Published in final edited form as:
J Bone Miner Res. 2012 March ; 27(3): 619–627. doi:10.1002/jbmr.1483.

Effect of One Year of an Intentional Weight Loss Intervention on Bone Mineral Density in Type 2 Diabetes: Results from the Look AHEAD Randomized Trial

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Abstract

Intentional weight loss is an important component of treatment for overweight patients with type 2 diabetes, but the effects on bone density are not known. We used data from the Look AHEAD trial to determine the impact of an intensive lifestyle weight loss intervention (ILI) compared to diabetes support and education (DSE) on changes in bone mineral density (BMD) over 12 months. Overweight and obese adults with type 2 diabetes were randomly assigned to ILI or DSE. In a sub-study of BMD conducted at 5 of 16 clinical centers, hip, spine and whole body dual x-ray absorptiometry scans were obtained at baseline and one year later on 642 of 739 ILI and 632 of 740 DSE participants. At baseline, mean age was 58.4 years, and average body mass index was 35.2 kg/m^2. Total hip BMD T-score was <−2.5 in 1% and <−1.0 in 8%. At one year, weight loss was greater in ILI than DSE (−8.6% versus −0.7%), and glycemic control and fitness were also

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Clinical trial registration number NCT00017953, ClinicalTrials.gov.

A complete list of the Look AHEAD Research Group may be found in the online appendix.

The following organizations have committed to make major contributions to Look AHEAD: FedEx Corporation; Health Management Resources; LifeScan, Inc., a Johnson & Johnson Company; Optifast ® of Nestle HealthCare Nutrition, Inc.; Hoffmann-La Roche Inc.; Abbott Nutrition; and Slim-Fast Brand of Unilever North America.

All other Look AHEAD staffs are listed alphabetically by site.

Author Contributions

A.S. wrote manuscript, A.H., K.J., A.P., S.K. and G.B. researched data, contributed to discussion, and reviewed/edited manuscript, M.N., C.W. and J.S. contributed to discussion and reviewed/edited manuscript, M.W. researched data and contributed to discussion.

improved. Bone loss over one year was greater in ILI at the total hip (−1.4% versus −0.4%; p<0.001) and femoral neck (−1.5% versus −0.8%; p=0.009), but change in BMD for the lumbar spine and whole body did not differ between groups. In ILI, bone loss at the total hip was independently associated with weight loss in men and women and with poorer glycemic control in men, but was not associated with changes in fitness. One year of an intensive lifestyle intervention in adults with type 2 diabetes, resulting in weight loss, was associated with a modest increase in hip bone loss despite improved fitness and glycemic control.

Keywords

bone mineral density; weight loss; type 2 diabetes; obesity; glycemic control; physical fitness

INTRODUCTION

Intentional weight loss in older adults without diabetes is associated with bone loss (1). However, there are no clinical trials assessing the effects of weight loss on bone loss in type 2 diabetes, and little has been published from observational data. Weight loss is a primary treatment strategy for type 2 diabetes, but this is also a population at higher risk of fracture (2). Although weight loss is associated with bone loss in other populations, weight loss in those with type 2 diabetes results in improved glycemic control, a change that may be beneficial for bone (3). Exercise may be effective as a means to prevent bone loss during weight loss, but only one study has examined this relationship in those with type 2 diabetes (4).

Look AHEAD is an ongoing trial assessing the long-term effects of intentional weight loss on cardiovascular disease in overweight and obese adults with type 2 diabetes. We examined the effect of the intensive lifestyle intervention in Look AHEAD, resulting in weight loss, on bone mineral density (BMD) during the first year of the trial. We also assessed the independent contributions of changes in weight, physical fitness and glycemic control to changes in BMD.

MATERIALS AND METHODS

Look AHEAD is a multi-center, randomized, clinical trial of the effects of an Intensive Lifestyle Intervention (ILI), aimed at loss of ≥7% of body weight, compared to a control condition of Diabetes Support and Education (DSE), in overweight and obese adults with type 2 diabetes (5). The ILI is designed to achieve weight loss in the first year and then maintain weight through decreased caloric intake and increased physical activity. The primary endpoint is the occurrence of major cardiovascular events.

