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EFFECTS OF INTENSIVE DIET AND EXERCISE ON KNEE JOINT LOADS, INFLAMMATION, AND CLINICAL OUTCOMES AMONG OVERWEIGHT AND OBESE ADULTS WITH KNEE OSTEOARTHRITIS

THE IDEA RANDOMIZED CONTROLLED TRIAL

Revision 4

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ABSTRACT

Context Knee osteoarthritis (OA), a common cause of chronic pain and disability, has biomechanical and inflammatory origins and is exacerbated by obesity.

Objective To determine whether a ≥ 10% reduction in body weight induced by diet, with or without exercise, would improve mechanistic (knee joint loads and inflammation) and clinical (pain, function, mobility, and health-related quality of life) outcomes more than exercise alone in overweight and obese older adults with knee OA.

Design, Setting, Participants IDEA was a single-blind, 18-month, randomized controlled trial conducted at Wake Forest University between July 2006 and April 2011, the final date of follow-up. The diet and exercise interventions were center-based with options for the exercise groups to transition to a home-based program, or integrate the two for months 7-18. Participants were 454 overweight and obese older ($27 \geq BMI \leq 41 kg \cdot m^{-2}$, age ≥ 55 yrs) community-dwelling adults with pain and radiographic knee OA.

Interventions Intensive diet-induced weight loss-plus-exercise (D+E), intensive diet-induced weight loss (D), or exercise (E).

Main Outcome Measures An intention-to-treat analysis focused on the two primary outcomes, knee joint compressive force and plasma interleukin-6 (IL-6)**;** secondary outcomes included self-reported pain (range, 0-20) and function (range, 0-68), mobility, and health-related quality of life (HRQL, range, 0-100).

Results 399 participants (88%) completed the study. Mean weight loss was: D+E, -10.6 kg (-11.4%); D, -8.9 kg (-9.5%); E, -1.8 kg (-2.0%). After 18 months, mean (95%CI, Δ = pairwise difference) knee compressive forces were lower in D (2487 N; 2393, 2581) compared to E (2687 N; 2590, 2784, $\Delta_{E \text{ vs } D}$ = 200 N; 55, 345; p = 0.007). IL-6 concentrations were lower in D+E (2.7 $pg \cdot ml^{-1}$; 2.5,3.0) and D (2.7 $pg \cdot ml^{-1}$; 2.4, 3.0) compared to E (3.1 $pg \cdot ml^{-1}$; 2.9, 3.4, $\Delta_{E \text{ vs } D+E}$ = 0.39 $pg \cdot ml^{-1}$; -0.03, 0.81; p = 0.007; $\Delta_{E \text{ vs } D}$ = 0.43 $pg \cdot ml^{-1}$; 0.01, 0.85, p = 0.006). The D+E group had less pain (3.6; 3.2,4.1) and better function (14.1;12.6, 15.6) than the D group (4.8; 4.3, 5.2, $\Delta_{D \text{ vs } D+E}$ =1.13, p_{pain} = 0.001;17.4; 15.9, 18.9, $\Delta_{D \text{ vs } D+E}$ = 3.30, $p_{function}$ = 0.003) and E (4.7; 4.2, 5.1, $\Delta_{E \text{ vs } D+E}$ = 1.02; 0.33, 1.71, p_{pain} = 0.004: 18.4; 16.9, 19.9, $\Delta_{E \text{ vs } D+E}$ = 4.29; 2.07, 6.50, $p_{function}$ = 0.0002). The D+E group (44.7; 43.4, 46.0) also had better physical HRQL scores than the E group (41.9, 40.5, 43.2, $\Delta_{E \text{ vs } D+E}$ =-2.81; -4.76, -0.86, p = 0.005).

Conclusions Among overweight and obese adults with knee OA, after 18 months, participants in the D+E and D groups had more weight loss and greater reductions in IL-6 levels than those in the E group; those in the D

group had greater reductions in knee compressive force than those in the E group, and those in the D+E group had less knee pain and better function than those in the D and E groups. While these differences are relatively modest, their clinical promise warrants further study.

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OA is the leading cause of chronic disability among older adults, and knee OA the most frequent cause of mobility dependency and diminished quality of life. [1;2;3] Obesity as a major risk factor for knee OA was first documented in 1945 and subsequently widely verified.[4-8] Current treatments for knee OA are inadequate; of patients treated pharmacologically, only about half experience a 30% pain reduction, usually without improved function.[9] The few studies of long-term weight loss in obese adults with knee OA showed equally modest improvements.[10;11]

Knee OA is considered an active disease process with joint destruction driven by both biomechanical and pro-inflammatory factors.[12] *In vitro*[13] and *in vivo*[14] animal models elucidate specific mechanical and biological factors that affect cartilage degradation and tissue changes associated with cartilage growth and remodeling. However, clinical studies are the best vehicle for determining the physiological basis of the biomechanical factors that affect OA pathogenesis and treatment.[12;15]

Considering the adverse effects of drug therapy,[16-18] the limited efficacy of surgical intervention in mild-to-moderate cases,[19] and the long-term public health benefits of an effective treatment for OA and obesity-related complications,[20] we tested the hypothesis that achieving sustained, significant weight loss, with or without increased exercise, would reduce joint loading and inflammation and improve clinical outcomes more than increased exercise alone. This translational study compared the effects of diet-induced weight loss plus exercise (D+E), diet-induced weight loss only (D), and exercise-only (E) interventions on mechanistic (knee-joint compressive force, IL-6) and clinical (pain, function, mobility, health-related quality of life) outcomes in overweight/obese adults with knee OA.

METHODS

Study Design

Intensive Diet and Exercise for Arthritis (IDEA) was a single-blind, single-center, 18-month, randomized controlled trial. Participants were randomized into one of three groups: D+E, D, or E. We designated E as the comparison group because our work[21] indicated that aerobic walking or resistance training should be part of the standard-of-care for knee OA patients. Interventionists' responsibilities were limited to exercise and dietary therapy interactions with patients (no data collection). Personnel responsible for data collection

without intervention responsibilities were blinded to group assignment. Trial design and rationale are detailed elsewhere.[22]

Study Oversight

IDEA was conducted at Wake Forest University and Wake Forest School of Medicine between July 2006 and April 2011. The study was approved by the Human Subjects Committee of Wake Forest Health Sciences. Informed consent was obtained in writing from all participants.

