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An Exploratory Investigation of Links Between Changes in Adipokines and Quality of Life in Individuals Undergoing Weight loss Interventions: Possible Implications for Cancer Research

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Abstract

OBJECTIVE—Obesity has been linked to a wide spectrum of malignancies, with the strongest association demonstrated for endometrial cancer. Although the mechanisms are not yet entirely clear, a number of risk biomarkers have been proposed, including altered adipokines. Systemic levels of these adipose derived molecules have also been linked in prior research to self-reported quality of life (QOL). They study objective was to examine the hypothesis that adipokine changes during intentional weight loss may be associated with changes in QOL.

METHODS—Fifty-two female participants were selected from two behavioral weight loss trials (SMART and PREFER) on the basis of achieving successful weight loss at 6 month assessment, availability of blood samples and completion of standard SF-36 QOL questionnaires. Levels of adiponectin, leptin, and resistin were measured using xMAP immunoassays. Changes in QOL

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were examined using linear regression models in relation to pre- and post-intervention changes in biomarker levels and BMI.

RESULTS—Significant changes between pre- and post-intervention were observed for leptin. Controlling for baseline BMI, leptin was the only biomarker that predicted change in QOL (Physical Component Scale, PCS). Linear regression models demonstrated that leptin continued to be a significant predictor of change in PCS when other possible predictor variables were included in the model.

CONCLUSIONS—This study is among the first to demonstrate that changes in PCS may be regulated by levels of both metabolic variables and adipokines. An improved understanding of biological mechanisms associated with weight loss and the role of QOL may help guide preventive strategies for obesity-associated cancers.

INTRODUCTION

Over two-thirds of the adult population of the United States is overweight or obese. Evidence indicates that obesity has a negative impact on health-related quality of life (QOL)(1-3). Higher body mass index (BMI) and greater number of comorbidities are associated with diminished QOL(4). Obesity is also key risk factor for a number of cancers, with a particularly large impact on the risk for endometrial cancer (EC), the most common gynecologic malignancy in the United States_(5). QOL and biomarkers associated with cancer risk are rarely investigated jointly despite potential links between the two for women at high risk for gynecologic cancer development. Previous research suggests that systemic levels of leptin, adiponectin, and the leptin-to-adiponectin ratio are associated with the risk of EC risk in postmenopausal female subjects (6). Here we explore the relationship between QOL and biologic markers, as part of a hypothesis-generating investigation of an important gap in our understanding of possible effects of biological consequences of weight loss and improved quality of life among women successfully completing behavioral weight loss programs.

Recent data support the idea that adipokines, cytokines secreted by adipose tissue, play an important role in multiple diseases and conditions including diabetes, cancer, and mental illness. Adipokine signaling is modulated by obesity and may play a role in carcinogenesis through various pathways, including chronic inflammation (7). For example, the adipose-derived hormone leptin, well known for its function in the control of energy homeostasis, was recently found to play a role in the regulation of mood and emotion (8). Circulating leptin levels are closely related to the percentage and amount of adipose tissue (9) and leptin has been implicated in the development of several adiposity associated malignancies including endometrial, postmenopausal breast, and colon cancer (10-13). We have focused on adipokines in this study, as obesity disrupts the dynamic role of the adipocyte in energy homeostasis, leading to inflammation and alteration of adipokine signaling (14), which is thought to ultimately be related to the risk of cancer development. Previous research has shown that in premenopausal women, negative mood is significantly related to adiponectin, independent of BMI, suggesting there may be an adiponectin-mediated pathway explaining in part how negative mood affects metabolic health (15).

Other adipokines have been implicated in playing a role in the association between obesity and cancer and between obesity and mood. For example, a recent population-based study demonstrated an association between major depression and lowered adiponectin levels(16). Adiponectin has anti-inflammatory function and its levels are negatively correlated with BMI and body fat. A recent case control study suggested that low serum level of middle molecular weight adiponectin was the only independent risk factor for EC (17). Additionally, while much is left to learn about the role of resistin in both chronic and mental disease, previous publications support the possibility of an association between resistin and depression(18). Hlavna *et al.*, reported that patients with EC have significantly increased circulating levels of resistin compared to control subjects(19).