A total of 5,145 participants were randomized into Look AHEAD at 16 U.S. clinical centers. As described previously (6,7), participation was open to persons with type 2 diabetes, 45 to 76 years old, with body mass index (BMI) ≥25 kg/m^2 (or ≥27 kg/m^2 if taking insulin). Applicants completed a maximal graded exercise test (GXT) (5,6), to ensure that they could safely adhere to the physical activity program in the ILI (8). At baseline and year 1 (Y1) clinic visits, weight and height were measured with a digital scale and a standard wall-mounted stadiometer. Participants brought all prescription medicines to the clinic for a medication inventory. Questionnaires were used to collect demographic characteristics, smoking history, and alcohol use. Calcium intake in the diet, but not supplement use, was assessed in a subset of participants using a 130-item food questionnaire. A submaximal GXT was administered at Y1. Change in fitness during the first year was the difference in estimated METS for the point during each test when >80% of age-predicted maximal heart

rate was attained or, for those using a beta-blocker, when the participant achieved 16 on the rating of perceived exercise scale (9). HbA1c was measured at the Northwest Lipid Research Laboratories, University of Washington, using a dedicated ion-exchange high-performance liquid chromatography instrument (Biorad Variant II) (7).

Interventions

Eligible participants were randomized to the ILI or DSE. The DSE group received information on healthy eating and physical activity but did not receive the comprehensive components of the weight loss intervention or the specific strategies for weight loss provided in the ILI group. A full description of the ILI and DSE during the first year of Look AHEAD has been published (8). For all participants, general medical and diabetes care continued to be delivered by the participant's personal physician.

Dual energy x-ray absorptiometry (DXA) sub-study

In a sub-study, hip, spine and whole body DXA scans were obtained at baseline and Y1 at five clinical centers (Baton Rouge, Boston- Massachusetts General Hospital, Houston, Los Angeles, Seattle). Sites were selected based on availability of DXA scanners and interest of the local investigators. The recruitment goal was 1,260 participants, the minimum needed for 90% power to detect a difference of 0.5% in BMD change over one year between treatment groups. Of 1,479 enrolled participants, 68 were ineligible because their weight exceeded the DXA scanner limit (>300 lbs), 137 did not have scans at both visits, and 1,274 are included in these analyses (Figure). Mean baseline age, BMI, HbA1c, and insulin use of these included participants were not statistically different from the 137 participants without scans at both visits. All DXA sites used Hologic fan beam densitometers, and any software upgrades during the study were approved by a DXA quality assurance center (San Francisco Coordinating Center, University of California San Francisco). Longitudinal performance was monitored with regular scanning of a spine and a whole body phantom on each densitometer. The coefficient of variation for spine and whole body phantom BMD ranged from 0.36%–0.39% and 1.6%–2.4%, respectively, at the five sites. Longitudinal corrections were applied to spine and hip BMD results at the Los Angeles site and to whole body BMD at the Houston site. Soft tissue results were corrected to account for under-estimation of fat mass (10). The quality of participant scans was centrally monitored. T-scores were calculated using NHANES III as the reference for total hip and the manufacturer's database for spine, with gender-specific references. If BMD loss was >10% for lumbar spine or total hip, the participant and primary care provider were notified.

Statistical analysis

For baseline characteristics, statistical tests for continuous variables were from linear models including gender, clinic, and randomization assignment. For categorical variables, the p-values were obtained from generalized linear models with a multinomial response probability distribution.

Changes in BMD, both absolute values and percent change, were compared across ILI and DSE groups. Analyses are also presented stratified by gender because of gender differences in BMD and bone loss. Differences by randomization assignment were tested with linear models adjusted for clinic, gender, baseline variables (Table 1) that differed across randomization assignment ($p < 0.10$), and the baseline value of the outcome change variable. Adjusted means and standard errors are reported. The results were similar for absolute and percent change, and only the percent change is reported here.

Within the ILI group, adjusted linear regression models were used to identify associations between change in hip BMD over one year and changes in other factors. Parameter estimates

(Beta coefficients) were reported. The change in absolute value of BMD, not percent change, was used in these models. Analyses were carried out using SAS v 9.2 (Cary, NC).

