OBJECTIVE
To determine whether an intensive lifestyle intervention (ILI) designed to sustain weight loss and improve physical fitness in overweight or obese persons with type 2 diabetes was associated with bone loss after 4 years of follow-up.

RESEARCH DESIGN AND METHODS
This randomized controlled trial of intensive weight loss compared an ILI with a diabetes support and education (DSE) group among 1,309 overweight or obese subjects. Bone mineral density was assessed at baseline and after 1 year and 4 years of intervention.

RESULTS
ILI was effective in producing significant weight loss (5.3% vs. 1.8% in ILI and DSE, respectively; \( P < 0.01 \)) and increased fitness (6.4% vs. −0.8%) at year 4. In men, ILI participants had a greater rate of bone loss during the first year (−1.66% vs. −0.09% per year in ILI and DSE, respectively). Differences between groups were diminished by one-half after 4 years (−0.88% vs −0.05% per year in ILI and DSE, respectively) but remained significant (\( P < 0.01 \)). The difference in rate of hip bone loss between groups over 4 years was related to increased weight loss in ILI. Among women, the rate of bone loss did not differ between ILI and DSE after 4 years.

CONCLUSIONS
A 4-year weight loss intervention was significantly associated with a modest increase in bone loss at the hip in men but not in women.

Type 2 diabetes affects a significant proportion of the population in North America, with an incidence directly proportional to the development of obesity (1). Weight loss has been shown to be effective in improving cardiovascular disease risk factors and slowing progression to type 2 diabetes among high-risk obese adults (2). However, weight loss has also been associated with diminished bone mineral density (BMD) (3–5).

The impact of type 2 diabetes on bone has been reviewed (6,7), but only two publications could be identified that characterized bone loss with weight loss and exercise in adults with type 2 diabetes (8,9). One study showed a reduction in bone loss with resistance training in addition to caloric restriction compared with caloric restriction alone (8). The Look AHEAD (Action in Health for Diabetes) Trial presents a unique opportunity to examine the longitudinal impact of lifestyle modification on bone mass in a large cohort of overweight and obese subjects with type 2 diabetes.
Data from the 1-year follow-up of the Look AHEAD Trial documented significant loss of bone at the total hip and femoral neck, which was proportional to weight loss (9). The intensive lifestyle modification was designed to promote substantial weight loss during the first year and to maintain weight in subsequent years. The impact of this intensive lifestyle modification, which sought to maintain the initial weight losses over time, on long-term changes in BMD remains unknown but may be of significance for the pathogenesis of fractures. The studies of Armamento-Villareal and colleagues (3-5) documented a protective effect of physical activity on hip bone loss resulting from loss of weight in an elderly non-diabetic obese cohort. This seminal work still leaves open whether the same effect may be characteristic of weight loss in overweight or obese people with type 2 diabetes.

This study examined whether individuals who participated in the intensive lifestyle intervention (ILI) for 4 years in the Look AHEAD Trial have a greater loss of BMD at the hip than participants in the standard diabetes support and education (DSE) (control) treatment arm. The BMD of the hip was chosen as the primary outcome variable because it is less susceptible to artifacts from degenerative changes that occur frequently in individuals >60 years of age (10). We also examined whether this change in hip BMD reflects that of the lumbar spine, femoral neck, and total body BMD and whether changes in BMD at the hip and lumbar spine were proportional to change in weight and fitness.