Study Sample

The sample consisted of ambulatory, community-dwelling persons age ≥ 55 years with: (1) Kellgren-Lawrence (KL) grade 2 or 3 (mild or moderate) radiographic tibiofemoral OA or tibiofemoral plus patellofemoral OA of one or both knees,[23] (2) pain on most days due to knee OA, (3) 27 ≤ Body Mass Index (BMI) ≤ 41 $kg \cdot m^{-2}$, and (4) a sedentary lifestyle (< 30 $min \cdot wk^{-1}$ of formal exercise for the past 6 months). Participants maintained and adjusted their usual medications as needed with their physician's consent. Eligibility, sample size calculations, and screening measurements are detailed elsewhere.[22] Race/ethnicity was determined by self-report.

Participants were recruited between November 2006 and December 2009. Eligibility was determined by initial phone screen and two in-person screening visits.[22] A stratified-block randomization method was used to assign all eligible persons to one of the three intervention arms, stratified by BMI and gender.

Interventions

The D group received the weight loss intervention, the E group received the exercise intervention, and the D+E group received both.

*Intensive weight loss intervention***.** The goal of this intervention was a mean group loss of at least 10% of baseline weight, with a desired range between 10% and 15%. The diet was based on partial meal replacements, including up to 2 meal-replacement shakes per day (Lean Shake®, provided by General Nutrition Centers, Inc., Pittsburgh, PA.). For the third meal, participants followed a weekly menu plan and recipes that were 500-750 kcals, low in fat, and high in vegetables. Daily caloric intake was adjusted according to the rate of weight change between intervention visits.

The initial diet plan provided an energy-intake deficit of 800-1000 kcals·d^{-1} as predicted by energy expenditure (estimated resting metabolism x 1.2 activity factor) with at least 1100 kcals for women and 1200 kcals for men. The calorie distribution goal was 15-20% from protein, < 30% from fat, and 45-60% from carbohydrates, consistent with the Dietary Reference Intakes for Energy and Macronutrients [24] and successful weight-loss programs.[25] As follow-up progressed, fewer meal replacements were consumed. Body weight was monitored weekly or biweekly during nutrition education and behavioral sessions: from months 1-6, one individual session and 3 group sessions per month, and from months 7-18, biweekly group sessions and an individual session every 2 months.

*Exercise Intervention***.** The exercise intervention was conducted for 1 hour 3 d·wk^{-1} for 18 months. During the first 6 months, participation was center-based. After 6-month follow-up (FU6) testing and a 2-week transition phase, participants could remain in the facility program, opt for a home-based program, or combine the two. The program consisted of aerobic walking (15 min), strength training (20 min), a second aerobic phase (15 min), and cool-down (10 min).

Techniques to improve adherence. Diet and exercise interventionists were trained in behavioral techniques based on social cognitive theory and group dynamics.[26;27] Adherence data were reviewed regularly to identify participants who needed additional counseling. Participants in both the D and E interventions self-monitored by completing daily logs. A behavioral "toolbox" for participants in the D+E and D groups who had difficulty achieving the weight-loss goal included additional individual and group counseling, social support, and incentives.

Measurements and Procedures

All participants were tested at baseline, FU6, and FU18. An initial symptom-limited, maximum exercise stress test excluded anyone with severe manifestations of coronary heart disease. The Modified Mini-Mental State Exam (3MSE) screened for cognitive deficiencies.[28]

Knee Joint Load. Bone-on-bone peak tibiofemoral (knee) compressive force was the primary measure of knee joint loading. Detailed description of instruments and calculation of knee joint compressive force can be found on the on-line supplement.

Plasma IL-6. Blood samples were collected in the early morning after a 10-hour fast at baseline, FU6, and FU18. The 6- and 18-month samples were collected at least 24 hours after the last acute bout of exercise training (D+E and E groups) and sampling was postponed (1-2 weeks after recovery from symptoms) in the event of an acute respiratory, urinary tract, or other infection. All blood was collected, processed, divided into aliquots, and stored at -80^{o}C until analysis.

The inflammation measure was plasma IL-6 pg·ml^{-1}. This cytokine is implicated in OA pathogenesis and showed significant improvement with weight loss in the Arthritis Diet and Activity Promotion Trial (ADAPT).[29] All samples were measured in duplicate using enzyme-linked immunosorbent assays (Quantikine® ELISA kits R&D Systems, Minneapolis, MN) with the average used for data analyses.

Pain. The Western Ontario McMasters Universities Osteoarthritis Index (WOMAC) pain subscale was used to measure self-reported pain.[30] Participants indicate on a scale from 0 (none) to 4 (extreme) the degree of pain experienced performing daily living activities in the last 48 hours due to knee OA. Total scores for the 5 items range from 0-20; higher scores indicate greater pain.[30;31] *Function.* Individual scores on the 17 items of the WOMAC self-reported function subscale were added to generate a summary score ranging from 0 to 68; higher scores indicate poorer function. A minimally clinically important difference of at least 20% improvement from baseline is required for both pain and function.[32]

*Mobility***.** We measured gait speed (m·s^{-1}) and 6-minute walk distance (m).[33]

*Weight, height, BMI***.** Weight, height, and BMI were obtained at baseline, FU6, and FU18 using standard techniques. D+E and D participants were weighed at each scheduled nutrition education and behavioral session.

Body composition. Whole body lean mass (LM) and fat mass (FM) were measured at baseline and FU18 by dual x-ray absorptiometry using a fan-beam scanner (Delphi A™, Hologic, Waltham, MA) and the manufacturer's recommendations for patient positioning, scanning, and analysis.

*Health-related quality of life (HRQL)***.** SF-36[34] was used to measure HRQL using two broad summary scores: physical and mental health, scaled from 0 (worst) to 100 (best).

X-ray. We used bilateral, posterioranterior, weight-bearing knee x-rays to identify tibiofemoral OA and sunrise views to identify patellofemoral OA. To visualize the tibiofemoral joint, we used a positioning device to flex knees 15 degrees, with the beam centered on the joint space.