RESULTS

Baseline characteristics

In this subgroup of Look AHEAD participants, average age was 58.4 years. Average BMI was 35.2 kg/m^2, and 83% were obese, similar to the total Look AHEAD population (7). The proportion with osteoporosis, based on T-score, was low. Spine BMD, weight, lean mass, metformin use, menopausal status and HbA1c, but not other baseline characteristics, differed at baseline in the ILI and DSE groups (Table 1).

Changes over 12 months

During the first year, ILI participants lost more weight than the DSE group ($p<0.001$) (Table 2). The ILI group lost an average of 10.0 kg (men) and 8.3 kg (women), compared with 0.5 kg (men) and 0.8 kg (women) in the DSE group. The ILI group also experienced improved glycemic control ($p<0.001$) and fitness ($p<0.001$), compared with the DSE group.

The average time between the baseline and Y1 DXA scans was 395 (SD 43) days, and did not differ between groups. Bone loss was greater in the ILI group compared with the DSE group for the total hip (−1.45% versus −0.39; $p<0.001$) and femoral neck (−1.50 versus −0.85%; $p=0.009$) (Table 2). Changes in spine BMD ($p=0.61$) and whole body BMD ($p=0.06$) did not differ by intervention group. At the total hip, the difference in bone loss between intervention groups was greater for men (−1.48% vs. 0.02%) than for women (−1.44% vs. −0.61%) (p for interaction = 0.04). There was no evidence of interaction at the other BMD sites.

Differences in bone loss between the ILI and DSE groups were similar in models excluding participants with thiazolidinedione (TZD) use at baseline (data not shown). During the first year of the trial, the proportion of participants using a TZD increased in the DSE group, 19.8% at baseline to 23.7% at Y1, and decreased in the ILI group, 18.4% to 15.9%. The proportion with osteoporosis increased in the ILI group and was stable in the DSE group, but remained small. At 12 months, 2.0% of the ILI group was osteoporotic based on total hip BMD, compared with 1% at baseline.

Factors affecting bone loss in the Intensive Lifestyle Intervention group

To assess the independent contributions of intentional weight loss, glycemic control and physical fitness, we analyzed the results for the ILI group separately. In unadjusted models, total hip bone loss increased with each increasing quartile of weight loss (data not shown). In linear regression analyses adjusted for age, gender, race and clinical site, weight loss correlated with total hip bone loss in the ILI group. Each additional kg of weight loss was associated with a decrease in total hip BMD of 0.0018 g/cm^2. However, there were no statistically significant correlations between bone loss and weight loss for femoral neck BMD. In models additionally adjusted for HbA1c change, physical fitness change, baseline use of diabetes medications (separate adjustment for TZDs, insulin, metformin and sulfonlyureas), current or past smoking, and alcohol use, weight loss continued to be associated with bone loss at the total hip in men and women (Table 3). In men, but not women, a decrease in HbA1c was associated with an increase in total hip BMD, but was not associated with femoral neck BMD changes. Improved physical fitness, as determined by a graded exercise test, was not associated with bone changes for men or women. When weight change was separated into changes in fat mass and lean mass as measured by DXA, losses in both compartments were associated with total hip, but not femoral neck, bone loss for men

and women in the ILI group. Results were similar when those reporting TZD use at baseline were excluded (data not shown).

DISCUSSION

We found that one year of intentional weight loss in overweight and obese adults with type 2 diabetes resulted in greater bone loss at the total hip and femoral neck, but not at the spine or whole body. To our knowledge, this is the first trial to assess the effects of an intentional weight loss intervention on bone in adults with type 2 diabetes.

Studies in broader populations have reported bone loss at the total hip, spine and whole body with weight loss (11,12). In obese patients undergoing bariatric surgery, bone loss appears to occur in proportion to the degree of weight loss (13). Bone loss with weight loss is likely due to less skeletal loading and reduced anabolic signals from muscle and fat mass (14–16). In observational studies, lower weight and intentional weight loss increase fracture risk (17,18). This relationship between lower weight and fracture is strong for BMI<25, but is weaker with higher BMI (17). In a small trial of a lifestyle intervention in obese older adults without diabetes, the intervention group had increased bone loss at the hip but not the spine or whole body, similar to our findings (19). Spine BMD changes are difficult to assess in older adults because of osteophytes and other degenerative changes. Whole body BMD has a higher proportion of cortical bone than hip BMD and may not be as sensitive to changes in weight.

