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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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HIGHLIGHTS

- 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.
- Change in leptin with weight loss is an independent predictor of improved physical quality of life above affects of BMI.

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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). The 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 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

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diminished QOL [4]. Obesity is also a 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 cancers [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 that 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 diseases, 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 and 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 month 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% to 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