Asia found higher CRP levels in men than in women.³⁵

Finally, decrease of CRP as well as its increase in response to weight change was more prominent in women, although the magnitude of CRP associations with BMI or anthropometric variables appeared weaker in women than in men. This finding implies the existence of the other determinants of CRP change especially in women. One such factor could be an imbalance of sex hormone. Excess adiposity in women, a state with high adipose tissue derived estrogen without an increase of progesterone,³⁶ resembles that observed in unopposed estrogen use, which was also associated with high CRP level.^{37, 2-5} In a practical setting, CRP change may have a limited utility as an indicator of weight loss intervention until we understand more about its other determinants although formal clinical epidemiological analysis has not been carried out in the present study.

There are several limitations in the present study. First, we have only several anthropometric measurements, making it impossible to clearly differentiate fat from lean tissue or subcutaneous from visceral fat. In order to understand precise physiological mechanisms under the present findings, further studies with such measurements would be meaningful. In addition, different measures of inflammation should also be included in such studies. Second, generalizability of the present finding to nonobese population or extremely obese patients may be limited since subjects were participants of voluntary weight loss program whose BMI ranged between 30 and 39. Furthermore, there were not enough subjects to carry out race-specific analysis. Finally, although we have used imputed datasets and did

sensitivity analysis on completers, about one-third of participants dropped out, leaving a possibility of potential bias in the observed pattern of CRP change or its association with anthropometrics. However, it seems unlikely that biological associations between anthropometric variables and CRP would differ by completer and non-completer.

Strengths of the present study include the use of a unique dataset with both men and women well represented, carefully standardized and detailed assessment of anthropometric and behavioral variables during the course of long-term follow-up, and clinically significant weight losses and regains. We have employed multiple imputation techniques for missing values to maintain statistical power which is a novel statistical approach.

In conclusion, BMI change generally correlated well with CRP changes in both men and women in the course of follow-up although there seemed to be some differences between the types of anthropometric measurements. Significant sex-difference in CRP level at baseline diminished at 12- and 18-month follow-up, when both sexes had maintained the lost weight.

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Figure 1.

Contents and session frequency by treatment assignment, LIFE Study, 2002–2005

Figure 2.

Means of body mass index (upper panel) and waist and hip circumferences (lower panel) during 30-month follow-up adjusted for age, race, education, job, marital status, medical history, smoking status, previous participation of formal dieting program and treatment assignment, LIFE Study, 2004–2008 (n=212). Open and solid marks indicate women and men, respectively. On average, weight decreased significantly and reached a nadir at 12-months. Weight increased thereafter in both men and women (P for month² <0.0001).

Figure 3.

Mean change in waist (upper panel) and hip (lower panel) circumference between two consecutive visits, LIFE Study, 2004–2008 (n=212). Open bar indicates women and solid bar, men. Waist circumference changes from 12- to 18-month in women and from 6- to 12-month and from 12- to 18-month follow-up in men were not significantly different from zero. Hip circumference changes from 6- to 12-month and from 12- to 18-month follow-up in both men and women were not significantly different from zero. There was a significant interaction by sex in hip change pattern over time ($P=0.02$).

Figure 4.

Means of C-reactive protein (upper) and differences in log-C-reactive protein and 95% confidence intervals during 30-month follow-up, LIFE Study, 2004–2008 (n=212). Open circle indicates women, solid square, men. CRP level in women at 30-month follow-up was not significantly different from that at baseline ($P=0.065$). In men, CRP level at 12-, 18- and 30-month follow-up was significantly different from that at baseline ($P<0.05$).

Table 1

Baseline characteristics (Mean, SD and Percentage) of participants according to sex (N=212), LIFE Study, 2004–2005

	Women (n=112)	Men (n=100)
Age (y, mean (SD))	47.2 (10.1)	50.4 (10.7)
Race (%)		
White	55.4	81.0
Black	32.1	14.0
Others	12.5	5.0
Education (%)		
Graduate degree	33.0	31.0
Undergraduate degree	39.3	40.0
Less than college degree	27.7	29.0
Marital status (%)		
Married	52.7	81.0
Others	47.3	19.0
Job type(%)		
Professional	57.1	59.0
Clerical	20.5	14.0
Blue collar/other job	10.7	18.0
Not employed	11.6	9.0
Formal dieting program		
Ever (%)	78.6	31.0
Smoking status (%)		
Never	65.2	57.0
Past	25.9	41.0
Current	8.9	2.0

