

Weight Loss Decreases Follicle Stimulating Hormone in Overweight Postmenopausal Women

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Objectives: To examine the impact of a weight loss intervention upon follicle stimulating hormone (FSH) levels in postmenopause.

Methods: Participants were postmenopausal, overweight, glucose-intolerant women not using exogenous estrogen ($n = 382$) in the Diabetes Prevention Program. Women were randomized to intensive lifestyle change (ILS) with the goals of weight reduction of at least 7% of initial weight and 150 min per week of moderate-intensity exercise, metformin 850 mg twice a day, or placebo administered twice a day.

Results: Randomization to ILS led to small increases in FSH between baseline and 1-year follow-up vs. placebo (2.3 IU/l vs. -0.81 IU/l, $P < 0.01$). Increases in FSH were correlated with decreases in weight ($r = -0.165$, $P < 0.01$) and estradiol (E2) ($r = -0.464$, $P < 0.0001$) after adjustment for age, race/ethnicity, and randomization arm. Changes in FSH were still significantly associated with changes in weight even after adjustment for E2 levels. Metformin users had reductions in weight but non-significant changes in FSH and E2 levels vs. placebo.

Conclusions: Weight loss leads to small increases in FSH among overweight, postmenopausal women, potentially through pathways mediated by endogenous estrogen as well as other pathways.

Obesity (2015) 23, 228–233. doi:10.1002/oby.20917

Introduction

Menopause, the permanent cessation of menstruation and fertility, has been classically characterized by elevated follicle stimulating hormone (FSH) and very low estradiol (E2) levels. Obesity may modify this relationship: FSH levels tend to rise more gradually and attain lower levels in overweight and obese women compared to lean women (1). In one report, about 20% of obese women had FSH levels <30 IU/l at 1 year after menopause, compared to about 2% of women of normal weight (2). The lower levels of FSH in overweight postmenopausal women compared to lean women have been attributed to increased production of endogenous estrogens by mesenchymal adipose tissue (3), which could potentially act centrally to

decrease FSH. This is in agreement with randomized trials of estrogen therapy, which demonstrate that randomization to either low or higher-dose estrogen therapy results in increased serum E2 (4) and a decline in FSH levels in both lean and obese women (5,6). Because of FSH fluctuations in the months surrounding the final menstrual period as well as lower levels in obese women, FSH is not currently recommended as a diagnostic test for menopause.

However, the link between adiposity and FSH is based on observational studies which generally document increases in both body weight and serum FSH with chronological and reproductive aging. Randomized studies of FSH responses to weight loss interventions

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Funding agencies: The project described was supported by Award Numbers U01DK048489, R01DK083297, and K23DK071552 from The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). The NIDDK provided funding to the clinical centers and the Coordinating Center for the design and conduct of the study and for collection, management, analysis, and interpretation of the Diabetes Prevention Program. The Southwestern American Indian Centers were supported directly by the NIDDK and the Indian Health Service. The General Clinical Research Center Program, National Center for Research Resources supported data collection at many of the clinical centers. Funding for data collection and participant support was also provided by the National Institute of Child Health and Human Development, the National Institute on Aging, the Office of Research on Women's Health, the Office of Research on Minority Health, the Centers for Disease Control and Prevention, and the American Diabetes Association. This research was also supported, in part, by the intramural research program of the NIDDK. McKesson BioServices Corp., Matthews Media Group, Inc., and the Henry M. Jackson Foundation provided support services under subcontract with the Coordinating Center.

Disclosure: None of the authors have a conflict of interest.

Author Contribution: CK conceived the research question, drafted the manuscript, and oversaw the statistical analysis and design; SK performed the statistical analysis; EBC reviewed manuscript drafts; BN reviewed the statistical analysis; JFR reviewed manuscript drafts, FL conducted the assays and reviewed manuscript drafts. All authors had final approval of the submitted and published versions.