A limitation of this study is the use of DXA to assess BMD changes in the setting of weight change, particularly in obese participants. With obesity, the reproducibility of BMD is reduced which is likely to attenuate any real associations between changes in weight and BMD (20). Changes in fat mass can affect the ability of DXA to identify bone edges and to accurately allow for the composition of soft tissue overlying bone, possibly introducing artificial changes in BMD (21). In a recent study using a Hologic densitometer, fat mass added to volunteers reduced the measured mean spine BMD but did not alter the results for mean hip BMD (22). In addition, with substantial weight loss, smaller hip circumference reduces the height of the bone above the densitometer table which may introduce fan beam magnification effects (23). The net effect of changes in fat mass on bone measurements vary with skeletal site and scanner model. However, in our analyses considering decreases in fat mass and in lean mass separately, we found that both were associated with total hip bone loss, suggesting that the observed association between weight loss and bone loss in this trial is not simply an artifact of changes in fat mass.

The ILI group experienced greater weight loss as well as improved physical fitness and glycemic control compared with the DSE group. Look AHEAD was not designed to identify whether these changes had separate effects on outcomes. However, it is plausible that weight loss results in bone loss while improved glycemic control and physical fitness have a positive effect on BMD. When we sought evidence for independent effects by considering the intervention group separately, we found that weight loss was associated with total hip bone loss in the intervention group even after adjustment for changes in HbA1c and physical fitness. TZD use, associated with bone loss and fracture in other studies (24), was greater in the DSE group during the first year and thus does not account for the differences in hip bone loss.

Improved HbA1c was associated with preservation of total hip BMD in men but not women. The relationship between glycemic control and changes in BMD has not been clearly established. In an uncontrolled trial, Gregorio et al. reported increased femoral neck bone mineral content in 50 type 2 diabetic adults with poor glycemic control after a year of

treatment that improved control (3). However, the investigators did not report on changes in weight. In Look AHEAD, most participants had good glycemic control at study entry (mean A1C ~ 7.2%) which may have limited any potential skeletal benefits of improved control.

Our analyses in the intervention group suggest that improved physical fitness during weight loss did not preserve bone. Physical activity was only measured on a subset of Look AHEAD participants using the Paffenbarger scale, but changes in physical activity over the first year of the trial correlated positively ($R = 0.25$, $p<0.0001$) with changes in physical fitness (9). Results from studies of the effects of exercise during weight loss on bone loss have been conflicting (25–27). One study in older type 2 diabetic adults reported that high-intensity resistance training reduced the effects of weight loss on total body BMD (4). The exercise intervention in Look AHEAD was not as intensive and did not emphasize resistance training which may account for the different findings.

Bone loss with intentional weight loss is primarily a concern because of the strong relationship between low BMD and fracture risk. However, the additional bone loss experienced in the ILI group averaged a modest 1%. Thus, the initial year of weight loss in Look AHEAD may not result in a clinically important increase in fracture risk, especially as subsequent years will focus on weight maintenance rather than additional weight loss. On the other hand, effects of weight loss on bone density might be greater in subsequent years as any skeletal remodeling response may lag behind the weight loss stimulus. This report is limited to one year of follow-up. For comparison, in a U.S. cohort of older women, an annual loss of 0.9% total hip BMD over 8 years, a cumulative loss of about 7%, was associated with a relative risk of subsequent hip fracture of 1.29 (28). Fracture events are not currently available for Look AHEAD, but are being collected and will be assessed at the end of the trial.

This study is the first to address the effects of a weight loss intervention on bone in a diabetic population. A strength of this study is the randomization of participants to the weight loss intervention. Thus, weight loss in the ILI group was generally intentional and not due to illness or frailty. A limitation of this study is the use of DXA in the setting of weight change. In addition, data were not collected on calcium or vitamin D supplement use. It is possible that the two groups used different amounts of these supplements. Another limitation is the lack of bone turnover markers to assess effects on bone resorption. These results may not apply to patients weighing more than 300 lbs, the weight limit for DXA measurements, or to patients with poor glycemic control.