Modified Mini-Mental State Exam (3MSE). This quantitative assessment of cognitive functioning examines orientation to time and place, recall, short-term memory, and arithmetic ability. Anyone scoring below 70 at baseline was ineligible.[28]

Statistical Analysis

Primary outcomes for IDEA were IL-6 and knee compressive force. IL-6 was log-transformed for sample size calculations and analyses. Standard deviations were obtained from the ADAPT[10] study which measured the same outcomes in a similar population. The sample size of 150 participants per group was calculated based on both primary outcomes to obtain 80% power to detect a 20% difference in IL-6 group mean ratios at month 18 and a 15% between group mean difference in knee compressive force at the 0.008 significance level adjusted for 2 outcomes, 3 treatment groups, and 80% retention. This sample size also provided 80% power for mean differences in secondary outcomes of 2.9 for WOMAC function and 1.0 in WOMAC pain at the 0.0167 (3 treatment groups) significance level.

Intention-to-treat analyses were conducted with SAS v9.2 (SAS Institute, Cary, NC). Two-sided nominal p-values are reported. One-way analyses of variance and chi-square tests addressed differences in baseline characteristics among groups. The interventions' effects on knee compressive forces, IL-6, WOMAC pain and function, walk speed, 6-minute walk, and SF-36 were determined using mixed model regression analyses adjusted for IDEA stratification factors (BMI, gender, and baseline values). Analyses included all follow-up data, and intervention effects were estimated at each follow-up visit. A contrast for the intervention effect at 18 months was tested in each model, using the E group as the reference group. Effect sizes were calculated by subtracting the E mean from the D+E and D least-squared means and dividing by their pooled standard deviations. Unadjusted percent change at FU18 for each group was obtained by subtracting the baseline mean from the 18-month mean and dividing by the baseline mean. When the overall FU18 p value was ≤ 0.025 for the primary outcomes, specific pairwise differences were noted, with the significance level adjusted for six

comparisons ($p \leq 0.008$). For the secondary outcomes, the significance levels were 0.05 and 0.0167 (3 treatment groups).

To assess whether our results were biased due to missing data, we performed a sensitivity analysis using multiple imputation for all 454 randomized individuals. We imputed 50 fully observed datasets with complete data at 6 and 18 month visits, analyzed each dataset using our previously stated analytic protocol, and aggregated the results. The imputation and aggregation were performed using PROC MI and PROC MIANALYZE, respectively, in SAS v9.3. Data from the multiple imputation analyses are presented below and the intention-to-treat completers-only analyses are shown in the on-line supplement.

The dose-response relationship between each outcome variable and continuous and categorical weight change (<5%, 5-9.9%, ≥ 10%) was assessed using mixed model regression analyses, controlling for BMI, gender, baseline values, and group assignment. The weight loss categories reflect the weight loss goals of ≥5% for ADAPT and ≥10% for IDEA.[10;22]

RESULTS

Retention and Adherence

Figure 1 and Table 1 show eligibility criteria, characteristics, and progress of the randomized cohort. Of the 454 participants, 399 (88%) completed the study (returned for FU18). Retention did not differ significantly among the groups (E, 89%; D, 85%; D+E, 89%), and non-completers did not differ significantly from completers in terms of age, sex, race, number of comorbidities, initial radiographic score, knee pain, or physical function.

Adherence to exercise (number of sessions completed/number scheduled) for the E group was 66% for the first 6 months and 54% for 18 months; for the D+E group, it was 70% and 58%, respectively. Adherence to the diet intervention (number of individual and class sessions attended/number scheduled) was 61% for the D group and 63% for the D+E group. Three non-serious adverse events related to the trial included a muscle strain and 2 trips/falls during exercise sessions that resulted in soreness and bruising. The external safety monitor determined that 10 serious adverse events were unrelated to the study (eTable 1). Seven participants underwent surgery during the study: E, 1 knee surgery, 3-knee replacements; D+E, 1-foot, 1-gall bladder, 1-hip replacement. All but the knee surgery patient returned to the study after surgery.

Weight Loss and Body Composition

Both diet groups lost significantly ($p < 0.0001$) more weight than the E group (Table 2). The D group lost 8.9 kg (9.5%) over 18 months; the D+E group lost an average of 10.6 kg (11.4%). Neither group regressed toward baseline values (see eFigure 1). The E group lost 1.8 kg, or 2.0% of baseline body weight. At baseline, 79.3% of all participants had a BMI ≥ 30 $kg \cdot m^{-2}$. At FU18, this was reduced to 55.5% including E = 69.0%, D = 54.6%, and D+E = 43.3%.

Total fat mass was significantly less in both diet groups relative to the E group after 18 months ($p < 0.0001$). Fat mass remained essentially unchanged (-0.4 kg) in the E group, while decreasing 6.5 kg (18%) and 4.8 kg (13%) at FU18 in the D+E and D groups, respectively. The D+E and D groups lost significantly more lean mass than the E group ($p<0.0001$), but the percent of lean mass at 18 months did not differ among the three groups.

Knee Joint Load and Inflammation

Evaluation of peak knee compressive force (our biomechanical outcome measure of joint loading) at 18 months demonstrated that the E group had decreased joint loading by 148 N (5%), D by 265 N (10%), and D+E by 230 N (9%) (Table 3). Of the pairwise between group comparisons, the E vs D comparison had the greatest difference in compressive force of 200 N ($p=0.007$; 55,345). The difference between the E vs D+E groups and the D vs D+E groups were not significant (Table 4).

Plasma IL-6 also differed significantly among the groups ($p = 0.0075$); pairwise between group comparisons revealed that the differences in the D+E and D groups relative to E were 0.39 $pg \cdot ml^{-1}$ (-0.03,0.81;$p=0.007$) and 0.43 $pg \cdot ml^{-1}$(0.01,0.85;$p=0.006$) respectively (Tables 3 and 4).

Pain and Function

Pairwise between group comparisons of WOMAC pain and function at 18 months revealed that the D+E group had less pain relative to the E (1.02; 0.33,1.71;$p=0.004$) and D (1.13; 0.44,1.82; $p=0.001$) groups (Table 4, Figure 2). Post-hoc analysis revealed that 38% of the D+E group reported little or no pain after 18 months with scores of 0 or 1 (0-20) compared with 20% and 22% of the participants in the D and E groups, respectively.

Pairwise between group comparisons revealed that WOMAC function score was significantly better in the D+E group relative to the E group (4.29; 2.07,6.50;p = 0.0002). Similarly, D+E had better function than D (3.30; 1.09, 5.51, p=0.003). The E vs D comparison showed no significant difference (Table 4).