With increasing fat mass, secretion of adipokines changes towards a pro-inflammatory, diabetogenic and atherogenic pattern(20). Lee *et al*, indicated that body fat reduction via caloric restriction positively affects the blood levels of adipokines and pro-inflammatory cytokines. Thus, there is potentially an overlap between biomarkers associated with diminished QOL, cancer, and weight loss. This association is particularly interesting in the context of EC because research demonstrated the relative risk of EC for morbidly obese women compared with normal BMI ranges between 4-11 (21).

Not yet examined is the possibility that changes in adipokines during weight loss may be associated with improved QOL beyond the contribution of BMI. The goal of this study was to evaluate the associations between adipokine levels and changes in QOL (including QOL subscales) occurring with weight loss in obese individuals who participated in the SMART (22) and PREFER (23, 24) trials, as our overarching research goal is identifying optimal strategies for reduction of the risk of cancer and other chronic diseases through weight loss. Specifically, we explored the possibility that changes in adipokine levels during successful behavioral weight loss interventions may be related to changes in QOL. We hypothesized that adipokine variations may be linked with QOL beyond the contribution of reduced BMI alone, which might suggest a potential commonality between cancer risk reduction through reduced adipokine levels and improved QOL for interventions targeting adipokine levels.

METHODS

Study design and participant population

The objective of the study was to explore longitudinal inflammatory biomarker changes in overweight and obese participants in the SMART (22) and PREFER (23, 24) behavioral weight loss trials with the goal of identifying how changes in inflammatory biomarkers are related to changes in QOL. SMART participants were recruited between 2006 and 2008, and PREFER participants were recruited between 2002 and 2004. The SMART weight loss intervention lasted 18 months with a treatment session on maintenance included at 21 months. Participants were assigned to use an eDiary, with daily, automated feedback, or a standard, paper diary to self-monitor diet and exercise. Semi-annual assessments were conducted for 24 months. Specific methods for each trial have been detailed elsewhere (22, 24). The PREFER intervention lasted 12 months with participants assigned randomly, or based on treatment preference, to follow a lacto-ovo-vegetarian low-fat diet or a standard low-fat diet. Both studies provided participants with standard behavioral treatment for

weight loss and were implemented to gain insight on how modifications to standard treatment may contribute to the efficacy of obesity treatment and prevention. In both trials, participants were able to enroll only if they were either depression free or on the same dose on antidepressant medications for six months prior to trial enrollment. In order to participate in either trial, participants had to be free of major comorbidities, including diabetes.

Similar numbers of participants were chosen for this investigation from SMART (n=27) and PREFER (n=25) research trials on the basis of clinically significant weight loss (at least 5% body weight lost for every participant), availability of serum samples, and completed SF-36 forms. For this study, we selected two assessment points, baseline and 6 months, as this is the time period where participants lost the highest number of BMI points and most of the intervention activities occurred. There were no additional assessments or biomarker samples available between baseline and 6 months and on average participants lost 4.84 BMI units at 6 months assessment.

Sample storage and laboratory assays

Fasting blood samples were obtained in the laboratory following a standard blood collection and processing protocol included in the SMART and PREFER studies (22, 24). Sera were separated by centrifugation, immediately aliquoted, frozen and stored at -80°C . Frozen, 1 mL serum samples were sent on dry ice to the Luminex Core Facility at the University of Pittsburgh Cancer Institute, where they were stored at -80°C until they were assayed. The xMAP bead-based technology (Luminex Corp., Austin, TX) permits multiplexed analysis of several analytes in one sample. Three bead-based xMAPTM immunoassays were utilized in this study. These included: leptin, adiponectin, and resistin. We focused on these adipokines because of their association with weight gain/loss, inflammation, as well as cancer development in previous studies. Intra- and inter-assay variability of the assays ranged from 5-6% and 13-15%, respectively. Luminex technology has been shown to be a reliable tool for measuring large number of analytes in healthy individuals (25-27).