**RESEARCH DESIGN AND METHODS**

**Subject Selection, DEXA, Physical Activity, Fitness, and Dietary Calcium Intake**

Subjects were recruited into the Look AHEAD Trial as previously described (9,11). Participation was limited to people with type 2 diabetes from 16 clinical centers in the U.S., those 45-76 years old, and those with a BMI ≥25 kg/m² (or ≥27 kg/m² if taking insulin). Subjects were randomized to either ILI, including a weight loss diet and increased physical activity, or DSE. The goal of ILI was a sustained 7% loss of weight during the first year, with weight maintenance thereafter. A substudy was conducted at five clinical sites to measure longitudinal changes in bone density and body composition by DEXA scanning as previously described (9). All randomized subjects at these five sites (1,479 of 5,145 total) were approached to participate in the DEXA substudy with the exception of those who weighed over the weight limit for the scanner (300 lb). A total of 1,373 subjects consented to and completed baseline assessments of body composition, including total body BMD (including the head), BMD of the lumbar spine (L1-L4), total hip, and the femoral neck of the hip, using a Hologic fan beam densitometer. Of these, 1,274 subjects had a scan 1 year after randomization (Y1) and 1,158 subjects after 4 years (Y4); 1,123 of the 1,158 Y4 subjects undergoing DEXA scans also had a Y1 scan. A total of 1,309 subjects within the current database had a DEXA scan at baseline and at least one follow-up assessment. The common reasons for missing data were loss to follow-up and weight >300 lbs. A complete accounting of the subjects is detailed in the Supplementary Data.

At baseline, Y1 and Y4 clinic visits, weight, height, prescription medication use, demographic characteristics, smoking history, alcohol use, calcium intake in the diet (but not supplement use), and A1C were obtained as described (9). Fitness, expressed in METs, was quantified from a submaximal graded exercise test (12). The MET level presented is that at 80% of the subject’s maximal heart rate. Graded exercise test measures were done at the same visit as the DEXA measures or within 1 week of each other if not on the same day. Physical activity was quantified in a subgroup of Look AHEAD participants in kilocalories per week at baseline, 1-year, and 4-year follow-up from a self-reported questionnaire developed by Paffenbarger et al. (13) for assessment of leisure time physical activity. Of 1,309 participants in the data set for this article, 564 have leisure time physical activity data (43%). Calcium intake from food was quantified from a food frequency questionnaire in a subgroup of 50% of the subjects seen at each clinic site and accounted for 54% of the current cohort (14). Data related to bone fractures, which was considered a final outcome measure for the larger trial, were not accessible for this article.

**Statistics**

Mean and SD were computed for continuous baseline measures, and percentages were computed for categorical baseline measures. Baseline data were analyzed to assess the effectiveness of the randomization and differences by sex. All analyses were conducted by sex.

BMD outcome measures were expressed as absolute differences in areal density (g/cm²), an accepted measure of bone mass per a two-dimensional space, which is the actual quantity obtained from a DEXA scan and as percent change from baseline [(Y4 BMD – baseline BMD) / baseline BMD] × 100. Additionally, mean and SD were calculated by treatment arm on the Y4 change in the BMD of lumbar spine and total hip and the Y4 change in continuous measures of interest: weight, fitness, physical activity, and A1C. These means were tested by treatment arm for differences using t tests. To examine the relationship between Y4 and Y1 changes in lumbar spine and total hip BMD, the Y4 changes were examined as a function of the Y1 changes. The within-arm mean baseline-to-Y4 change was tested for equality to zero using t tests for the outcome measures. ANOVA was used to test for differences in change between the ILI and DSE arms. The categorical measures (smoking status, alcohol use in the past year, menopausal status, proteinuria) and arm of the study completed the list of independent variables of interest.

Generalized linear modeling (GLM) procedures, adjusting for site, were used to examine the relationship between Y4 BMD change (response variables) and predictor variables identified as correlated with the outcome measures. As noted, fewer paired Y1 scans were available than for the Y4 cohort, and to take this into account, an available data method as opposed to a complete case method was used. No imputed data (e.g., last observation carried forward) was used.

