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Improvement in the Spatial Distribution of Pain, Somatic Symptoms, and Depression After a Weight Loss Intervention

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Abstract: **Weight loss is known to improve pain localized to weight-bearing joints but it is not known how weight loss affects the spatial distribution of pain and associated somatic symptoms like fatigue. We sought to determine if weight loss using a low-calorie diet improves pain, affect, and somatic symptoms commonly associated with chronic pain conditions in an observational study. We also documented changes in inflammatory markers in serum before and after weight loss. Participants were 123 obese individuals undergoing a 12- to 16-week calorie restriction weight loss intervention. The spatial distribution of pain, symptom severity (eg, fatigue, sleep difficulties), depression, and total fibromyalgia scale scores were measured before and after weight loss. Pain ($P = .022$), symptom severity ($P = .004$), depression ($P < .001$), and fibromyalgia scores ($P = .004$) improved after weight loss; men showed greater improvement than women on somatic symptoms and fibromyalgia scores (both $P < .01$). Those who lost at least 10% of body weight showed greater improvement than those who lost <10%. Levels of the regulatory cytokine interleukin-10 increased after the intervention ($P = .002$). Weight loss may improve diffuse pain and comorbid symptoms commonly seen in chronic pain participants.**

Perspective: ***This article presents the effect of a weight loss intervention on characteristics of chronic pain, including the spatial distribution of pain and comorbid somatic symptoms. Weight loss appeared to produce larger improvements in somatic symptoms for men.***

Key words: *Obesity, inflammation, widespread pain, weight loss.*

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According to 2011 to 2012 estimates, approximately 35% of adult Americans are obese.[26] Compared with their nonobese counterparts, a larger proportion of these obese individuals also suffer from pain, fatigue, cognitive difficulties, depression, and nonrefreshing sleep.[2,19] A number of explanations have been proposed to explain the link between pain and obesity. Many studies have focused on the mechanical load in weight-bearing joints. For instance, a recent investigation determined that significant weight loss after bariatric surgery was associated with a substantial reduction in knee and hip pain.[20] Meta-analyses have also determined that obesity is strongly associated with low back pain.[35] Pain in obesity is not limited to weight-bearing joints, however, and reduced physical

and mental well-being also play a large role in the reduced quality of life associated with obesity, even in individuals without obesity-linked chronic conditions.[17] The co-occurrence of all these symptoms suggests that systemic neurobiological and psychological mechanisms may contribute to their expression.[19,27] Understanding how the spatial distribution of pain and symptoms like fatigue are affected by weight loss may help develop more rational approaches to treatments for obese individuals with chronic pain.

A large number of neuroimaging studies have investigated abnormalities in pain processing networks in individuals with high levels of widespread pain and associated clusters of systemic symptoms suggesting the potential of a common mechanism.[29] In addition, studies of single nucleotide polymorphisms affecting mood as well as neurotransmission suggest commonalities between widespread pain and these systemic symptom clusters.[21] Finally, drugs that primarily modulate central neurotransmission have been reported to be effective in treating widespread pain as well as having benefit for associated symptomatology.[14] The underlying propensity to experience more widespread pain and a larger number of somatic symptoms has been shown to relate to important outcomes in complex chronic pain conditions without obvious organic pathology as well as in patients with clear signs of peripheral nociceptive input.[6] As examples, surrogate measures of this spectrum, such as the American College of Rheumatology (ACR) survey criteria for fibromyalgia (FM), have proven effective at identifying patients at risk for persistent pain and analgesic nonresponsiveness after joint replacement and hysterectomy.[3,16]

The symptom cluster containing sleep difficulties, pain, anxiety, depression, and low energy/fatigue has been described as a common symptomatic pentad that confers added impairment, treatment complications, and undermines health and functioning when present in the general population.[9] This symptom cluster is similar to that of cytokine-induced sickness behavior studied in animal models[8] and more recently has been documented in human clinical populations.[15] One possibility is that proinflammatory modulation of central nervous system processes play a role in the expression of these symptoms.[10] Obesity is strongly related to plasma/serum levels of proinflammatory cytokines.[5] Preclinical models show that obesity leads to the accumulation of macrophages in adipose tissue[40] and a switch in sentinel immune cells to a proinflammatory phenotype.