Mobility and Health-Related Quality of Life

At 18 months, the D+E group walked 0.04 $m \cdot s^{-1}$ faster relative to the E group (-0.07, -0.02; p = 0.003). The E vs D and D vs D+E comparisons were not significant. 6-minute walk distance was 21.3 m farther in the D+E group relative to the E group (-36.3,-6.4;p=0.005). The D+E group also walked 41.5 m farther than the D group (-56.4,-26.6;p<0.0001), and E walked further than D (20.2 m; 5.0, 35.4; p = 0.009). The greatest difference in the SF-36 physical subscale was 2.81 units in D+E relative to the E group (-4.76,-0.86; p=0.005). Changes in the SF-36 mental subscale did not reach significance between any groups (Tables 4).

Sensitivity Analysis

Results from the intention-to-treat completers-only analyses that did not use multiple imputations are shown in eTables 2-3. Pairwise comparisons for knee joint compressive load, IL-6, pain, and function were statistically unchanged between the intention-to-treat and multiple imputation analyses. Comparisons between D+E and E for 6-minute walk distance and SF-36 physical subscale reached statistical significance only in the multiple imputation analysis (D+E was better than E, p = 0.005).

Dose Response to Weight Loss

We examined the relationship of percent weight change to 18-month mean [SE] mechanistic and clinical outcomes adjusted for intervention, BMI, gender, and baseline values. Independent of group assignment, the cohort was divided into 3 categories based on 18-month weight loss: high (H): -32.5% to -10.1%; medium (M): -9.9% to -5.0%, and low (L): -4.9% to +9.9%. We found significant weight-change dose-response effects in knee compressive force, IL-6, pain, and function; participants in the high category had significantly lower joint loads, less systemic inflammation and pain, and better function at FU18 (eTable 4).

COMMENT

In this translational study of weight loss and exercise among overweight and obese adults with knee OA, we found that after 18 months mean weight loss was greater in the D+E group and the D group compared

with the E group. In addition, when compared with the E group, the D+E group had less inflammation, less pain, better function, faster walking speed, and better physical health related quality of life.

Primary Outcomes

Peak knee compressive forces decreased and walking speeds increased in all three groups after the 18-month intervention period. In pairwise between group comparisons, peak knee compressive forces were 200 N (45 lb) per step less in the D group than in the E comparator group (Table 4). The clinical importance of this difference is unknown, although it appears that weight loss reduces knee-joint loading even as preferred walking speed increases.

Whether inflammation constitutes a separate OA disease pathway, or instead is the downstream result of chronic excessive biomechanical stress is debated.[12;35] Systemic inflammation markers, including IL-6, distinguished knee or hip OA patients from controls,[36] and higher systemic levels of IL-6 have been associated with increased odds of developing knee OA.[37] Diffusion of such cytokines from the synovial fluid into the cartilage could contribute to cartilage matrix loss by stimulating chondrocyte catabolic activity and inhibiting anabolic activity.[12;38] In addition to these direct effects on the joint, inflammatory mediators can affect muscle function and lower the pain threshold.[39] IL-6 concentrations less than 2.5 $pg \cdot ml^{-1}$ have been shown to reduce the risk of mobility disability and improve markers of metabolic syndrome.[40] Participants in all 3 groups exceeded this level (mean = 3.1 $pg \cdot ml^{-1}$) at baseline, with significant improvements in D+E and D relative to E at 18 month follow-up. Our study was powered to detect a 15% and 20% difference in knee compressive force and IL-6, but found differences of approximately 8% and 14%, respectively. Results need to be interpreted with this in mind.

Secondary Outcomes

With regard to pain, between group differences in WOMAC score were 1.02 and 1.13 units in the D+E vs E and the D+E vs D groups, with D+E having less pain. The D+E group reached an adjusted 45% (3.0 points) and 42% (10.3 point) within group change in pain and function at 18 months, respectively. This within-group pain reduction and a similar improvement in function may be clinically important; however, the difficulty in interpreting the meaning of between- and within- group changes, especially in pain, must be

acknowledged.[41] Hence, the clinical significance of 1.02- and 1.13-point between group differences in the WOMAC pain scale remains uncertain.

Post-hoc analysis revealed that nearly 40% of D+E participants had WOMAC pain scores of 0-1 (no or little pain) at 18 month follow-up compared to 20% of the D and E groups; pain worsened from baseline in 10% of the D+E group compared to 22% in the D and 28% in the E groups. The D group, which had similar decreases in joint loads and inflammation, experienced only half the D+E pain reduction. Reasons for this finding are unclear. The E group's pain reduction, despite increased joint loads, inflammation, and walk speed, may indicate psycho-physiological effects of exercise on the central[42] and peripheral nervous systems.[43]

Patients in our cohort reported relatively mild pain at baseline (averaging 6.5 on a 0-20 scale), similar to participants in previous long-term OA clinical trials.[10;11;44] This entry level may have been an advantage because lack of adherence due to extreme pain was uncommon, but it left little room for improvement.

Despite use of an active comparison group with level 1 evidence of efficacy,[45] the D+E group had better clinical outcomes (i.e., pain, function, and mobility), with an effect size (Cohen's d)[46] for pain of 0.4. Adherence to exercise for the D+E and E groups was 70% and 66%, respectively, during the first 6 months of center-based activity. As participants incorporated home-based exercise after month 6, adherence decreased to 58% and 54% after 18 months. The D+E group's improvement in function and mobility was modest but significantly greater than either the D or E groups' and greater than that achieved by the ADAPT D+E group.[10] Improvements also exceeded those observed in a randomized controlled trial that compared a very low-energy diet to an attention control group[11] in which function improved in the diet group at 3-month follow-up but regressed toward baseline values by 12 months. We attribute our results to challenging yet attainable weight-loss and exercise goals with a social cognitive behavioral framework.

Walk speed and 6 min walk distance, measures of mobility, were below normative values for healthy older adults at baseline.[47;48] At FU18, the D+E group exceeded these normative values, with significant pairwise differences relative to the E and D groups (see Table 4). Himann et al.[47] found that walking speed decreased 1-2% per decade of adult life until age 62, when the decline was a startling 12-16% per decade. Our cohort reversed this trend by increasing their walking speed and 6 minute walk distance, D+E significantly more than

the E and D groups. These improvements, in part, may have been due to the significant reduction in knee pain. The D+E group significantly improved the physical health dimension of HRQL relative to the E group with a pairwise difference of 2.81 and an improvement from baseline of 8 units. A minimally important improvement from baseline of 4.11 in the physical subscale has been reported for patients with psoriatic arthritis.[49] There were no between group difference in mental subscale scores.