In conclusion, one year of an intensive lifestyle intervention in overweight and obese men and women with type 2 diabetes that resulted in weight loss, improved glycemic control and enhanced physical fitness, also resulted in a modest increased bone loss at the hip. The extent to which this additional bone loss may increase fracture risk is not known. Further research, including fracture outcomes in Look AHEAD, is needed to elucidate the effects of intentional weight loss on fracture risk in older adults with type 2 diabetes.

Acknowledgments

This study is supported by the Department of Health and Human Services through the following cooperative agreements from the National Institutes of Health: DK57136, DK57149, DK56990, DK57177, DK57171, DK57151, DK57182, DK57131, DK57002, DK57078, DK57154, DK57178, DK57219, DK57008, DK57135, and DK56992. The following federal agencies have contributed support: National Institute of Diabetes and Digestive and Kidney Diseases; National Heart, Lung, and Blood Institute; National Institute of Nursing Research; National Center on Minority Health and Health Disparities; Office of Research on Women's Health; the Centers for Disease Control and Prevention; and the Department of Veterans Affairs. This research was supported in part by the Intramural Research Program of the National Institute of Diabetes and Digestive and Kidney Diseases.

Additional support was received from The Johns Hopkins Medical Institutions Bayview General Clinical Research Center (M01RR02719); the Massachusetts General Hospital Mallinckrodt General Clinical Research Center (M01RR01066); the University of Colorado Health Sciences Center General Clinical Research Center (M01RR00051) and Clinical Nutrition Research Unit (P30 DK48520); the University of Tennessee at Memphis General Clinical Research Center (M01RR0021140); the University of Pittsburgh General Clinical Research Center (M01RR000056 44) and NIH grant (DK 046204); and the VA Puget Sound Health Care System/University of Washington, Medical Research Service, Department of Veterans Affairs; Frederic C. Bartter General Clinical Research Center (M01RR01346)

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Federal Sponsors

National Institute of Diabetes and Digestive and Kidney Diseases: Barbara Harrison, MS; Van S. Hubbard, MD PhD; Susan Z. Yanovski, MD

National Heart, Lung, and Blood Institute: Lawton S. Cooper, MD, MPH; Jeffrey Cutler, MD, MPH; Eva Obarzanek, PhD, MPH, RD

Centers for Disease Control and Prevention: Edward W. Gregg, PhD; David F. Williamson, PhD; Ping Zhang, PhD