Despite the acknowledged overlap between chronic pain and obesity, the symptom cluster described previously has not been explored in a prospective study designed to promote weight loss. To address the hypothesis that the spatial distribution of pain, affect, and somatic symptoms would each improve after weight loss, we conducted a prospective study designed to achieve weight reduction in obese individuals using a well established and successful caloric restriction weight loss intervention.[31] We hypothesized that the spatial distribution of pain as well as severity of associated somatic symptoms would improve after weight loss. In a subsample of participants, we also measured inflammation-linked cytokines before and after weight loss to determine if inflammatory measures changed after the intervention.

Methods

Recruitment and Participants

The Weight Management Program is a 2-year multidisciplinary, multicomponent intensive behavioral lifestyle program designed for obese participants (to be eligible individuals must have a body mass index (BMI) ≥30, or ≥28 in Asian American individuals). Participants were referred to the program by clinicians in the University of Michigan Health System and by community physicians. The program has been described in detail previously.[31] Initially, 241 individuals enrolled in the study and provided baseline data. Of these, 157 completed the weight loss program (65%). Of the 84 who did not complete the program, 42 were lost to follow-up (50%) and 42 (50%) withdrew. Common reasons for withdrawal included change in life circumstances (eg, moving, pregnancy), socioeconomic factors, and change in insurance coverage. Those who did and did not complete the program were compared using 1-way analysis of variance on key study variables at time of study entry (see Results). Of the 157 individuals who completed the program 124 (79%) reported pain at baseline or after the intervention. One participant gained weight during the intervention and was excluded from further analyses. Therefore, 123 participants were included in longitudinal analyses of centralized pain characteristics. The study was approved by the University of Michigan Institutional Review Board.

Intervention

Weight loss was introduced via a very low calorie diet (800 kcal/d) in the form of total liquid meal replacement for a period of approximately 12 weeks to promote approximately 15% weight loss from baseline weight. The rationale for this approach is multifold: liquid meal replacement limits food choices, reduces unreported caloric intake, eliminates the palatability related to chewing food, divorces participants from unhealthy consumptive behaviors, promotes faster absorption of nutrients, and enhances initial as well as long-term weight loss. During the program participants were also encouraged to increase their physical activity gradually to a total of 40 minutes per day of low to moderate intensity, such as walking during the first 12 weeks and to 60 to 90 minutes of moderate to vigorous physical activity on at least 4 days per week, thereafter. Weight and height were assessed at each of the monthly scheduled visits to a physician and/or dietitian for calculation of BMI. Participants who struggle to adhere to the regimen and lose weight are counseled at these visits, and an additional 4 weeks may be added to the intervention phase to increase the chance of successful weight loss.

Measures

Demographic, Medical Information, and Physical Activity

Basic information including age, sex, level of education, and smoking status (never/ever) were collected according to self-report. The presence/absence of a physician diagnosis of 16 conditions were collected using a standardized form and include history of hypertension, dyslipidemia, and macrovascular disease. Physical activity was assessed with a 4-point measure ranging from "no physical activity weekly" (0) to "vigorous physical activity for at least 20 minutes three or more times per week" (3).

The Spatial Distribution of Pain, Somatic Symptoms, and Affect

The ACR preliminary diagnostic criteria for FM modified for clinical and epidemiological studies[43] was used to assess diffuse pain as well as the presence and severity of comorbid symptoms typically seen in centralized pain states. The ACR modified criteria consists of 2 scales: the Widespread Pain Index (WPI) contains 19 body sites that can be endorsed as painful (shown in Fig 1) and Symptom Severity Index (SSI) that measures several symptoms considered part of the centralized pain continuum (fatigue, unrefreshing sleep, cognitive difficulties, depressed mood, abdominal pain, headache.) These scales have been validated against other measures of bodily pain and somatic symptoms.[43] Use of the modified criteria in the general population indicates a dimensional, rather than categorical construct, supporting the use of the ACR score as an indicator of the underlying centralized pain construct.[42] This modified score (range = 0-31) has subsequently been shown to predict important features of complex chronic pain, including a failure to respond to surgical procedures intended to relieve pain.[3,16] The 30-item Inventory of Depressive Symptomology[32] (IDS) self-report was used to measure symptoms of depression.