A multiple imputation analysis revealed minimal differences from our original intention-to-treat analysis, indicating the strength of the primary analysis. This was due to the low drop-out rate relative to similar studies.[21;50] Drop-out did not occur differentially with respect to randomization group, gender, or baseline BMI ($p>0.05$).

Independent of group assignment, participants who lost ≥ 10% of body weight improved function and reduced knee compressive force, systemic IL-6 concentrations, and pain more than those who lost 5-9.9% or <5% of their baseline weight. These data are consistent with the NIH recommendation for overweight and obese adults to lose 10% of baseline weight as an initial goal.[20] Weight-loss programs for older adults are not without risks. In addition to fat mass, weight loss reduces lean mass, which is associated in older adults with muscle weakness, greater risk of falls and injury, and loss of independence and mobility, although exercise can attenuate it.[51] Both diet groups lost substantial fat mass (D+E, -10.6 kg, -18%; D, -8.9 kg, -13%) and -4.7 kg (-9%) and -4.2 kg (-8%), respectively, of lean mass. However, relative to total body weight at FU18, lean mass actually increased 3% in the D+E group and 2% in the D group.

This study has several limitations. Patients in this study had mild-to-moderate radiographic knee OA at baseline (KL scores of 2-3) and similar levels of knee pain. Whether patients with more severe knee OA (KL score = 4) and higher levels of pain would benefit from this long-term intervention is unknown. The IDEA trial also benefited from its single-site design, as single-site studies tend to have larger treatment effects than multi-center trials.[52] The musculoskeletal model used to calculate knee compressive forces has several limitations. Several knee ligaments are not included; it assumes that the hip flexors and hip abductors do not co-contract during stance; and its lumped muscle model design cannot distinguish between smaller muscle anatomical units. Nonetheless, we have used this model extensively[53-56] and as we recently demonstrated[55] our muscle

and joint force predictions are in excellent agreement with those based on a variety of other models[57;58] and from measured forces from instrumented knee joint prostheses.[59;60]

OA and other obesity-related diseases place an enormous physical and financial burden on the US healthcare system.[61] The estimated 97 million overweight and obese Americans are at substantially higher risk for many life-threatening and disabling diseases, including OA.[20] Our data suggest that intensive weight loss may have both anti-inflammatory and biomechanical benefits; when combined with exercise, compliant patients can safely achieve a mean long-term weight loss of >10% with associated improvement in symptoms greater than with either intervention alone.

Among overweight and obese adults with knee OA, after 18 months, participants in the D+E and D groups had more weight loss and greater reductions in IL-6 levels than those in the E group; those in the D group had greater reductions in knee compressive force than those in the E group; and those in the D+E group had less knee pain and better function than those in the D and E groups and improved physical HRQL than those in the E group. While these differences are relatively modest, their clinical promise warrants further study.

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Online-Only Material: eFigure 1 and eTables 1-4, Methods: *Knee Joint Load*.

Competing Interests

The authors declare that they have no competing interests

Authors' contributions

SPM had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. He also conceived the study, participated in its design and coordination, carried out the gait analysis, and drafted the manuscript. SLM participated in study design, and coordinated patient compliance and adherence protocols. CL participated in study design, was responsible for the statistical analyses and data management. GDM participated in study design, and designed the nutrition intervention. BJN participated in study design and coordination and was responsible for IL-6 measurements. PD participated in study design, and helped coordinate the gait analysis and the measurement of knee compressive forces. ML carried out the participant evaluation of GXT results, and made decisions regarding inclusion/exclusion based on medical tests and medical history. DJH participated in study design and coordination. FE participated in study design and coordination. JDW participated in study design and coordination, and was the medical director of the trial. JJC participated in study design and coordination. DB participated in the statistical analyses. RFL participated in study design, addressed participant's issues related to exercise adherence due to joint symptoms, and coordinated x-ray readings, and assisted in the

analysis of IL-6. All authors read and made comments on previous drafts of the manuscript, and approved the final manuscript.

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Figure legends

Figure 1. Participant progress through the Intensive Diet and Exercise for Arthritis (IDEA) trial.

Figure 2. Mean (±95%CI) unadjusted Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain scores across the 18-month intervention period.

eFigure 1. Mean (95%CI) month-by-month weight loss of the D and D+E groups. If a participant was absent on weigh-in day the weight from the previous month was carried forward for that month.

Table 1. Mean (SD) demographic and clinical characteristics of the study participants at baseline.

Baseline Characteristics	Overall	Exercise	Diet	Diet + Exercise	P Value
	(N = 454)	(N = 150)	(N = 152)	(N = 152)	
Age (yrs)	66 (6)	66 (6)	66 (6)	65 (6)	0.86
Female No. (%)	325 (72)	108 (72)	108 (71)	109 (72)	0.98
Nonwhite No. (%)	85 (19)	30 (20)	25 (16)	30 (20)	0.68
Weight (kg)	93 (14.7)	92 (14.5)	93 (15.2)	93 (14.4)	0.82
Height (m)	1.66 (0.09)	1.66 (0.09)	1.66 (0.09)	1.66 (0.09)	0.91
BMI (kg/m^2)	33.6 (3.7)	33.5 (3.7)	33.7 (3.8)	33.6 (3.7)	0.90
Annual household income No. (%)					0.63
<$20 000	40 (9)	14 (9)	15 (10)	11 (7)	
$20 000-$34 999	68 (15)	27 (18)	21 (14)	20 (14)	
$35 000-$49 999	86 (19)	32 (22)	25 (17)	29 (20)	
>$50 000	253 (57)	75 (60)	90 (51)	88 (59)	
Education No. (%)					0.35
≤ High School	72 (16)	29 (19)	21 (14)	22 (14)	
>High School	380 (84)	120 (81)	130 (86)	130 (86)	
Comorbid illness, No. (%)					
Obesity (BMI ≥ 30 $kg \cdot m^{-2}$)	360 (79)	118 (79)	121 (80)	121 (80)	0.97
Arthritis in other joints	265 (61)	92 (63)	84 (57)	89 (62)	0.59
Hypertension	273 (61)	89 (60)	93 (63)	91 (61)	0.85
Cardiovascular heart disease	42 (10)	12 (8)	19 (13)	11 (8)	0.22
Diabetes	59 (13)	18 (12)	18 (12)	23 (15)	0.64
Kellgren-Lawrence grade	2.56 (0.59)	2.53 (0.56)	2.58 (0.60)	2.59 (0.60)	0.64
WOMAC function (range 0-68)	24.2 (10.9)	23.1 (10.3)	24.8 (10.4)	24.6 (11.7)	0.33
WOMAC pain (range 0-20)	6.5 (3.1)	6.1 (2.9)	6.6 (3.0)	6.7 (3.4)	0.24

Table 2. Mean (95%CI) body composition values for the three groups across the 18-month intervention period.