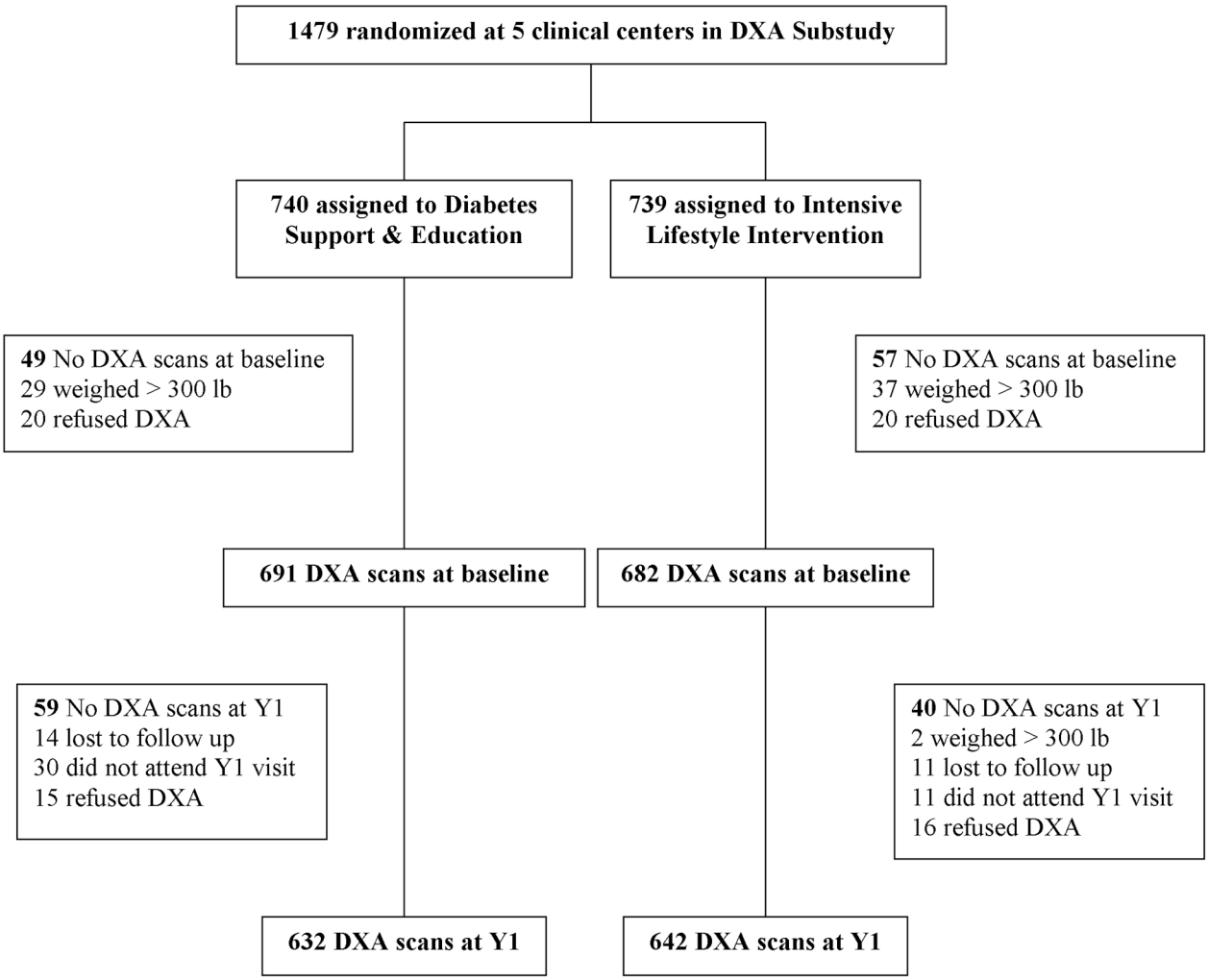

Figure.
Flowchart for Look AHEAD DXA sub-study participants

J Bone Miner Res. Author manuscript; available in PMC 2013 March 04.

Table 1

Baseline Characteristics[a] of Look AHEAD Trial Participants with Bone Density Scans at Baseline and One-Year Visits