Inflammatory Data

Fasting blood serum was collected in ethylenediaminetetraacetic acid (EDTA) tubes and stored at –80°C before the intervention and again after weight

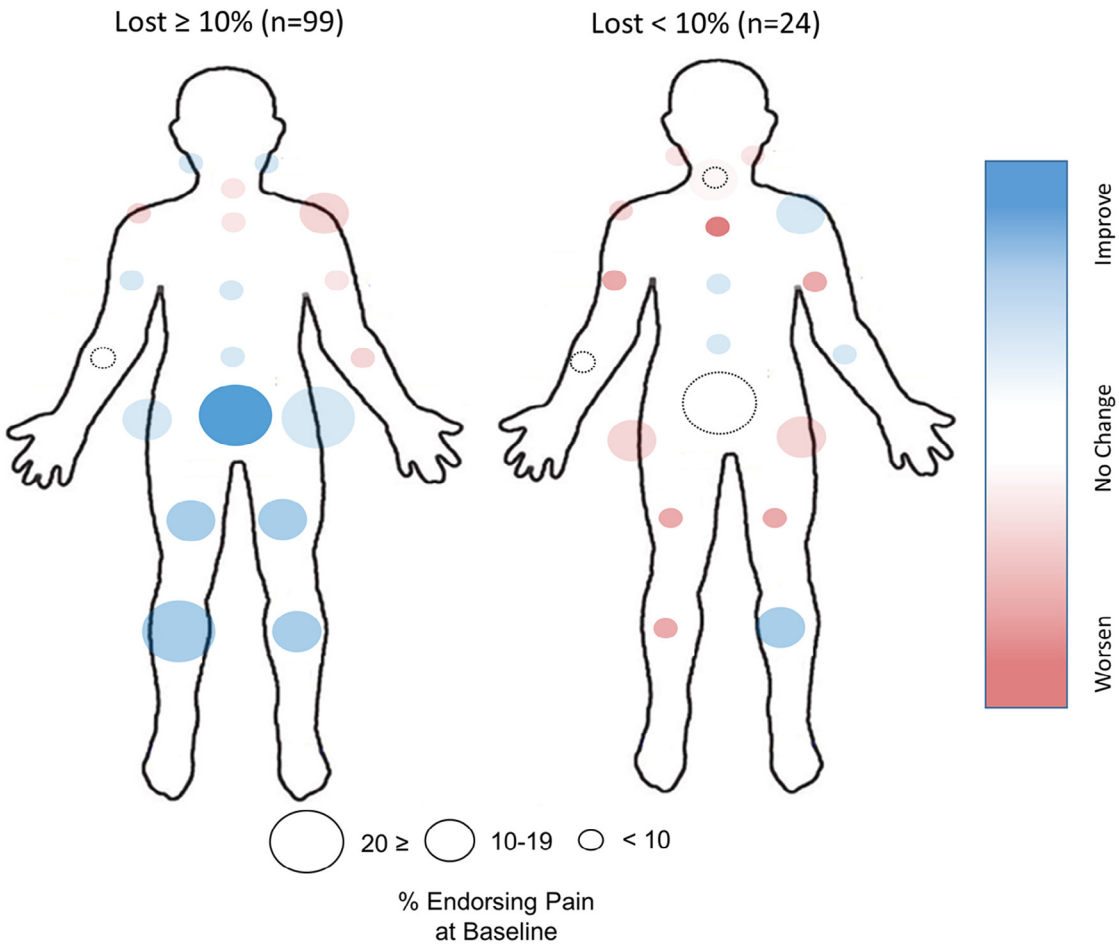

Figure 1. Illustration of change in pain after weight loss in individuals who lost 10% or more and <10% of body weight. Left and right panels: the largest circles are body areas where 20% or more of individuals endorsed pain at baseline; medium circles are areas where 10 to 19% of individuals endorsed pain at baseline; small circles are areas where <10% of individuals endorsed pain at baseline. Blue represents areas where the proportion of individuals endorsing pain after weight loss decreased (ie, improvement), whereas red represents areas where the proportion increased (ie, worsening). Color intensity corresponds to the magnitude of change.