Measures

Baseline demographic characteristics were collected via self-administered, standardized questionnaires. Information obtained included: age, race, marital status, education, and income. Change in weight was the primary outcome for the parent studies. At baseline and semi-annually thereafter, weight was assessed in the outpatient clinic of the Clinical and Translational Research Center (CTRC) of the University of Pittsburgh using a digital scale (Tanita Corporation of America, Inc., IL) with participants wearing light clothing and no shoes. Height was determined at baseline by stadiometer assessment.

Quality of life

The Medical Outcome Study 36-Item Short Form Health Survey (SF-36) is one of the most commonly applied generic QOL instruments (28). It yields an eight-scale profile of functional health and well-being scores, psychometrically-based physical and mental health summary measures, and a preference-based health utility index. The SF-36 has proven useful in surveys of general and specific populations, comparing the relative burden of diseases, and in differentiating the health benefits produced by a wide range of different

treatments. The two summary scales of the SF-36 have satisfactory validity in research participants with morbid obesity (29). In this investigation all eight of the SF-36 tool have been evaluated, including physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health. In the SMART and PREFER trials, SF-36 scale was administered to participants during the semi-annual assessments.

Statistical analysis

Descriptive statistics were used to summarize participant characteristics. Age (years), weight (kg), height (cm), BMI (kg/m^2), and BMI loss from baseline were included as continuous variables; race was a dichotomous variable (white/other, respectively). SF-36 QOL scores at baseline, 6 months, and changes from baseline were evaluated for Physical and Mental Health summary scores (PCS and MCS) and each sub-scale separately. Linear regression was used to evaluate the association of change in BMI from baseline to 6 months on improvement in two QOL summary scores: PCS and MCS, controlling for age, ethnicity, and BMI baseline. In the initial step of statistical analysis, each biomarker was analyzed individually as a predictor of change in physical quality of life (controlling for baseline PCS). In secondary analysis, factors that have been identified as important were entered into linear regression models to identify the joint contribution of biomarkers and metabolic factors on QOL. Statistical analyses were done using SAS Version 9.2 (SAS Institute, Cary, NC) and R. All statistical tests were two-sided with α -level for significance set at $p < 0.05$.

RESULTS

Of the study sample, 48% were participants of PREFER (25 subjects), and 52% were participants of SMART (27 subjects). The mean age of participants was 46.81 years ($SD=9.06$, range=23-59). There were 41 subjects categorized as “white”, and 11 as other racial groups. The mean weight of participants at baseline was 90.52 kg ($SD=12.36$, range=67.74-119.48). The mean BMI level at baseline was $33.14 \text{ kg}/\text{m}^2$ ($SD=4.19$, range=25.64-42.03). After the six month intervention, the mean BMI of the study cohort decreased to $28.30 \text{ kg}/\text{m}^2$ ($SD=4.30$), a statistically significant average reduction of 4.84 BMI units at 6 months ($p < 0.05$).

Descriptive statistics at baseline, six months, and change from baseline (n, mean, standard deviation) for QOL are presented in Table 1. All 52 participants had assessments at baseline and 6 months. There was a consistent increase in mean values for each two summary scores: PCS and MCS.

Table 1A and B shows basic demographic characteristics, as well as means and standard deviations of changes in variables among study participants. Participants had significant decreases in BMI, waist circumference, and leptin ($p < 0.0001$) after the weight loss intervention.

Linear regression

When changes in each biomarker were analyzed individually as statistical predictors of change in physical quality of life (controlling for baseline PCS), only the change in leptin was significantly related to the change in the physical summary score of the SF-36 (Table

2). We also observed that change in BMI was significantly related to physical summary score. None of the biomarkers or metabolic factors was a significant predictor of QOL mental summary score (data not shown).

In secondary analysis, we focused on leptin and BMI to determine whether the change in leptin continued to be a significant predictor of change in PCS when the other possible predictor variables were included in the model. This analysis demonstrated that both baseline leptin and change in leptin continued to be important predictors of PCS when BMI data and baseline PCS were included. This finding emphasized that leptin variability predicts changes in QOL, even when analyzed in conjunction with other well established predictor variables, including BMI. Exploratory analysis indicated that leptin contributed to changes in three subscales of the PCS including physical functioning, role physical, and general health (data not shown). Overall, decreases in leptin were associated with improvements in quality of life in the physical domain.