Received: 29 June 2014; **Accepted:** 11 September 2014; **Published online** 8 October 2014. doi:10.1002/oby.20917

in postmenopausal women are lacking. Because it is unknown whether weight loss results in significant increases in FSH levels, it is not clear whether associations between adiposity and FSH reflect other factors associated with aging. In addition, studies have generally compared lean women to those who are overweight and obese. It is possible that hypothalamic-pituitary-gonadal axis sensitivity is relatively reduced in obese women (7), and therefore it is unknown if FSH levels would be sensitive to weight loss among mid-life women who are overweight and obese, currently 66% of mid-life women (8). It is unknown whether any FSH changes would be primarily explained by an increase in endogenous estrogens such as E₂, or whether weight loss is still associated with FSH even after consideration of E₂ levels. It is possible that changes in adipose tissue volume modify FSH via other markers apart from estrogens; observational studies suggest that increases in waist circumference in the perimenopause predict changes in FSH, even prior to significant declines in E₂ (9). Moreover, among premenopausal women, overweight women have lower FSH levels than lean women, despite similar or even lower E₂ levels (10).

We (11) and others (12-14) have previously reported upon sex hormones among glucose intolerant women, and specifically that higher levels of E₂ and lower levels of sex hormone binding globulin are associated with poorer glucose tolerance. However, FSH, a component of the hypothalamic-pituitary-gonadal axis which regulates sex steroid production, has not been as extensively characterized. It is not known whether FSH levels continue to be low further from the final menstrual period in overweight and obese women with glucose intolerance, whether FSH levels would increase to an extent that would be clinically significant in response to weight loss, and to what extent FSH reflects sex steroid levels vs. other factors. The Diabetes Prevention Program (DPP) randomized overweight glucose-intolerant participants to a program of intensive lifestyle modification (ILS), metformin, or placebo (15). Participants randomized to interventions had maximal weight loss at 1 year after randomization (15), and we have previously reported that this pattern was also observed in the subpopulation of postmenopausal women (11). To determine the impact of intentional weight loss on FSH levels, we conducted a secondary analysis where we examined the association between randomization assignment and changes in FSH between baseline and 1 year, as well as the correlation between the magnitude of changes in FSH, weight, waist circumference, and serum E₂ among women who did not use estrogen therapy. We hypothesized that randomization to ILS would lead to increases in FSH, which would be correlated with decreases in weight and waist circumference. We also hypothesized that changes in FSH would be correlated with changes even after adjustment for E₂ levels.

Methods

Characteristics of DPP participants have been reported (15). Briefly, the DPP inclusion criteria included age ≥ 25 years, body mass index (BMI) ≥ 24 kg/m² (≥ 22 kg/m² for Asian Americans), and a fasting plasma glucose of 95-125 mg/dl and 2-h plasma glucose of 140-200 mg/dl following a 75-g glucose load. Written informed consent was obtained from all participants before screening, consistent with the guidelines of each participating center's institutional review board. Eligible DPP participants were randomly assigned to one of three interventions: 850 mg metformin twice daily, placebo twice daily, or ILS. The goals of ILS were to achieve and maintain a weight reduc-

tion of at least 7% of initial body weight through consumption of a low-calorie, low-fat diet, plus moderate physical activity for at least 150 min per week (15). Dietary intake was assessed by interview using a modified Block food-frequency questionnaire (16). Total MET-hours per week of physical activity were assessed by the 1-year recall Modifiable Activity Questionnaire (17). Weight and waist circumference were measured semiannually. At the time of randomization, all women completed a questionnaire about their menses, gynecological history including surgeries, and estrogen use (contraceptive and postmenopausal therapy). Medication use was reassessed every 6 months.

Participants in this ancillary study included women who were postmenopausal at randomization, who had an available stored blood sample, and who consented for participation in ancillary studies. Women were classified as postmenopausal if they met any of the following criteria: bilateral oophorectomy, lack of menses for at least one year while retaining uterus and at least one ovary, cessation of menses prior to hysterectomy, or cessation of menses with hysterectomy and age ≥ 55 years. For the purposes of this report, we examined two postmenopausal women who did not use estrogen or testosterone therapy at baseline or 1-year follow-up ($n = 382$). Women who used any type of estrogen therapy at either baseline, interim, or 1-year follow-up were excluded.