Variable	Diabetes Support and Education (DSE)		Intensive Lifestyle Intervention (ILI)		DSE vs. ILI *P* value[b]
	Men	Women	Men	Women	
N	246	386	237	405	
Age (yr)	60.0 ± 6.4	57.8 ± 6.5	60.4 ± 6.5	57.0 ± 6.6	0.39
Ethnicity					0.77
Black	17 (7%)	52 (13%)	9 (4%)	55 (14%)	
White	178 (72%)	192 (50%)	167 (70%)	208 (51%)	
Other	51 (21%)	142 (37%)	61 (26%)	142 (35%)	
Height (cm)	175.5 ± 6.5	160.4 ± 6.7	174.3 ± 6.9	160.3 ± 6.9	0.14
Weight (kg)	104.9 ± 14.3	93.5 ± 16.0	102.9 ± 15.3	92.1 ± 16.7	0.07
BMI (kg/m^2)	34.0 ± 4.3	36.3 ± 5.5	33.9 ± 4.6	35.8 ± 5.7	0.20
Obese[c]	197 (80%)	335 (87%)	190 (80%)	335 (83%)	0.24
Whole body lean soft-tissue mass (kg)	64.9 ± 7.1	48.1 ± 6.2	63.6 ± 6.9	47.9 ± 6.7	0.07
Whole body fat mass (kg)	36.8 ± 8.8	43.0 ± 10.3	36.0 ± 9.7	42.0 ± 10.7	0.11
Total hip BMD (g/cm^2)	1.099 ± 0.138	1.027 ± 0.142	1.077 ± 0.122	1.028 ± 0.140	0.31
Total hip BMD T-score					
T-score < −2.5	4 (2%)	4 (1%)	1 (0%)	3 (1%)	0.23
−2.5 < T-score < −1	17 (7%)	27 (7%)	16 (7%)	30 (7%)	0.88
Femoral neck BMD (g/cm^2)	0.887 ± 0.123	0.865 ± 0.134	0.868 ± 0.120	0.865 ± 0.137	0.33
Spine BMD (g/cm^2)	1.152 ± 0.175	1.079 ± 0.157	1.115 ± 0.143	1.068 ± 0.164	0.02
Spine BMD T-score					
T-score < −2.5	2 (1%)	10 (3%)	2 (1%)	10 (2%)	0.94
−2.5 < T-score < −1	40 (16%)	64 (17%)	39 (16%)	73 (18%)	0.68
Whole body BMD (g/cm^2)	1.192 ± 0.118	1.111 ± 0.123	1.170 ± 0.103	1.110 ± 0.121	0.20
Statin use	120 (49%)	134 (35%)	120 (51%)	150 (37%)	0.39
Insulin use	34 (14%)	60 (16%)	46 (19%)	59 (15%)	0.47
Metformin use	152 (62%)	216 (56%)	155 (65%)	261 (64%)	0.01
Sulfonylurea use	129 (52%)	171 (44%)	126 (53%)	178 (44%)	0.99
TZD use	64 (26%)	65 (17%)	56 (24%)	62 (15%)	0.45

Variable	Diabetes Support and Education (DSE)		Intensive Lifestyle Intervention (ILI)		DSE vs. ILI *P* value[b]
	Men	Women	Men	Women	
Hormone therapy use	0 (0%)	239 (62%)	0 (0%)	257 (64%)	0.62
Osteoporosis medication use	0 (0%)	12 (3%)	1 (0%)	17 (4%)	0.28
Graded exercise test: Maximal value (MET)	8.4 ± 2.1	6.9 ± 1.6	8.3 ± 2.1	7.1 ± 1.7	0.66
Dietary calcium[d] (mg/day)	850 ± 592	851 ± 536	825 ± 510	838 ± 436	0.67
Smoking status					0.71
Never	97 (39%)	250 (65%)	93 (39%)	259 (64%)	
Past	138 (56%)	120 (31%)	129 (54%)	131 (32%)	
Current	11 (4%)	16 (4%)	15 (6%)	15 (4%)	
Consumed alcohol in past year	161 (65%)	184 (48%)	170 (72%)	196 (48%)	0.24
Menopausal status					0.06
Post-	0 (0%)	297 (77%)	0 (0%)	289 (71%)	
Pre-	0 (0%)	42 (11%)	0 (0%)	50 (12%)	
Unknown	0 (0%)	47 (12%)	0 (0%)	66 (16%)	
HbA1c (%)	7.2 ± 1.2	7.4 ± 1.2	7.2 ± 1.2	7.2 ± 1.2	0.06

[a] Mean ± standard deviation, or N(%)

[b] *P* value for comparison between treatment groups (DSE and ILI) adjusted for gender and clinic

[c] BMI ≥ 30 kg/m^2

[d] Calcium intake in diet, not including supplements. Available on a subset of participants (N= 697).

Table 2

Change from Baseline to Year 1 by Randomized Group[a]