DISCUSSION

This paper evaluated the novel concept of the relationship between weight loss, changes in PCS scores, and three adipokines associated with chronic disease, inflammation, and cancer risk. Decreases in leptin were associated with decreases in BMI and also appear to be an important contributor to increased (improved) QOL PCS. These findings are important because statistically changes in leptin appear to be associated with improvement in PCS score beyond the contribution of BMI. Additional research is needed to elucidate possible mechanisms underlying the associations identified here and to explore the possible impact of changes in leptin for continued maintenance of weight loss. These findings may be particularly important to EC prevention research due to the close association between BMI and EC development.

This study shows that decreases in leptin occurring through behavioral weight loss intervention are associated with improved QOL. Both changes in BMI and leptin were significant predictors of changes in QOL PCS. Several studies have implicated circulating leptin in adiposity-associated cancer development (12, 13, 30-32); reduction of leptin in this study cohort and its association with improved quality of life provides support for further investigation in cancer prevention research. Taking into account its numerous endocrine activities (including the regulation of immune function, hematopoiesis, angiogenesis, and bone development), leptin may be considered the prototype for all adipose tissue derived hormones (33). Recent publications demonstrate that improvements in PCS after bariatric surgery were observed as early as three months after intervention and were independently associated with weight loss and improvements in comorbidities (34).

With the growing burden of obesity and the plethora of available weight loss options (e.g., lifestyle and surgical methods), investigation of psychological and biobehavioral issues in this population has moved to the forefront of research. Accumulating evidence suggests that weight loss can improve QOL (35-37). In research on effects of bariatric surgery, long-lasting weight reduction has been reported to have long-standing positive outcomes on QOL (38), with literature showing that QOL improves dramatically immediately after bariatric

surgery, declines slightly between three and six months, then improves through the end of the first year (39). While numerous studies report on QOL in bariatric patients and obese patients, there is a paucity of studies examining the link between QOL and biological markers associated with chronic disease in participants enrolled into non-surgical weight loss interventions. The study of the association between QOL PCS and biological markers may help add understanding to the systemic, beneficial effects of weight loss, especially in the area of cancer prevention.

This study has two main limitations. First, this analysis was limited to 52 women who achieved clinically significant weight loss. Second, our sample was relatively heterogeneous in relation to amount of weight loss achieved. Another limitation of our study is that the mechanisms linking changes in QOL to changes in biomarkers has not been clearly established. We hope to address this question in our future work and to develop a model linking biological and biobehavioral markers.

This study also had several strengths. The design of this study allowed us to observe the relationships between adipokine change and QOL changes from baseline to 6 months during intentional weight loss, which to our knowledge has not been addressed in previous literature; we investigated a novel concept and found sufficient evidence to suggest an association between weight loss and a stabilization of biomarkers involved in chronic disease development and cancer risk. Although larger studies are needed to confirm these results, this initial analysis suggests that additional investigation of this topic is warranted.

An improved understanding of biological mechanisms associated with weight loss and the role of QOL, if replicated by additional research, may help guide preventive strategies for obesity-associated cancer development, especially EC. This study is one of the first to simultaneously investigate the link among BMI, QOL, and adipokines. Our findings supported previous reports that weight loss is associated with biomarker changes (40). This study, however, is the first to demonstrate the link between leptin and PCS. Further research is now warranted to better understand these relationships and their applicability to clinical and public health practice.

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Highlights

Both quality of life and adipokines change in overweight individuals undergoing intentional weight loss.

BMI and leptin were significant predictors of quality of life physical summary score improvement occurring with weight loss.