loss. Several cytokines were selected that are known to have proinflammatory as well as regulatory effects: interleukin (IL)-6, 1β, 10, tumor necrosis factor-α and interferon-γ were assayed in duplicate using Luminex xMap technology with a high-sensitivity multiplex panel (MILLIPLEX HCYTOMAG-60K [EMD Millipore Corporation, Billerica, MA]; interassay coefficient of variation [CV]<20%, intra-assay CV <5%) and C-reactive protein (CRP) using high-sensitivity immunoturbidimetric assay (Sekure Chemistry 082 [Sekisui Diagnostics P.E.I. Inc., Charlottetown, PE, Canada]; inter- and intra- assay CV <10%) at the Michigan Diabetes Research Center Chemistry Laboratory. The assay ranges were for CRP: .1 to 80 mg/L; IL-6: .18 to 750 pg/mL; IL-1β: .49 to 2,000 pg/mL; IL-10: 1.46 to 6,000 pg/mL; tumor necrosis factor-α: .45 to 1,750 pg/mL; and interferon-γ: .61 to 2,500 pg/mL. Samples were limited to a subset of participants who consented to this optional blood draw at both time points (n = 31). These individuals were compared with the rest of the cohort on key study variables using 1-way analysis of variance (see Results).

Statistical Analyses

Longitudinal Analyses

To determine if the symptoms changed after the intervention, the SSI score, total ACR modified criteria score, and total IDS score, were compared using paired-sample t-test, and Wilcoxon signed rank test for physical activity data, between baseline (before weight loss) and again at the end of the weight loss intervention. Nonparametric tests were used to evaluate physical activity because of the limited range and ordinal nature of the scale (0-3). We evaluated the spatial distribution of pain using a mixed effects logistic regression model, with the primary outcome being the probability of endorsing any of the 19 sites as painful and the predictor being the time of evaluation (baseline or after weight loss). These models use random intercepts for subject as well as the site on the body map. This model reflects the probability of having pain at any given site while accounting for the variance associated with subject-specific response patterns and specific body sites. This approach is intended to model the propensity toward generalized hyperalgesia—the model accounts for the greater likelihood that an individual will have pain in the lower back, for instance, than the forearm, while also accounting for subject-specific response patterns. This model allows for a more accurate estimation of the effect of time (ie, weight loss or other changes during the intervention) on the overall likelihood of having pain at any site on the body. The appropriateness of including these random effects was confirmed using likelihood testing of nested models. Analyses were conducted in SPSS version 24 (IBM Corp, Armonk, NY) and R (https://www.r-project.org).

Secondary Analyses

To consider the effects of sex and magnitude of weight loss on symptom change, we used general linear models in which the outcome was the symptom change score (baseline symptom-postintervention symptom), with baseline symptom levels, sex, weight loss group, and physical activity group, as primary predictors. Weight loss groups were defined according to percentage body weight lost: <10% (n = 24), and >10% (n = 99). Physical activity groups were defined as those who increased physical activity over the course of the intervention (n = 63) and those who did not (n = 49). Estimated marginal means (EMMs) of change scores were compared according to group. A similar analytic procedure was used to test sex differences and weight loss magnitude effects on the change in the spatial distribution of pain. Sex × Time, Weight loss group × Time, and Physical activity group × Time interaction terms were tested to determine if these variables were associated with significantly different effects of time (baseline vs postintervention) on the probability of having pain at any site on the body map.

We also conducted correlations between Δ scores for depression, the SSI, the WPI, and the total ACR score, to determine if improvements in each domain were associated with each another.

Cytokine Data

More than 98% of the cytokine values were within detectable limits (365 of 372). The remaining 7 values were below detectable limits and set to 0 for subsequent analyses. Nonparametric paired sample tests were performed on the cytokine values using Wilcoxon ranked tests. In addition to raw cytokine values, the ratio of anti-inflammatory cytokine IL-10 to proinflammatory IL-6 and CRP was calculated for each time point and compared using Wilcoxon ranked test as well.

Inflammation and Symptoms

The association between levels of each cytokine and modified ACR score was tested using nonparametric correlation with Spearman rank procedures. The change in cytokine values that were significantly altered after weight loss were correlated with symptom change scores using Spearman rank procedures. We used the Spearman rank procedure because it is less affected by outliers and non-normal data than Pearson correlations.