	Exercise				Diet				Diet + Exercise				P
	Months				Months				Months				
	0	6	18	Δ	0	6	18	Δ	0	6	18	Δ	
Weight (kg)	92.3	92.4	90.5	-1.8	93.4	85.5	84.5	-8.9	93.0	84.3	82.4	-10.6	<0.0001[a]
CI	89.9,94.6	89.7,95.2	87.7,93.2	-5.7,1.8	91.0,95.8	82.8,88.1	81.8,87.1	-12.4,-5.3	90.6,95.3	81.8,86.8	79.7,85.1	-14.1,-7.1	
N for weight	150	122	115		152	115	120		152	133	121		
Fat Mass (kg)	37.0		36.7	-0.4	36.3		31.5	-4.8	36.8		30.3	-6.5	<0.0001[a]
CI	35.7,38.4		34.9,38.4	-2.5,1.8	34.9,37.6		29.7,33.3	-7.0,-2.6	35.5,38.1		28.6,32.0	-8.6,-4.4	
% Fat Mass	40		41	1	40		38	-2	40		37	-3	
Lean Mass (kg)	56.1		53.5	-2.6	55.3		51.1	-4.2	55.6		50.8	-4.7	<0.0001[a]
CI	54.0,58.1		51.2,55.7	-5.7,0.5	53.2,57.6		48.8,53.4	-7.4,-1.1	53.6,57.6		48.7,53.0	-7.7,-1.8	
% Lean Mass	60		59	-1	60		62	2	60		63	3	
N for fat/lean	131		94		128		88		136		102		

[a]D+E and D < E

Table 3. IDEA outcomes from multiple imputation-based model that used 50 multiply imputed datasets per variable. Mixed effects model adjusts for baseline BMI, gender, and baseline values. Knee compressive force and IL-6 significance levels were set at 0.025; for secondary outcomes the significance level was 0.05.

	Exercise					Diet					Diet + Exercise					P
	Months				Month 18 adjusted	Months				Month 18 Adjusted	Months				Month 18 Adjusted	
	0	6	18	Δ (%)		0	6	18	Δ (%)		0	6	18	Δ (%)		
Comp Force (N)	2768	2877	2620	--148 (-5)	2687	2626	2466	2361	-265 (-10)	2487	2655	2593	2425	-230 (-9)	2543	0.019#
95% CI	2612,2925	2720,3034	2475,2765		2590,2784	2480,2773	2333,2598	2242,2481		2393,2581	2506,2804	2460,2725	2306,2544		2448,2637	
IL-6 ($pg \cdot mL^{-1}$)	3.0	2.9	3.0	0.1 (0)	3.1	3.2	2.7	2.7	-0.5 (16)	2.7	3.2	2.8	2.7	-0.5 (15)	2.7	0.0075#
95% CI	2.6, 3.3	2.6, 3.3	2.7, 3.3		2.9,3.4	2.8, 3.6	2.4,3.1	2.3,3.0		2.4,3.0	2.9, 3.6	2.5,3.2	2.4, 3.1		2.5,3.0	
Pain	6.1	4.5	4.4	-1.7 (-28)	4.7	6.6	4.9	4.8	-1.8 (-27)	4.8	6.7	4.6	3.7	-3.0 (-45)	3.6	0.002*
95% CI	5.6,6.6	4.0,5.1	3.9,4.9		4.2,5.1	6.1, 7.1	4.4,5.3	4.2, 5.3		4.3,5.2	6.1, 7.2	4.1,5.1	3.1,4.2		3.2,4.1	
Function	23.1	17.7	17.6	-5.5 (-24)	18.4	24.8	18.3	17.7	-7.1 (-29)	17.4	24.6	16.5	14.2	-10.3 (-42)	14.1	0.0004*
95% CI	21.4,24.8	15.9,19.5	15.8,19.4		16.9,19.9	23.2, 26.5	16.6,20.0	15.7,19.8		15.9,18.9	22.7, 26.5	14.7,18.3	12.4,16.1		12.6,15.6	
WalkSpeed ($m \cdot s^{-1}$)	1.23	1.32	1.30	0.07 (6)	1.29	1.18	1.25	1.27	0.09 (8)	1.29	1.20	1.32	1.33	0.12 (10)	1.33	0.008†
95% CI	1.20,1.26	1.29,1.35	1.27,1.33		1.27,1.31	1.15, 1.21	1.22,1.28	1.25,1.30		1.27,1.31	1.17, 1.23	1.28,1.35	1.29,1.36		1.31,1.35	
6 minute walk (m)	480	533	525	45 (9)	525	475	505	502	26 (6)	505	467	537	537	70 (15)	546	<0.0001‡
95% CI	466,495	518,547	511,540		515,535	462, 488	492,518	488,515		495,515	453-481	522,552	520,553		536,556	
SF-36 Physical	36.8	41.5	42.0	5 (14)	41.9	36.0	41.8	42.0	6 (17)	42.4	36.6	43.5	44.7	8 (23)	44.7	0.013"
95% CI	35.3,38.2	39.9,43.1	40.3,43.6		40.5,43.2	34.5, 37.4	40.2,43.4	40.3,43.7		41.1,43.7	35.1, 38.1	41.9,45.0	43.1,46.2		43.4,46.0	
SF-36 Mental	56.5	56.1	55.4	-1.0 (-2)	55.6	55.9	55.0	54.9	-1.0 (-2)	55.3	57.2	56.9	56.1	-1.1 (-2)	55.8	0.853
95% CI	55.1,57.8	54.8,57.5	54.0,56.8		54.4,56.7	54.5, 57.2	53.6,56.4	53.6,56.1		54.2,56.5	56.2, 58.3	55.7,58.2	54.9,57.2		54.7,57.0	

#D+E and D < E; *D+E<E and D; †D+E>E and D; ‡D+E>E and D, E>D. "D+E>E

Table 4. Pairwise between group differences (mean and 95% confidence interval) at 18-month follow-up for primary and secondary outcomes using multiple imputation adjusted for baseline BMI, gender, and baseline values. Knee compressive force and IL-6, significance levels were set at a 0.008; for secondary outcomes the significance level was 0.0167.