We examined correlations to identify potential confounding or colinear variables. The variables change in weight and change in fitness were identified as predictor variables based on a visual examination of the bivariable scatterplots, biological plausibility, and significant change over the 4-year interval. Change in A1C was added to the list because of
its clinical significance as a marker of diabetes disease control. All models were adjusted for age, diagnosed diabetes duration, baseline BMI, site, race, baseline insulin, thiazolidinedione (TZD) use, menopausal status (for women), proteinuria, smoking status, and baseline level of the response and predictor measures. Repeated-measures (mixed) modeling was used to assess the relationship between time and change in BMD and was more fully adjusted for Y1 changes in weight and BMD. For the GLM and the repeated-measures modeling, the by-arm interaction was evaluated for all significant main effects among the independent measures. Rate of change (β) estimates are reported for continuous measures, and adjusted means are reported for categorical measures. Significance was determined using a fixed α = 0.05. All analyses were performed using SAS 9.2 (SAS Institute, Cary, NC) software. The significance of the total hip BMD results were also assessed using a calculation of Cohen’s d for estimating the effect size (15) for the ILI arm compared with the DSE arm.

Sensitivity analyses were performed to examine the impact of age and glucocorticoid and TZD use because they have been shown to be deleterious to bone; 5.4% was using oral steroids known to cause bone loss; and 1.5% was using bisphosphonates, a medication known to increase BMD measures. The use of steroids was similar in the ILI and DSE groups. There also was no significant difference (P = 0.355) in TZD use across arms of the DEXA substudy or by sex. Adjusting for age did not significantly change the results. For example, the rates of bone loss at the hip at Y4 in women for the ILI and DSE groups were −1.38 and −1.31% per year with adjustment for age vs. −1.33 and −1.27% per year after removing the age adjustment. Of the 1,309 participants included in these analyses (i.e., those who had baseline and at least one follow-up DEXA scan), 19 reported having bariatric surgery by the time of the Y4 visit (6 in ILI, 13 in DSE). Only 2 of these 19 participants (1 in each arm) had bariatric surgery by the time of their Y1 visit. There are no significant differences at Y1 in weight loss and bone loss of those with and without bariatric surgery by Y4. By Y4, those in both the ILI and DSE arms with the bariatric surgery had significantly more weight loss and bone loss than those without the surgery. The GLM models representing the data in Fig. 1 were rerun with the 19 bariatric surgery participants removed, showing only slight changes in the estimate values and no change in significance. There was no significant difference in hip and

**RESULTS**

**Subject Characteristics**

The baseline characteristics of subjects in the two study groups are summarized in Table 1, as are the variables describing the DEXA subsample and the full Look AHEAD cohort (Supplementary Data). Randomization was generally successful in distributing subjects equally for demographic variables in the overall trial; however, weight differed significantly across treatment groups (P = 0.049). There was a very low prevalence of osteoporosis (defined as a T-score < -2.5) at any site of measurement at baseline and no difference in prevalence between groups.

The demographic variables of the subsample of the Look AHEAD cohort participating in the bone substudy differed from the total Look AHEAD cohort (Supplementary Data), reflecting the Latino population at these participating centers. The DEXA cohort was shorter, weighed less, had a lower BMI, was more fit, was more likely never to have smoked, was treated less frequently with TZDs and steroids, and comprised fewer blacks and non-Latino whites.

**Changes in BMD Comparing ILI and DSE**

Men randomized to ILI had a twofold greater rate of bone loss at the hip (−0.78% per year) than those randomized to DSE (−0.36% per year, P < 0.01) at Y4, with an effect size of 0.42. However, no intervention effect on lumbar spine BMD (0.34% vs. 0.33% per year, P = 0.99) was found. The changes in male total hip BMD were also reflected in similar changes at the femoral neck. Women in both treatment arms had decreases in all measures of BMD (0.26–1.31% per year), and in contrast to men, there were no significant differences (P ≥ 0.24) in mean BMD loss between treatment groups by Y4 at any site.