Results

Baseline Comparison of Study Completers and Noncompleters

At baseline there were no statistically significant differences between the 84 participants who withdrew from the study or were lost to follow-up compared with the 157 completers on the ACR modified total score ($P = .196$), WPI ($P = .904$), IDS score ($P = .788$), number of comorbidities ($P = .139$), or BMI ($P = .282$). The difference in the SSI score trended toward significance ($P = .057$) such that noncompleters appeared to have slightly higher SSI scores (noncompleter mean = 4.55, SD = 2.15; completer mean = 3.90, SD = 2.72).

Table 1. Participant Characteristics (n = 123)

Characteristic	Value
ACR total score	6.42, 0 to 20 (4.26)
WPI	2.30, 0 to 11 (2.24)
SS	4.12, 0 to 11 (2.24)
IDS Score	17.40, 3 to 48 (9.23)
Number of Chronic Conditions	3.05, 0 to 9 (1.62)
Age	50.77, 23 to 69 (10.96)
BMI	40.34, 30 to 60 (6.46)
Weight (kg)	115.83, 73 to 195 (23.28)
Physical activity	
No physical activity weekly	9
Only light physical activity in most weeks	52
Vigorous physical activity for at least 20 minutes once or twice a week	23
Vigorous physical activity for at least 20 minutes 3 or more times per week	14
Female sex	67
Smoker	
Current	4
Former	29
Never	67
College degree	81
Employed	85

Data are presented as mean, range (SD), or %.

Demographic and Medical Information

The 123 participants included in the longitudinal analyses were middle-aged (mean age = 51 years [SD = 10.96, range = 23-69 years], 67% were female, and most were educated (81% with a college degree), and employed (85%). See Table 1. The average baseline weight and BMI were 116 kg (SD = 23.27) and 40 (SD = 6.45), respectively. The average number of comorbid conditions was 3.06 (SD = 1.64) and the 3 most common conditions were dyslipidemia (48%), hypertension (44%), and depression (38%). Additionally, osteoarthritis was reported by 19% of the sample.

Weight Loss

On average, participants lost 16.05% of their baseline weight (SD = 6.54%; range = 2-30% loss). Eighty percent (n = 99) lost at least 10% of their body weight. There were no statistically significant differences between men and women on initial BMI (men: mean = 40.54, SD = 6.99; women: mean = 40.28, SD = 6.23; $P = .84$), percent of body weight lost (men: mean = 16.3%, SD = 7.5%; women: mean = 15.95%, SD = 6.08%; $P = .810$), or proportion of individuals who lost ≥10% body weight (men = 78.05%, women = 81.71%; $P = .63$).

Postintervention Changes

The total 2011 modified ACR score declined significantly after weight loss (mean [SD]: baseline = 6.42 [4.26], after weight loss = 5.42 [3.47]; $P = .004$) as did the SSI score (baseline = 4.12 [2.87], after weight loss = 3.49 [2.48]; $P = .002$), and the IDS (baseline = 17.40 [9.22], after weight loss = 11.78 [6.95]; $P < .001$). A total of 112 participants reported physical activity levels at both time points. Of these 56% (n = 63) increased physical activity (≥1 point increase on the 4-point scale).

Spatial Distribution of Pain

The probability of a participant endorsing pain at any given site on the body map declined approximately 20% after weight loss (odds ratio [OR] = .799, 95% confidence interval [CI] = .661-.968; $P = .022$). The areas where change appeared to be greatest were the lower legs, lower back, chest, and jaw. See Fig 1.

Secondary Analyses

Men showed greater reductions in the total ACR FM score (EMM [standard error (SE)], men = –1.702 [.486], women = .102 [.382]; $P = .002$) and SSI (EMM [SE], men = –1.052 [.306], women = –.099 [.245]; $P = .009$) compared with women. There were no significant differences in IDS change scores (EMM [SE], men = –5.559 [.965], women = –4.309 [.744]; $P = .275$) or in pain reduction (Sex × Time interaction term, $P = .973$).