	Exercise vs. Diet	p	Exercise vs. Diet + Exercise	p	Diet vs. Diet + Exercise	p
Knee Comp Force N	200 (55,345)	0.007	144 (1,287)	0.05	-56 (-199, 88)	0.45
IL-6 $pg \cdot mL^{-1}$	0.43 (0.01, 0.85)	0.006*	0.39 (-0.03, 0.81)	0.007*	-0.04 (-0.47, 0.40)	0.98*
Pain	-0.11 (-0.81, 0.59)	0.76	1.02 (0.33, 1.71)	0.004	1.13 (0.44, 1.82)	0.001
Function	0.98 (-1.24, 3.20)	0.38	4.29 (2.07, 6.50)	0.0002	3.30 (1.09, 5.51)	0.003
Walk Speed ($m \cdot s^{-1}$)	-0.01 (-0.04, 0.02)	0.59	-0.04 (-0.07, -0.02)	0.003	-0.04 (-0.07, -0.01)	0.02
6 minute walk (m)	20.2 (5.0, 35.4)	0.009	-21.3 (-36.3, -6.4)	0.005	-41.5 (-56.4, -26.6)	<0.0001
SF-36 Physical	-0.55 (-2.53, 1.43)	0.59	-2.81 (-4.76, -0.86)	0.005	-2.26 (-4.30, -0.23)	0.03
SF-36 Mental	0.23 (-1.47, 1.93)	0.79	-0.26 (-1.95, 1.43)	0.76	-0.49 (-2.25, 1.26)	0.85

***p-value from the log-adjusted variable comparisons.**

eTable 1. Serious adverse events. All were unrelated to the study.

Serious Adverse Event	Completed Study (Y/N)	Diet	Exercise	Diet + Exercise
Heart Palpitations	Y		x	
ALS	N			x
Stroke	N			x
Lung Hypertension	Y		x	
Lung Infection	Y			x
Cancer	Y			x
Cancer	N	x		
Cancer	Y		x	
Cancer	N			x
Staph Infection	Y			x

eTable 2. Intention-to-treat completers-only analysis. Unadjusted mean (95%CI) mechanistic and clinical outcomes at baseline (0), and 6 and 18-month follow-up by group and 18-month outcomes adjusted for gender, BMI, and baseline values. The adjusted data were used to determine between-group P values and effect sizes. Knee compressive force and IL-6 significance levels were set at 0.025; for secondary outcomes the significance level was 0.05.

	Exercise					Diet					Diet + Exercise					P
	Months – unadjusted				Month 18 adjusted	Months - unadjusted				Month 18 Adjusted [ES]	Months - unadjusted				Month 18 Adjusted [ES]	
	0	6	18	Δ (%)		0	6	18	Δ (%)		0	6	18	Δ (%)		
Comp Force (N)	2816	2946	2662	--154 (-5)	2728	2676	2478	2377	-299 (-11)	2526 [-0.4]	2690	2599	2444	-246 (-9)	2585 [-0.3]	0.019#
95% CI	2657,2975	2800,3092	2513,2810		2622,2834	2509,2843	2326,2629	2224,2531		2417,2634	2528,2852	2454,2744	2296,2592		2479, 2690	
N	133	119	111		111	125	109	103		103	134	122	110		111	
IL-6 ($pg \cdot mL^{-1}$)	2.9	2.9	3.0	0.1 (3)	3.2	3.2	2.7	2.7	-0.5 (16)	2.7 [-0.3]	3.3	2.9	2.8	-0.4 (13)	2.7 [-0.3]	0.0005#
95% CI	2.5, 3.2	2.5, 3.3	2.6, 3.4		2.89,3.51	2.8, 3.6	2.3,3.0	2.3,3.0		2.34,2.97	2.9, 3.7	2.5,3.2	2.4, 3.1		2.39,3.01	
N	133	125	117		117	128	113	114		114	137	129	119		119	
Pain	6.0	4.4	4.3	-1.7 (-28)	4.3	6.4	4.8	4.8	-1.6 (-25)	4.8 [0.2]	6.7	4.6	3.3	-3.4 (-51)	3.3 [-0.4]	0.0001*
95% CI	5.5,6.4	3.8,5.0	3.8,4.9		3.8,4.9	5.9, 6.9	4.2,5.4	4.3, 5.4		4.3,5.3	6.2, 7.3	4.1,5.2	2.7,3.9		2.8,3.8	
N	127	119	127		127	124	115	124		124	138	130	129		129	
Function	22.5	17.2	17.4	-5.1 (-23)	17.2	24.3	18.3	17.8	-7.0 (-29)	17.3 [0.0]	24.5	16.4	13.0	-11.5 (-47)	13.0 [-0.5]	0.0001*
95% CI	20.8,24.3	15.2,19.2	15.4,19.4		15.6,18.8	22.4, 26.2	16.3,20.3	15.8,19.8		15.7,18.8	22.5, 26.6	14.5,18.3	11.1,15.0		11.5,14.6	
N	128	119	127		127	124	116	124		124	138	131	129		129	
WalkSpeed ($m \cdot s^{-1}$)	1.24	1.33	1.30	0.06 (5)	1.30	1.20	1.26	1.28	0.08 (7)	1.30 [0.0]	1.21	1.32	1.34	0.13 (11)	1.34 [0.3]	0.013†
95% CI	1.21,1.27	1.29,1.36	1.27,1.34		1.28,1.32	1.16, 1.23	1.23,1.29	1.25,1.32		1.28,1.32	1.18, 1.24	1.29,1.36	1.30,1.37		1.32,1.36	
N	128	121	108		108	124	112	111		111	138	132	117		117	
6 minute walk (m)	483	538	528	45 (9)	530	481	505	502	21 (4)	499 [-0.5]	466	538	541	75 (16)	548 [0.3]	<0.0001‡
95% CI	468,499	528,553	513,544		519,541	468, 495	489,520	487,518		489,510	451-481	523,553	526,556		537,558	
N	127	118	106		106	124	109	107		107	137	129	116		116	
SF-36 Physical	37.3	41.6	42.4	5 (13)	43.1	36.2	42.1	42.2	6 (17)	42.5 [-0.2]	36.3	43.4	45.1	9 (25)	44.8 [-0.0]	0.054
95% CI	35.7,38.9	39.8,43.3	40.6,44.2		41.6,44.5	34.6, 37.9	40.3,43.8	40.5,45.0		41.1,43.9	34.8, 37.9	41.8,45.1	43.4,46.8		43.5,46.2	
N	127	118	121		121	122	112	124		124	137	131	124		124	
SF-36 Mental	56.7	56.2	55.4	-1.3 (-2)	55.8	56.4	55.0	55.1	-1.0 (-2)	55.5 [-0.1]	57.5	57.2	56.5	-1.0 (-2)	56.0 [0.2]	0.863
95% CI	55.3,58.0	54.8,57.6	54.0,56.9		54.5,57.0	55.0, 57.9	53.6,56.5	53.7,56.6		54.3,56.7	56.4, 58.5	55.9,58.5	55.1,57.9		54.7,57.2	
N	127	118	121		121	122	112	124		124	137	131	124		124	