**Effects of Treatment Arm on Alcohol Intake, Smoking Status, Dietary Calcium Intake, Weight, and Fitness at Y4**

Primary explanatory variables believed to affect change in BMD from baseline are summarized in Table 2, stratified by sex and intervention arm. There was a statistically significant effect of ILI to reduce body weight and BMI and increase fitness in both groups, but physical activity was only increased in men. No statistically significant effect of treatment arm on alcohol intake in the past year, smoking status, or dietary calcium intake in either men or women was found.

**Effect of Sex, Weight Loss, and Glucose Control on Bone Loss to Y4 Adjusted for Weight**

Among men, the magnitude of weight loss was significantly correlated with bone loss at the hip (β = 0.03, P < 0.001) but with some gain in spine BMD (β = −0.02, P = 0.005) (Table 3). In women, the magnitude of weight loss was also significantly correlated with bone loss at the hip (β = 0.05, P < 0.001) but not at the spine (β = −0.008, P = 0.251). Hip bone loss did not correlate with change in fitness in either sex. Improved glycemic control, as reflected by lower A1C levels, correlated with loss of bone in the lumbar spine in men and hip bone loss in women. A statistically significant −0.4% (4 mmol/mol, P < 0.01) decrease in HbA1c in the ILI arm compared with the DSE arm was observed in men only in this DEXA cohort, which can be estimated to account for 0.04% per year spine BMD loss.

For change in total hip BMD in men, there was no longer a significant difference by Y4 between the ILI and DSE arms (rate of BMD loss −0.53%, P = 0.93) after adjustment for postrandomization changes in weight. In women, after adjusting for these changes, ILI was associated with less (−1.01% per year) Y4 hip bone loss compared with DSE (−1.27% per year, P = 0.005).

In a sensitivity analysis that excluded subjects using any steroid, TZD, or bisphosphonate at baseline, the results were similar. Only 12.8% of the sample was using inhaled or topical steroids not generally believed to be detrimental to bone; 5.4% was using oral steroids known to cause bone loss; and 1.5% was using bisphosphonates, a medication known to increase BMD measures. The use of steroids was similar in the ILI and DSE groups. There also was no significant difference (P = 0.355) in TZD use across arms of the DEXA substudy or by sex. Adjusting for age did not significantly change the results. For example, the rates of bone loss at the hip at Y4 in women for the ILI and DSE groups were −1.38 and −1.31% per year with adjustment for age vs. −1.33 and −1.27% per year after removing the age adjustment. Of the 1,309 participants included in these analyses (i.e., those who had baseline and at least one follow-up DEXA scan), 19 reported having bariatric surgery by the time of the Y4 visit (6 in ILI, 13 in DSE). Only 2 of these 19 participants (1 in each arm) had bariatric surgery by the time of their Y1 visit. There are no significant differences at Y1 in weight loss and bone loss of those with and without bariatric surgery by Y4. By Y4, those in both the ILI and DSE arms with the bariatric surgery had significantly more weight loss and bone loss than those without the surgery. The GLM models representing the data in Fig. 1 were rerun with the 19 bariatric surgery participants removed, showing only slight changes in the estimate values and no change in significance. There was no significant difference in hip and
spine BMD for insulin users versus non-users stratified by randomization arm and visit.

Effect of Interventions on the Rate of Interval Bone Loss Between Years 0 and 1 and 1 and 4
The results of a fully adjusted repeated-measures GLM are summarized in Fig. 1. The purpose of this model was to determine whether the effect of the intervention on the annual rate of bone loss varied over time. A visual inspection of Fig. 1 shows marked differences in the pattern of bone loss and weight with time in men and women. There is a striking parallel between the changes in weight and hip BMD in men and a significant (P < 0.001) correlation between percent change in lean mass and percent change in hip BMD at both Y1 (r = 0.294) and Y4 (r = 0.339). There was also a significant (P < 0.001) correlation between percent change in total body fat and percent change in hip BMD at both Y1 (r = 0.294) and Y4 (r = 0.339). A significant (P < 0.0001) time × arm interaction for hip BMD was found in men as well as in women. As a percentage of the initial BMD, these estimated hip losses for men and women, respectively, were −1.38% and −0.88% per year for ILI over the 1- to 4-year follow-up intervals. This model showed a greater rate of bone loss at Y1 compared with Y1–Y4 at the hip for both men and women. There was no significant effect on the lumbar spine (P value for time × arm interaction = 0.591 and 0.935 in men and women, respectively).