Losing more than 10% of body weight was associated with greater reductions in the ACR FM score (EMM [SE], ≥10% group= –1.621 [.302], < 10% group = .022 [.580], $P = .012$) and the IDS score (EMM [SE], ≥10% group = –6.433 [.595], <10% group = –3.435 [1.124]; $P = .018$) but not with the SSI (EMM [SE], ≥10% group = –.932 [.194], <10% group = –.219 [.374]; $P = .09$). Similarly, losing more than 10% of body weight was associated with a greater reduction in the spatial distribution of pain after intervention (Time × Weight loss group interaction term, $P = .019$). Individuals who lost ≥10% of body weight were approximately 30% less likely to endorse pain at any body site after the intervention (OR = .699, 95% CI = .548-.891) whereas individuals who lost <10% showed no significant change in the likelihood of reporting pain (OR = 1.284, 95% CI = .798-1.959). The distribution of these changes is shown in Fig 1.

There were no significant effects of change in physical activity on any measure of symptom reduction (all $P > .43$).

The change in the WPI and the SSI were associated (r = .208, $P = .021$), and the ACR total score (r = .221, $P = .015$) and SSI change (r = .348, $P < .001$) were both associated with the change in depression. The change in depression and WPI were not associated (r = .030, $P = .74$).

Inflammatory Data

Comparison of the Subsample With Inflammatory Data With the Rest of the Cohort

Individuals who provided blood at both time points for inflammatory analyses did not differ on baseline symptom characteristics, number of comorbid conditions, BMI, or symptom changes (all $P > .19$).

Table 2. Inflammatory Values Before and After Weight Loss (n = 31)

Cytokine	Baseline	After Intervention	Wilcoxon Signed Rank Test, P
Interferon-γ	6.00, 2.90 to 14.20	6.00, 3.10 to 15.70	.150
Tumor necrosis factor-α	5.90, 4.60 to 7.00	5.50, 4.70 to 6.90	.657
IL-1β	.90, .70-1.40	1.00, .70-1.60	.863
IL-6	3.10, 1.90 to 4.10	3.00, 2.40 to 6.30	.081
IL-10	17.10, 3.80 to 26.00	22.00, 7.70 to 40.70	.002
CRP	4.50, 2.70 to 8.50	4.10, 1.50 to 8.10	.222
IL-10/IL-6 ratio	5.17, 1.81 to 8.19	5.95, 3.61 to 8.29	.010
IL-10/CRP ratio	2.55, 1.43 to 5.91	6.33, 1.63 to 13.30	<.001

Data are presented as median, interquartile range, except where otherwise noted.

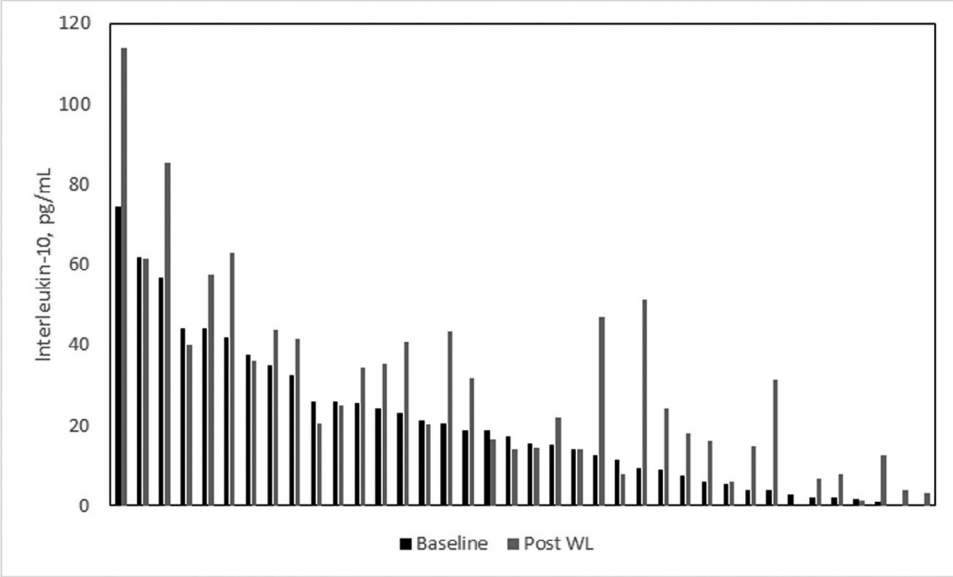

Figure 2. IL-10 values at baseline and after weight loss (WL) for all 31 participants with inflammatory data.