Venous blood was sampled between 7 a.m. and 11 a.m. after an overnight fast. FSH was measured at EndoCeutics using ELISA (Bioline) with interassay coefficients of variation of 3.6 and 4.4 at 27.1 and 72.9 mIU/ml, respectively. E₂ was analyzed using gas chromatography/mass spectrometry at EndoCeutics; these methods have been previously described (11). The limits of detection were 3.0 pg/ml for total E₂ with an interassay coefficient of variation for E₂ at 17.5% at 4.7 pg/ml. We have previously reported (11) that bioavailable levels of E₂ (accounting for serum levels of sex hormone binding globulin) were calculated according to the method described by Sodergard and colleagues (courtesy of Frank Stanczyk, University of Southern California) assuming a fixed albumin concentration of 4.0 g/dl (18). Associations between randomization arm and E₂ levels were similar for analyses examining bioavailable fractions compared to total hormone levels, so only results with total hormone levels are presented.

Statistical analysis

Baseline characteristics were described using percentages for categorical variables and means (SD) for quantitative variables. For variables where the distribution was skewed, median values were presented as indicated in Table 1. To assess the association between randomization assignment and changes in weight and waist circumference, *T* tests were used to compare changes by randomization arm. ANOVA was used to determine if there were significant differences in the mean values across groups. Change was calculated as year 1 hormone level - baseline hormone level. Changes in FSH and E₂ between baseline and year 1 follow-up, as well as measures of physical activity and dietary intake, were not normally distributed, so we used Wilcoxon rank-sum tests to compare changes between randomization arms in pairwise comparisons and log-transformed measures for comparisons in mean values across groups.

To determine if the observed changes in FSH between baseline and year 1 were associated with changes in weight, waist circumference,

TABLE 1 Baseline characteristics of participants unless otherwise indicated; change indicates difference between baseline and year 1

	Overall <i>n</i> = 382	Lifestyle <i>n</i> = 133	Metformin <i>n</i> = 122	Placebo <i>n</i> = 127
Age (years)	58.7 (9.0)	59.2 (9.1)	57.9 (8.8)	59.0 (9.2)
Race/ethnicity				
Caucasian	53	18	15	19
African-American	28	9	10	9
Hispanic	16	6	5	5
Asian	3	2	1	0
Type of menopause				
Bilateral oophorectomy	20	8	6	6
Natural menopause	67	24	21	22
Age ≥ 55 years and hysterectomy	16	4	4	5
Hysterectomy	37	13	12	12
Years since final menstrual period	15 (10)	15 (10)	15 (11)	14 (9)
Alcohol intake per day (grams)	1.26 (2.90)	1.73 (3.70)	0.89 (2.20)	1.11 (2.47)
Total caloric intake per day (kcal)	1876 (956)	1855 (895)	1876 (975)	1897 (1006)
Percent calories from fat	32.9 (7.4)	32.5 (7.4)	33.9 (6.8)	32.4 (7.8)
Leisure-time physical activity (MET-hours/week)	13.5 (19.0)	12.6 (21.4)	12.5 (13.7)	15.6 (20.6)
Baseline weight (kg)	91.0 (19.7)	89.0 (19.8)	92.9 (20.8)	89.9 (18.5)
Baseline waist circumference (cm)	104 (14)	103 (14)	105 (14)	104 (14)
Baseline BMI (kg/m ²)	34.6 (6.8)	34.1 (6.7)	35.2 (7.1)	34.5 (6.6)
Baseline FSH (IU/l)	55.3 (26.6)	54.8 (28.6)	51.5 (24.2)*	59.3 (26.1)
Baseline SHBG (nmol/L), median (IQR)	33.2 (18.3)	34.5 (17.8)	31.6 (17.1)	34.0 (21.8)
Baseline total E2 (pg/ml), median (IQR)	8.5 (8.0)	8.3 (7.6)	9.2 (7.0)	8.4 (9.6)

Means (SD) or percentages or medians (interquartile ranges) are shown.

Bold type and * indicates significant difference ($P < 0.05$) between intervention and placebo.

and E2 levels between baseline and year 1, we used partial Pearson correlation coefficients to estimate the relationship between FSH and each of these measures, after adjustment for randomization arm. We also adjusted for age and race/ethnicity, as these variables have been previously been reported to be associated with FSH (2,19). To determine whether associations between changes in FSH and changes in weight and waist circumference were present after adjustment for changes in E2, we created an additional set of coefficients that adjusted for changes in E2 levels. The SAS analysis system was used for all analyses (SAS Institute, Cary, NC).