Δ = 18-month follow-up minus baseline for participants that completed the study (i.e., returned for 18-month testing)
ES = Effect size compared to Exercise-only group
#D+E and D < E; *D+E<E and D; †D+E>E and D; ‡D+E>E and D, E>D. All P values and ES based on 18-month adjusted means.
For more detail on pairwise comparisons see eTable 3.

eTable 3. Intention-to-treat completers-only analysis. Pairwise between group differences (mean and 95% CI) at 18-month follow-up for primary and secondary outcomes. Knee compressive force and IL-6 t-tests were set at a 0.008 significance level; for secondary outcomes the significance level was 0.0167.

	Exercise vs. Diet	p	Exercise vs. Diet + Exercise	p	Diet vs. Diet + Exercise	p
Knee Comp Force N	202 (56, 348)	0.007	142 (1, 285)	0.05	-60 (-205, 86)	0.42
IL-6 $pg \cdot mL^{-1}$	0.54 (0.11, 0.98)	0.0007*	0.50 (0.07, 0.93)	0.0007*	-0.05 (-0.48, 0.38)	0.97*
Pain	0.43 (-1.15, 0.29)	0.24	1.05 (0.33, 1.78)	0.004	1.48 (0.78, 2.18)	< 0.0001
Function	0.04 (-2.31, 2.24)	0.97	4.21 (1.93, 6.49)	0.0003	4.25 (2.04, 6.45)	0.0002
Walk Speed ($m \cdot s^{-1}$)	0.00 (-0.03, 0.03)	0.92	-0.04 (-0.07, -0.01)	0.01	-0.04 (-0.07, -0.01)	0.009
6 minute walk (m)	30.5 (15.2, 45.9)	0.0001	-17.8 (-33.1, -2.6)	0.02	-48.3 (-63.1, -33.6)	<0.0001
SF-36 Physical	0.55 (-1.48, 2.58)	0.60	-1.78 (-3.82, 0.25)	0.09	-2.33 (-4.29, -0.36)	0.02
SF-36 Mental	0.26 (-1.54, 2.06)	0.78	-0.22 (-2.04, 1.59)	0.81	-0.48 (-2.23, 1.27)	0.59

***p-value from the log-adjusted variable comparisons.**

eTable 4: Mean (SE) dose response to weight change with knee compressive force, IL-6, pain, and function independent of group assignment.

% Weight Change	Compressieve Force (N)	IL-6 ($pg \cdot ml^{-1}$)	Pain	Function
High -32.5% to -10.1%	2482 (44)	2.64 (0.12)	3.72 (0.28)	13.27 (0.88)
Medium -9.8% to -5.0%	2708 (47)	2.75 (0.14)	4.62 (0.29)	16.46 (0.87)
Low -4.9% to 9.9%	2842 (35)	3.07 (0.11)	4.33 (0.23)	17.17 (0.69)
P value	<0.001	0.02	0.02	0.01

Methods (On-line Supplemental Material)

Knee Joint Load. Bone-on-bone peak tibiofemoral (knee) compressive force was the primary measure of knee joint loading. A 25-reflective marker set, arranged in the Cleveland Clinic full-body configuration, and a 6-camera Motion Analysis (Santa Rosa, CA) system set to sample data at 60 Hz were used to collect 3-D kinematic data, which were tracked, edited, and smoothed, using EVaRT 4.4 software, and a Butterworth low-pass filter with a cut-off frequency of 6 Hz. The processed data were compiled using OrthoTrak 6.0 β4 clinical gait analysis software.

A 6-channel force platform (Advanced Mechanical Technologies, Inc., Newton, MA) was integrated with the motion capture system for simultaneous kinetic data collection at 480 Hz. Six successful trials were collected on each participant with 3 chosen for subsequent analysis. A successful trial was defined as one in which the participant's entire foot was placed on the surface area of the force platform while walking within ± 3.5% of freely chosen speed. The smoothed coordinate data, ground reaction, and gravitational and inertial forces informed an inverse dynamics model to calculate 3-D hip flexion and extension; knee flexion, extension, abduction, internal rotation, and external rotation; and ankle plantar- and dorsiflexion moments.

A musculoskeletal model developed by DeVita and Hortobagyi[56] was used to calculate knee joint compressive force and has two basic components. First, joint moments and joint-reaction forces are calculated from kinematic, physiological, and force-plate data. Then they are used to calculate individual muscle forces and compressive and shear forces in three steps: (1) determining the forces in the gastrocnemius, hamstrings, and quadriceps muscles and lateral support tissues in the knee; (2) applying them along with joint-reaction forces onto the tibia; and (3) determining knee-joint forces. The model, its limitations, and a comparison of its predictions with other models are discussed elsewhere.[22;55]