Pre- and Post Weight Loss

After weight loss, levels of IL-10 increased significantly ($P = .002$) whereas the other cytokine levels did not significantly change (all $P > .05$). See Table 2 and Fig 2. The ratio of IL-10 to IL-6 and CRP also increased significantly after weight loss (both $P < .05$), suggesting an increase in anti-inflammatory tone after caloric restriction. The increase in IL-10 remained statistically significant after correction for multiple comparisons ($P < .05$).

Relationship Between Cytokines and Symptoms

At baseline, higher levels of IL-6 were associated with higher modified ACR total scores (Spearman r = .424, $P = .017$), and post weight loss, higher levels of IL-6 (Spearman r = .360, $P = .047$) and IL-1β (Spearman r = .362, $P = .046$) were associated with higher modified ACR total scores. Other cytokines were not associated with modified ACR scores (all $P > .05$). See Table 3. At baseline, BMI was not related to levels of any cytokine (all $P > .05$) whereas after weight loss, higher levels of CRP were related to greater BMI (Spearman r = .431, $P = .016$). Levels of physical activity were unrelated to cytokine values at either time point (all $P > .05$).

The change in IL-10 was not significantly associated with the change in the WPI ($P = .23$), SSI score ($P = .385$), total ACR modified score ($P = .13$), depression score ($P = .89$), or the percentage of weight lost ($P = .11$).

Discussion

This study's chief finding is that after weight loss induced by a low-calorie diet the spatial distribution of pain and somatic symptoms improved, 2 hallmarks of complex chronic pain conditions. These results appear to be the serendipitous result of weight loss, because the participants were not seeking treatment for pain/somatic symptoms. After the intervention fewer individuals had pain in weight-bearing areas like the lower back and lower leg as has been noted in many previous studies,[24,25] but there was also some improvement in nonweight-bearing regions like the jaw, chest, and abdomen. These patterns were not consistent with a simple global reduction in pain, but seemed to vary according to site because there was some pattern of worsening in the upper back, neck, and shoulders. In addition to the composite measure of symptom severity (ie, fatigue, sleep difficulties) depression scores improved sub-

Table 3. Association Between Levels of Inflammation-Linked Cytokines and ACR Total Score Before and After Weight Loss

	Baseline		Postintervention	
Cytokine	Spearman Correlation	P	Spearman Correlation	P
Interferon-γ	.238	.197	.218	.239
Tumor necrosis factor-α	.088	.638	.232	.209
IL-1β	.220	.234	.362	.046
IL-6	.424	.017	.360	.047
IL-10	.263	.153	.201	.278
CRP	.212	.235	.345	.057

stantially. Those who lost >10% of their initial body weight showed greater improvement in depression, pain, and total modified ACR scores. Over four-tenths of those who lost >10% of their body weight showed at least a 30% reduction in ACR scores, a metric that, when applied to other pain measures, corresponds well with patients' ratings of "much improved."[36] Finally, men appeared to improve more in somatic symptoms and on the total ACR score than women after the intervention. Although physical activity increased from baseline to postintervention, this change was not associated with the change in symptoms. Those who completed the study were not substantially different from those lost to follow-up or withdrawal, which suggests that selection effects do not play a large part in our results.

Our analytic approach was designed to assess a general vulnerability to bodily pain. In the current study, examining specific regions of improvement and worsening between those who did and did not lose 10% of body weight suggests the greatest improvement in the lower back and other weight-bearing areas, with some improvement in the jaw, chest, and abdomen. This finding coupled with the association between improvements in pain and somatic symptoms, is consistent with some component of the observed changes involving a global neurobiological or psychological mechanism, although it is also possible that improvements in pain governed by local mechanisms ultimately lead to improvements in energy, sleep, and affect. A previous study using resting state functional connectivity reported that obese individuals show increased connectivity to the salience network from several regions including the amygdala and insula,[13] a pattern of connectivity that has been linked to an increased likelihood of finding experimental stimuli painful.[41] It is possible then, that weight loss may alter such patterns of connectivity in a manner that is beneficial for the perception of pain. Improved sleep quality is a well established correlate of weight loss in obese individuals with apnea,[1] but sleep quality is also reduced in obese individuals without apnea.[38] Improved sleep may therefore play a role in improved pain, somatic symptoms, and affect.[39] Depression improved substantially and was consistent with improved affect, self-efficacy, and self-esteem noted in other weight loss studies.[11]