CONCLUSIONS
After 1-year follow-up, we found the intensive weight loss intervention of Look AHEAD to be associated with more rapid bone loss at the hip but not at the spine in both men and women (9). In men, a

### Table 1—Baseline data for subjects from the Look AHEAD trial used for longitudinal assessment of BMD

| Variable                        | DSE Men | DSE Women | ILI Men | ILI Women | P value^ |
|---------------------------------|---------|-----------|---------|-----------|----------|
| Number                          | 252     | 403       | 239     | 415       | 0.390    |
| Age (years)                     | 60.0 (6.4) | 57.8 (6.4) | 60.4 (6.4) | 57.0 (6.5) | 0.390    |
| Ethnicity (number, %)           |         |           |         |           |          |
| Black                           | 17 (7)  | 56 (14)   | 9 (4)   | 55 (13)   | 0.585    |
| White                           | 182 (72) | 196 (49)  | 169 (71) | 212 (51)  |          |
| Other                           | 53 (21) | 151 (37)  | 61 (26) | 148 (36)  |          |
| Height (cm)                     | 175.4 (6.7) | 160.4 (6.7) | 174.3 (6.9) | 160.2 (6.9) | 0.157    |
| Weight (kg)                     | 104.9 (14.4) | 93.5 (16.0) | 103.0 (15.3) | 91.9 (16.7) | 0.049    |
| L/S spine BMD (g/cm²)           | 1.15 (0.17) | 1.08 (0.16) | 1.12 (0.14) | 1.07 (0.17) | 0.017    |
| Mean T-score L/S spine          | 0.49 (1.57) | 0.15 (1.40) | 0.19 (1.31) | 0.06 (1.47) | 0.027^* |
| T-score <−2.5 for L/S spine     | 2 (0.8)  | 10 (2.5)  | 2 (0.8)  | 13 (3.2)  | 0.567    |
| Total hip BMD (g/cm²)           | 1.10 (0.14) | 1.03 (0.14) | 1.08 (0.12) | 1.03 (0.14) | 0.390    |
| Mean T-score total hip          | 0.30 (0.96) | 0.51 (1.10) | 0.18 (0.85) | 0.53 (1.09) | 0.562    |
| T-score <−2.5 for total hip     | 1 (0.4)  | 0 (0)     | 0 (0)    | 0 (0)     | N/A      |
| BMI (kg/m²)                     | 34.1 (4.3) | 36.3 (5.5) | 33.9 (4.6) | 35.7 (5.7) | 0.142    |
| Diabetes duration (years)       | 7.2 (6.2) | 6.5 (6.1) | 7.3 (6.8) | 5.8 (5.5) | 0.244    |
| Calcium intake (mg/d)#          | 850.2 (589.8) | 844.3 (530.5) | 822.3 (508.7) | 838.3 (437.1) | 0.732^* |
| Insulin use                     | 34 (13)  | 66 (16)   | 46 (19)  | 61 (15)   | 0.601^*  |
| T2D use                         | 66 (26)  | 68 (17)   | 56 (23)  | 63 (15)   | 0.355    |
| Steroid use                     | 7 (2.8)  | 86 (21.4) | 9 (3.8)  | 79 (19.1) | 0.564    |
| Bisphosphonate use              | 0 (0)    | 7 (1.7)   | 1 (0.4)  | 10 (2.4)  | 0.349    |
| Fitness (METs)                  | 6.0 (1.7) | 5.0 (1.4) | 5.9 (1.6) | 5.0 (1.3) | 0.710    |
| Leisure time physical activity (kcal/week) | 1,067.8 (1,608.5) | 594.0 (1,549.4) | 819.9 (1,108.0) | 520.8 (824.2) | 0.196    |
| Smoking status                  |         |           |         |           |          |
| Never                           | 98 (39) | 258 (64)  | 94 (39) | 267 (64)  | 0.898    |
| Past                            | 143 (57) | 127 (32)  | 129 (54) | 132 (32)  |          |
| Present                         | 11 (4)  | 17 (4)    | 16 (7)  | 16 (4)    |          |
| Alcohol in past year            | 165 (65) | 187 (47)  | 172 (72) | 200 (48)  | 0.160    |
| Menopausal status               |         |           |         |           |          |
| Postmenopausal                  | —       | 311 (77)  | —       | 297 (72)  | 0.054    |
| Premenopausal                   | —       | 43 (11)   | —       | 50 (12)   |          |
| Unknown                         | —       | 49 (12)   | —       | 68 (16)   |          |
| Proteinuria (mg albumin/mg creatinine ≥0.3 on spot urine) | 5 (2) | 9 (2) | 4 (2) | 14 (3) | 0.499^* |
| A1C (%)                         | 7.3 (1.2) | 7.4 (1.2) | 7.2 (1.2) | 7.3 (1.2) | 0.101^*  |
| A1C (mmol/mol)                  | 55 (13) | 56 (13)   | 55 (13) | 55 (13)   |          |