Table 2

Mean (SE) values of anthropometric variables^a during 30 months of follow-up, LIFE Study 2004–2008 (N=212)

		Baseline	6 months	12 months	18 months	30 months	P (month) ^b	P (month ²) ^b
<i>Women</i>	Body mass index (kg/m ²)	34.8 (0.35)	32.8 (0.37)	31.5 (0.41)	31.8 (0.39)	33.4 (0.41)	<.0001	<.0001
	Waist (cm)	104.1 (1.02)	98.1 (1.05)	96.1 (1.16)	97.0 (1.08)	100.7 (1.24)	<.0001	<.0001
	Hip (cm)	123.0 (0.85)	117.1 (0.89)	115.7 (1.04)	116.4 (1.00)	119.1 (1.05)	<.0001	<.0001
	Waist-to-hip ratio	0.85 (0.01)	0.84 (0.01)	0.83 (0.01)	0.83 (0.01)	0.85 (0.01)	0.052	0.0007
<i>Men</i>	Body mass index (kg/m ²)	35.0 (0.34)	32.7 (0.34)	31.8 (0.38)	32.0 (0.39)	32.9 (0.38)	<.0001	<.0001
	Waist (cm)	117.2 (1.04)	109.6 (1.05)	108.2 (1.16)	108.9 (1.13)	111.3 (1.12)	<.0001	<.0001
	Hip (cm)	118.4 (0.72)	113.7 (0.73)	113.3 (0.80)	113.4 (0.77)	114.2 (0.78)	<.0001	<.0001
	Waist-to-hip ratio	0.99 (0.01)	0.96 (0.01)	0.95 (0.01)	0.96 (0.01)	0.97 (0.01)	<.0001	<.0001

^a Each estimate is a summary estimate of five repeated analyses for five imputed dataset. Each analysis used a random effect model with random intercept for individual, adjusted for age, race, education, job, marital status, medical history, smoking status, previous participation of formal dieting program and treatment assignment.

^b P values are derived from a random growth model with random intercept for individual allowing random slope for time and time-squared. Adjustment factors are same as above. Time in linear scale was used.

Table 3

Associations of changes in C-reactive protein with changes in anthropometric variables between each consecutive visit, LIFE Study (2004–2008) (n=212)

Sex	Anthropometric variable	From baseline to 6-month		From 6-month to 12-month		From 12-month to 18-month		From 18-month to 30 month	
		β	p	β	p	β	p	β	p
<i>Women</i>	Body mass index	2.37	0.024	3.24	0.004	2.38	0.042	2.67	0.017
	Waist circumference	1.80	0.075	2.28	0.030	2.24	0.044	1.83	0.10
	Hip circumference	2.48	0.015	2.28	0.037	1.66	0.140	1.97	0.085
	Waist-to-hip ratio	0.02	0.99	0.50	0.62	1.19	0.24	0.64	0.53
<i>Men</i>	Body mass index	3.48	0.001	4.59	<.0001	5.08	<.0001	5.37	<.0001
	Waist circumference	3.78	0.001	4.99	<.0001	3.91	0.0007	4.45	0.0002
	Hip circumference	2.41	0.020	3.35	<.0001	3.04	0.0007	2.20	0.045
	Waist-to-hip ratio	3.23	0.002	3.61	0.0004	2.23	0.052	4.24	<.0001

Standardized coefficient (β) was derived from random effects model using PROC MIXED in SAS with unstructured covariance matrix. Model adjusted for race, education, job, marital status, histories of heart disease, high blood pressure, and high cholesterol, smoking status, previous participation in a formal dieting program, and treatment assignment as well as changes in total energy and alcohol intake, % energy intakes from fat, carbohydrates, and sweet, and weekly energy expenditure.

Both C-reactive protein and anthropometric variables were divided by one standard deviation of its baseline measurement.

C-reactive protein, total energy intake, physical activity, alcohol and sweet intake were logarithmically transformed for their skewed distribution. Analyses were done separately for men and women, and values in the table are summary estimates of five results using five different imputed datasets, derived from PROC MIANALYZE in SAS.