Results

Baseline characteristics of the postmenopausal cohort are shown in Table 1. Reflecting DPP recruitment criteria, all women were overweight or obese at baseline. Approximately 15 years had elapsed since the last menstrual period, and about one quarter of women had experienced their final menstrual period at 7 years prior to randomization. There were no significant differences at baseline between women randomized to ILS ($n = 133$), metformin ($n = 122$), or placebo ($n = 129$), the exception that women randomized to metformin had slightly lower levels of FSH. Changes in anthropometrics, FSH, and E2 by randomization arm are shown in Table 2. Randomization to ILS led to significant reductions in percent calories from fat and increases in physical activity compared to placebo. Randomization

to ILS or metformin led to significant reductions in weight, waist circumference, and BMI compared to placebo. Significant increases in FSH were observed among women randomized to ILS compared to placebo, although these differences were relatively small compared to the mean baseline FSH value. Significant increases in FSH were not observed among women randomized to metformin compared to placebo. Significant changes in E2 were not observed by randomization arm.

Shows partial correlation coefficients between changes in FSH with changes in weight, waist circumference, and E2 after adjustment for age, race/ethnicity, and randomization arm. FSH changes were inversely associated with changes in weight, waist circumference, and E2, with the strongest associations observed between changes in FSH and changes in E2. Correlations between changes in FSH and changes in weight ($r = -0.165$, $P = 0.003$) remained significant after further adjustment for changes in E2 ($r = -0.130$, $P = 0.036$), suggesting that changes in FSH were partially but not entirely explained by changes in E2. Correlations between changes in FSH and changes in waist circumference ($r = -0.142$, $P = 0.011$) were of borderline significance after further adjustment for changes in E2 ($r = -0.109$, $P = 0.069$). To determine whether time closer to the last menstrual period was associated with greater FSH changes, we conducted analyses that stratified by time elapsed since the last menstrual period in the most recent quartile (<7 years) vs. longer (results not shown). Similar patterns were observed among

TABLE 2 Changes in anthropometrics, FSH, and E2 between baseline and year 1 by randomization arm

	Lifestyle	Metformin	Placebo	P value for lifestyle vs. placebo	P value for metformin vs. placebo	P value for overall difference between arms
Change in alcohol intake per day (g)	-0.11 (3.50)	0.64 (4.74)	-0.16 (1.19)	0.81	0.54	0.13
Change in total kcal consumption (kcal)	-434 (809)	-297 (691)	-310 (883)	0.13	0.91	0.35
Change in percent calories from fat	-5.8 (8.2)	-1.5 (7.7)	-0.7 (7.0)	<0.0001	0.41	<0.0001
Change in leisure-time physical activity (MET-hours/week)	5.0 (22.6)	-0.3 (15.3)	4.4 (33.1)	0.0002	0.43	0.18
Change in weight (kg)	-6.5 (6.0)	-3.2 (5.3)	-1.0 (3.6)	<0.0001	0.0001	<0.0001
Change in waist circumference (cm)	-6.5 (6.1)	-3.0 (5.3)	-1.3 (5.3)	<0.0001	0.01	<0.0001
Change in BMI (kg/m ²)	-2.5 (2.3)	-1.2 (2.1)	-0.4 (1.4)	<0.0001	<0.0001	<0.0001
Change in FSH (IU/l)	2.3 (10.9)	1.3 (8.6)	-0.81 (8.9)	0.0006	0.24	0.11
Change in E2 (pg/ml)	-8.3 (7.6)	-9.2 (7.0)	-8.4 (9.6)	0.26	0.45	0.71

women who had a more recent menopause compared to women who did not.