Data are mean (SD) or n (%) unless otherwise indicated. L/S, lumbar spine. ^P value for randomization arm adjusted for sex and clinic. *Sex effect not significant at the 0.05 α level. #Diet data were only collected on a subset of the Look AHEAD cohort. Numbers for calcium intake were 708 for total cohort, 258 for men, and 450 for women.
pattern of increased hip bone loss with ILI continued through Y4. An accelerated rate of hip bone loss in women at Y1 decreased with ILI by 4 years of follow-up but persisted in the DSE group such that the rate of hip bone loss was equivalent between groups by Y4. ILI was effective in producing significant weight loss and increased fitness throughout 4 years of follow-up but did not result in increased physical activity among women in the DEXA subset.

Hip bone loss in men was only modestly increased with ILI, a difference of ~0.4% per year or 1.6% over 4 years in BMD. The hip bone loss with ILI in men may reflect the greater weight loss in this group and correlated with loss of both lean mass and fat mass. Men in the ILI arm experienced an average weight loss of 9.8% in the first year, whereas DSE participants had stable weight. In the subsequent 3 years, there was a small regain of weight in the ILI arm (mean weight increase 4.1 kg in men, 1.5% per year weight regain). Of note, despite this weight regain, more rapid bone loss in the ILI group persisted after Y1, although the rate was reduced compared with the first year of the trial. Average weight remained lower in the ILI arm than in the DSE arm, which may account for the lower, yet persistent rate of hip bone loss. Neither increased fitness nor increased physical activity appeared to lessen the accelerated rate of hip bone loss observed in the ILI group in men. Explanations for the increased spine BMD observed in the ILI group continue to maintain lower weight than the DSE group, there was no longer a difference in the rate of hip bone loss across intervention groups after 4 years of follow-up, suggesting that more rapid bone loss in the ILI group occurred during the rapid weight loss phase. When this phase was over and weight regain began (+3.6 kg from Y1 to Y4), the rate of bone loss from Y1 to Y4 decreased in the ILI group but continued unabated in the DSE group, which continued to lose weight (~1.3 kg). By the end of 4 years, the amount of bone loss in the ILI and DSE groups thus converged.