	Adjusted Mean (SE) Change[b]		Treatment *P* value[c]
	Diabetes Support and Education	Intensive Lifestyle Intervention	
ALL			
Total hip BMD (%)	−0.39 (0.12)	−1.45 (0.12)	<.001
Femoral neck BMD (%)	−0.85 (0.19)	−1.50 (0.18)	0.009
Lumbar spine BMD (%)	−0.08 (0.14)	0.01 (0.14)	0.61
Whole body BMD (%)	−0.16 (0.12)	0.13 (0.12)	0.06
Weight (kg)	−0.87 (0.24)	−9.06 (0.24)	<.001
HbA1c (%)	−0.11 (0.04)	−0.69 (0.04)	<.001
Graded exercise test (MET)	0.19 (0.06)	1.17 (0.06)	<.001
MEN			
Total hip BMD (%)	0.02 (0.15)	−1.48 (0.16)	<.001
Femoral neck BMD (%)	−0.50 (0.23)	−1.18 (0.24)	0.04
Lumbar spine BMD (%)	0.57 (0.22)	0.80 (0.22)	0.45
Whole body BMD (%)	0.27 (0.17)	0.39 (0.18)	0.63
Weight (kg)	−0.49 (0.39)	−10.01 (0.40)	<.001
HbA1c (%)	−0.12 (0.06)	−0.69 (0.06)	<.001
Graded exercise test (MET)	0.23 (0.10)	1.27 (0.10)	<.001
WOMEN			
Total hip BMD (%)	−0.61 (0.17)	−1.44 (0.16)	<.001
Femoral neck BMD (%)	−1.13 (0.26)	−1.74 (0.25)	0.07
Lumbar spine BMD (%)	−0.56 (0.18)	−0.52 (0.18)	0.86
Whole body BMD (%)	−0.52 (0.15)	−0.15 (0.15)	0.07
Weight (kg)	−0.84 (0.28)	−8.27 (0.27)	<.001
HbA1c (%)	−0.08 (0.05)	−0.65 (0.05)	<.001
Graded exercise test (MET)	0.12 (0.07)	1.09 (0.06)	<.001

[a] Adjusted for clinical site, gender, baseline value of outcome, and baseline values of spine BMD, lean body mass, metformin use, HbA1c and, for women, menopausal status.

[b] SE = standard error

[c] *P* value for comparison between treatment groups

Table 3

Associations with One-Year Change in Hip BMD in the Intensive Lifestyle Intervention Group

	1-year Change in Hip BMD (mg/cm^2)			
	Total Hip		Femoral Neck	
	Beta	***P* value**	**Beta**	***P* value**
ALL[a]				
Weight change (per kg)	1.77	<.001	0.11	0.69
HbA1c change (per %)	−1.58	0.21	1.78	0.29
Graded exercise test change (per MET)	−1.24	0.20	−0.12	0.93
MEN[a]				
Weight change (per kg)	1.65	<.001	0.02	0.95
HbA1c change (per %)	−5.89	<.001	0.88	0.65
Graded exercise test change (per MET)	−1.77	0.17	−1.26	0.37
WOMEN[a]				
Weight change (per kg)	1.96	<.001	0.04	0.93
HbA1c change (per %)	1.29	0.46	1.87	0.46
Graded exercise test change (per MET)	−0.47	0.74	1.11	0.58
ALL[b]				
Lean soft-tissue mass change (per kg)	1.99	<.001	0.34	0.68
Fat mass change (per kg)	1.81	<.001	0.20	0.65
HbA1c change (per %)	−1.44	0.26	1.74	0.31
Graded exercise test change (per MET)	−1.04	0.28	0.00	0.10
MEN[b]				
Lean soft-tissue mass change (per kg)	2.41	0.002	0.46	0.59
Fat mass change (per kg)	1.29	0.005	−0.17	0.75
HbA1c change (per %)	−5.00	0.005	1.20	0.54
Graded exercise test change (per MET)	−1.94	0.12	−1.25	0.38
WOMEN[b]				
Lean soft-tissue mass change (per kg)	2.06	0.02	0.23	0.85
Fat mass change (per kg)	2.15	<.001	0.26	0.69
HbA1c change (per %)	1.28	0.46	1.80	0.48
Graded exercise test change (per MET)	−0.11	0.94	1.19	0.56

[a]Model includes change in weight, HbA1c and graded exercise test, and baseline values for age, gender, race, clinic site, baseline use of insulin, metformin, sulfonylureas, TZDs, smoking, and alcohol use, and for women menopausal status and hormone therapy use.

[b]Model includes change in lean soft tissue mass, fat mass, HbA1c and graded exercise test, and baseline values for age, gender, race, clinic site, baseline use of insulin, metformin, sulfonylureas, TZDs, smoking and alcohol use, and for women menopausal status and hormone therapy use.