Improvements in mood may be an important component of improvement in somatic symptoms, but do not appear to be associated with improvements in pain in our study. This may be because we measured the spatial distribution of pain, rather than intensity, because it is the latter outcome that has been shown to improve significantly with improving mood.[33] It was somewhat surprising that changes in physical activity were not associated with greater changes in symptoms, because this has been suggested specifically as a means to improve chronic pain in obesity.[28] It may be that calorie restriction at this level is not conducive to moderate or major increases in physical activity that would show stronger relationships with symptom change. We suspect that the improvements noted in this study are the result of dynamic and complementary factors that will require more assessments to characterize the relevant causal pathways.

The change in symptoms is particularly noteworthy because they were detectable in a sample of individuals with relatively low levels of baseline symptoms (ie, an average of 2 painful body sites), who were not seeking treatment for pain, mood, or somatic symptoms. This suggests that pain and somatic symptoms do not need to be at "pathological" or severe levels to improve after weight loss. This raises the important question of whether individuals with chronic pain would show levels of improvement relative to their baseline symptoms similar to the participants in this study. The greater improvement shown by men on the SSI and ACR score is important, because women disproportionately suffer from conditions characterized by the somatic symptoms measured in the SSI (ie, chronic fatigue syndrome)[37] and these results would suggest that weight loss is more beneficial for pain and affect symptom domains. A recent meta-analysis reported that men who lose weight experience a substantial rebound in total and free testosterone,[7] which have been associated specifically with self-reported physical vigor/well-being.[44]

The anti-inflammatory cytokine IL-10 appeared to be greatly increased after the intervention, and this remained true when levels of IL-10 were compared with concurrent levels of inflammation-promoting cytokines. These increases however, were not associated with the magnitude of change in symptoms. An increase in IL-10 was previously reported after weight loss in an exercise/caloric restriction intervention in 78 obese individuals[18] and studies have indicated that levels of IL-10 and the IL-10 response to immune provocation are reduced in individuals with metabolic syndrome.[12] In vitro studies show

that IL-10 inhibits nuclear factor-κB activity in adipocytes, reducing proinflammatory signaling,[22] and animal models show that IL-10 protects adipocytes from macrophages with a proinflammatory phenotype[23]; this may explain why the number of adipose tissue-infiltrating macrophages is reduced after bariatric surgery.[4] These findings suggest that IL-10 reduces inflammatory tone in adipose tissue and may be helpful in reducing inflammation in/near vulnerable joints. Also, IL-10 treatment has been shown to improve centrally induced hyperalgesia in animal models.[30] A recent study has shown convincingly that IL-10 reduces the number of voltage-gated sodium channels in the dorsal root ganglion of animals after peripheral nerve injury and attenuates mechanical nerve injury.[34] Therefore, there are plausible pathways by which IL-10 activity could limit peripherally as well as centrally mediated sensitivity to pain. Additional assessments of inflammatory activity to determine if shifts in inflammatory tone precede symptom improvement or simply parallel them are needed.

Limitations

Our inflammatory analyses were limited to a subsample of participants. The analyses relied on 2 time points, making true longitudinal inferences difficult to determine. The measure of pain we used only considers the distribution, rather than the intensity of reported pain. The lack of an objective measure of physical activity is likewise a limitation. Similarly, without a control group it is not possible to calculate possible regression to the mean type effects.

Conclusions

These analyses suggest that caloric restriction and weight loss positively affect several symptom domains that commonly affect chronic pain populations. It is therefore plausible that similar interventions could positively affect pain, affect, and somatic symptoms in clinical populations. In addition to measures of complex chronic pain and related measures of clinical pain, future studies using quantitative sensory testing techniques may provide important mechanistic information about hyperalgesia in obesity. Sex differences in the effects of weight loss on different symptom domains should be replicated and expanded. A better understanding of the mechanisms behind these effects, including any role for inflammatory processes, may be gleaned from longitudinal studies with more assessments.

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