The rate and magnitude of bone loss at the hip attributable to ILI, adjusting for all covariates, is small. The effect size is modest (13). The hip and lumbar spine BMD values with ILI observed at 4 years of follow-up in the current study were comparable to values previously reported in type 2 diabetic and age- and sex-matched control subjects who were not subject to sustained weight loss (27). Sensitivity analyses suggest that several potentially confounding factors did not affect the results, including the use of steroids, TZDs, or bisphosphonates; age; or the disproportionate

| Table 2—Summary results for changes in BMD and explanatory (predictor) variables that may affect change in BMD, stratified by study arm and sex |
| Variable | ILI (n = 208) | DSE (n = 218) | P value | ILI (n = 368) | DSE (n = 364) | P value |
| BMD measure | | | | | | |
| L/S spine BMD change (g/cm²) | 0.01 ± 0.05 | 0.02 ± 0.06 | 0.72 | −0.03 ± 0.05 | −0.03 ± 0.06 | 0.38 |
| % change in L/S spine BMD/year | 0.3 ± 1.1 | 0.3 ± 1.2 | 0.99 | −0.7 ± 1.2 | −0.6 ± 1.4 | 0.24 |
| Total hip BMD change (g/cm²) | −0.03 ± 0.05 | −0.02 ± 0.04 | <0.01 | −0.04 ± 0.05 | −0.04 ± 0.05 | 0.44 |
| % change in hip BMD/year | −0.8 ± 1.0 | −0.4 ± 0.9 | <0.01 | −1.1 ± 1.3 | −1.0 ± 1.3 | 0.46 |
| Explanatory variable | | | | | | |
| Weight change (kg) | −5.9 ± 7.8 | −1.7 ± 7.0 | <0.01 | −4.7 ± 7.4 | −2.1 ± 8.1 | <0.01 |
| % weight change | −5.7 ± 7.1 | −1.6 ± 6.6 | <0.01 | −5.0 ± 7.9 | −2.0 ± 7.9 | <0.01 |
| BMI change (kg/m²) | −1.9 ± 2.5 | −0.6 ± 2.3 | <0.01 | −1.8 ± 2.9 | −0.7 ± 3.1 | <0.01 |
| % BMI change | −5.5 ± 7.0 | −1.6 ± 6.6 | <0.01 | −4.9 ± 7.9 | −1.8 ± 8.0 | <0.01 |
| Change in fitness (METs) | 0.3 ± 1.5 | 0.1 ± 1.5 | <0.01 | 0.2 ± 1.3 | 0.2 ± 1.3 | <0.01 |
| % change in fitness | 7.3 ± 26.1 | −0.2 ± 25.0 | <0.01 | 5.8 ± 26.5 | −1.4 ± 24.8 | <0.01 |
| Change in dietary calcium (mg/day) | −51.1 ± 608 | −47.4 ± 656 | 0.97 | −81.8 ± 431 | −164.7 ± 534 | 0.10 |
| % change in dietary calcium | 18.0 ± 82.4 | 167.9 ± 92.8 | 0.91 | 7.3 ± 60.5 | −3.7 ± 64.4 | 0.09 |
| Change in leisure time physical activity (kcal/week) | 466.2 ± 1,612 | −62.7 ± 1,659 | 0.03 | 204.5 ± 1,105 | 8.8 ± 1,653 | 0.21 |
| % change in leisure time physical activity | 361.6 ± 1,053 | 192 ± 739 | 0.26 | 286 ± 921 | 266 ± 978 | 0.87 |
| Change in A1C (%) | −0.4 ± 1.0 | 0.05 ± 1.2 | <0.01 | −0.1 ± 1.5 | 0.0 ± 1.6 | 0.51 |
| Change in A1C (mmol/mol) | −4 ± 11 | 0.5 ± 13 | <0.01 | −1 ± 17 | 0 ± 18 | 0.01 |
| Change in fat mass (g) | −2,601 ± 5,467 | 166 ± 4,842 | <0.01 | −1,900 ± 5,588 | −416 ± 5,959 | <0.01 |
| Alcohol use in past year | 153 (73.6) | 148 (67.9) | 0.20 | 177 (48.1) | 174 (47.9) | 0.96 |
| Menopause | | | | | | |
| Post | N/A | N/A | N/A | 260 (70.7) | 282 (77.5) | 0.08 |
| Pre | | | | 45 (12.2) | 39 (10.7) | |
| Unknown | | | | 63 (17.1) | 43 (11.8) | |
| Smoking status | | | | | | |
| Never | 81 (38.9) | 87 (39.9) | 0.33 | 231 (62.8) | 224 (64.5) | 0.73 |
| Past | 114 (54.8) | 124 (56.9) | 0.8 | 121 (32.9) | 117 (32.2) | |
| Present | 13 (6.3) | 7 (3.2) | | 16 (4.4) | 12 (3.3) | |