Changes in leptin with weight loss are an independent predictor of improved physical quality of life above and beyond effects of BMI

Table 1A

Basic Demographic Variables

Factor	Mean and SD (n=52)
Age, mean (SD)	46.81 ± 9.06
Race, n (%)	
Caucasian	41 (79)
African-American	11 (21)
Study, n (%)	
PREFER	25 (48)
SMART	27 (52)
Weight (kg), mean (SD)	
Baseline	90.52 ± 12.36
6 months	77.36 ± 12.74
Height (cm), mean (SD)	
Baseline	165.2 ± 5.44

Table 1B

Summary statistics of BMI and Quality of Life scores

Variable	N**	Baseline (M ± SD)	N	Pre to Post Change (M ± SD)	p-value*
Biomarkers (units)					
Adiponectin (ug/ml)	51	15.89 ± 7.75	49	-0.75 ± 6.27	0.4093
Leptin (ng/ml)	51	41.33 ± 29.86	49	20.88 ± 12.36	<0.0001
Resistin (ng/ml)	51	22.44 ± 8.16	49	1.19 ± 6.11	0.1798
Metabolic Factors					
BMI	52	33.14 ± 4.19	52	4.84 ± 1.81	<0.0001
Waist	52	101.87 ± 27.25	52	12.04 ± 5.81	<0.0001
Age	52	46.81 ± 9.06			
Quality of Life Measures					
Physical	52	51.38 ± 7.38	52	-2.36 ± 7.02***	0.0188
Mental	52	49.39 ± 9.07	52	-2.46 ± 10.44***	0.0957

* P-values are based on one sample T-Test

** N varies for each measurement, as anthropometric assessments were not available for each participant. Also, for biomarker measurement we took a conservative approach in which values were included only if they were within the range of the standard curve

*** Pre to post change is calculated by subtracting T2 (6 month visit) from T1 (baseline) for all variables in all tables. Therefore, a positive value for pre and post change implies a decrease (BMI), while a negative value implies increase (QOL)

Table 2

Estimated effect of predictors of Physical Summary Score of QOL SF-36 scale, when controlling for baseline QOL of life physical summary score

Predictor**	N*	Estimated Effect	Standard Error	95% CI lower bound	95% CI upper bound	Standardized Coefficient	p-value
Biomarkers (units)							
Adiponectin (ug/ml)	46	0.05563	0.12817	-0.1596	0.2709	0.0483	0.6663
Leptin (ng/ml)	46	-0.17532	0.06111	-0.278	-0.0727	-0.2999	0.0063*
Resistin (ng/ml)	46	-0.1525	0.1307	-0.372	0.067	-0.1289	0.2492
Metabolic Factors							
BMI	49	-1.2588	0.4069	-1.9413	-0.5763	-0.324	0.0033*
Waist	49	0.308	0.1252	-0.5179	0.098	-0.2549	0.0175
Age	49	0.0064	0.0849	-0.136	0.1488	0.0082	0.9404

* N varies for biomarker and anthropometric measurements as in regression models; if even one value was missing, list wise deletion resulted in the loss of the participant for that row of the analyses

** All variables, other than age, are deltas (changes from baseline)

Table 3

Linear regression models exploring contribution of Leptin and BMI to PCS

Predictor	N	Estimated Effect	Standard Error	95% CI lower bound	95% CI upper bound	Standardized Coefficient	p-value
Model 1							
Quality of Life Physical Summary Score (baseline)	49	0.5473	0.1082	0.3659	0.7287	0.5755	<0.0001
BMI (baseline)	49	0.0913	0.0913	-0.2141	0.3967	0.0545	0.6185
Change in BMI	49	-1.2588	0.4069	-1.9413	-0.5763	-0.3241	0.0033
Model 2							
Quality of Life Physical Summary Score (baseline)	44	0.7127	0.11823	0.514	0.9115	0.7397	<0.0001
BMI (baseline)	44	0.0122	0.1969	-0.3188	0.3432	0.0069	0.9508
Change in BMI	44	-0.4962	0.4463	-1.2465	0.2542	-0.1279	0.2725
Leptin (baseline)	44	0.0766	0.0307	0.0251	0.1282	0.3219	0.0163
Change in Leptin	44	-0.1789	0.0626	-0.2840	-0.0737	-0.306	0.0065