Data are mean (SD) or n (%). All differences are Y4 – baseline. Continuous and categorical measures were tested with t test and χ² test, respectively. N/A, not applicable.
number of individuals receiving bariatric surgery for weight loss in the different arms of the study.

The impact of voluntary weight loss on BMD in other studies of nondiabetic subjects has been variable and reported mostly in obese women (28–30). In two of these studies, bone loss was found with weight loss (28,29), but the other study focused on premenopausal women (30). In one study of overweight men, bone loss was found with weight loss and was comparable between diet-induced and exercise-induced weight loss (31). Other studies of nondiabetic subjects have shown a variable impact of exercise, a component of the current lifestyle modification intervention, on BMD. Exercise increased BMD in premenopausal compared with postmenopausal women in one study (32), but other studies have described both increased (33–38) and decreased (28) BMD in postmenopausal women. Exercise appears to increase BMD in men (38,39), but the effect is small and not seen in all studies (40).

The data from the current study suggest that a comprehensive lifestyle modification program does not completely compensate for the bone loss associated with weight loss. The results differ from those observed in nondiabetic elderly obese subjects where weight loss induced by much more intensive physical activity increased hip BMD (32–36). This may reflect different participant selection, a much more intensive physical activity intervention in the latter study, limitations of using a physical activity questionnaire for assessment of physical activity in the current study, or some aspect of type 2 diabetes rendering such individuals refractory to increasing BMD from lifestyle intervention.

The current findings suggest that the improved glycemic control associated with weight loss was also associated with greater bone loss. Our observations agree with epidemiological evidence (27) that individuals with worse glycemic control (higher A1C levels) have greater BMD either directly or indirectly through its association with increased BMI and elevated insulin levels, which may protect bone. In contrast, after 1 year of follow-up in Look AHEAD, improved glycemic control, reflected in a lower A1C, was associated with
reduced total bone loss at the hip in men but not in women (9). Strengths of the current study include it being the largest clinical trial to date of lifestyle modification with long-term follow-up and a randomized prospective design that successfully produced weight loss and focused specifically on individuals with type 2 diabetes. This study also is the first to show a positive time × intervention arm effect on hip BMD of ILI in men and women.

There are a number of potential limitations to the current study, including lack of data on calcium/vitamin D supplement use, the prevalence of bisphosphonate use in the postmenopausal women, and the possible underlying secondary hyperparathyroidism from deteriorating kidney function. However, there is no a priori reason that any of these factors should have been disproportionally represented in either arm of the study. No direct measures of vitamin D were included in the current study. The change in physical activity by the questionnaire was modest and limited to a subset of the DEXA group, with limited power due to sample size. The questionnaire captured leisure time physical activity, but this questionnaire has never been validated for assessing the risk of bone loss or fracture, does not distinguish between weight bearing and non-weight-bearing aerobic activity, and remains a major weakness of the study.

In conclusion, we have found that in diabetic patients who lose a substantial amount of weight over 1 year through ILI and then maintain their weight for the subsequent 3 years that there is no overall effect on hip bone loss in women compared with DSE. For men, hip bone loss is more rapid through ILI compared with DSE, but the amount of additional bone loss is modest. These results do not suggest a clinically important effect of weight loss on the skeleton; however, fracture results are needed to be confident of this conclusion.

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