Discussion

Among postmenopausal overweight and obese women, we found that randomization to lifestyle change was associated with weight loss compared to placebo and increases in FSH over a 1-year period, although the magnitude of the FSH increase was small compared to the baseline FSH value. Among women who did not use estrogen, increases in FSH occurred in the lifestyle change arm compared to placebo despite lack of statistically significant change in E2 levels, although women in all randomization arms had decreases in E2 levels. Changes in FSH were strongly correlated with changes in E2, but FSH increases were correlated with weight and waist circumference decreases even after adjustment for changes in E2.

Our results support the hypothesis that weight loss increases FSH levels among overweight and obese postmenopausal women. This is consistent with previous observational studies that have reported that body mass is associated with FSH levels. Using data from the Study of Women's Health Across the Nation (SWAN), Tepper et al reported that FSH levels followed 3 patterns over the menopausal transition: low, medium, and high FSH increases (2). Approximately 20% of obese women had FSH levels that fell into the low trajectory, with average FSH levels of about 20 IU/l at 1 year after the final menstrual period and of about 35 IU/l at 8 years after the final menstrual period. Conversely, obese and overweight women were less likely than lean women to fall into the high trajectory; lean women were more likely to have FSH levels that exceeded 100 IU/l at 1 year after the final menstrual period. Freeman et al have also reported that FSH level is inversely associated with BMI category, with heavier women having lower FSH levels in the postmenopause (1). Wildman et al., (9) also using SWAN data, reported that current

waist circumference levels predicted future FSH. Among postmenopausal women with FSH levels of ~60 IU/l, each centimeter increase in waist circumference was associated with approximately a 0.8 IU/l lower FSH.

We observed smaller increases in FSH subsequent to changes in body size than observed in previous observational studies, perhaps because women in the DPP were still overweight and centrally obese even after significant weight loss. Our results demonstrate that reductions in BMI as small as 2.5 kg/m² in obese women (equivalent to a loss of about 6.5 kg or 14 pounds) led to increases in FSH. This suggests that the hypothalamic-pituitary-gonadal axis in overweight and obese women is still sensitive to weight changes among women who have been postmenopausal for years, even though women were, on average, still overweight or obese even after significant weight loss, and the FSH changes were fairly small. These results in postmenopausal women contrast with a small study in premenopausal obese women (mean weight, 120 kg) that reported no FSH change even with 13 kg of weight loss (20). This suggests that the FSH levels in obese premenopausal women might be insensitive to weight fluctuations if obesity was still present after weight loss, perhaps due to greater amounts of E2 produced by functioning ovaries.

We also found that FSH increases tended to track more strongly with E2 decreases rather than body mass changes. In the DPP, weight loss was achieved through a combination of percent fat reduction and physical activity in the lifestyle modification arm, and due to the randomization scheme, the separate impact of these two modifications apart from weight could not be examined by randomization arm; however, correlations between FSH or E2 with changes in percent fat intake, alcohol intake, total caloric intake, and leisure-time physical activity were not significant. Previous studies have suggested that weight loss achieved through dietary changes (particularly reduction in fat) and exercise are linked to changes in E2, although the effects of macronutrient intake and activity appear to be minimal if significant weight loss does not occur (21-23). To our


TABLE 3 Partial correlation coefficients between changes in FSH, weight, waist circumference, and E2 adjusted for age, race/ethnicity, and randomization arm (ILS vs. metformin vs. placebo)

	Δ FSH	Δ Weight	Δ Waist circumference	Δ E2	Δ Alcohol intake	Δ Total caloric intake	Δ Percent calories from fat	Δ Leisure-time physical activity
Δ FSH	1.00	-0.165; <i>P</i> = 0.003	-0.142; <i>P</i> = 0.011	-0.464; <i>P</i> < 0.0001	-0.019; <i>P</i> = 0.73	-0.019; <i>P</i> = 0.74	-0.039; <i>P</i> = 0.49	0.056; <i>P</i> = 0.32
Δ Weight		1.00	0.539; <i>P</i> < 0.0001	0.047; <i>P</i> = 0.41	0.020; <i>P</i> = 0.71	0.11; <i>P</i> = 0.04	0.12; <i>P</i> = 0.02	-0.12; <i>P</i> = 0.02
Δ Waist circumference			1.00	-0.009; <i>P</i> = 0.87	0.08; <i>P</i> = 0.13	0.16; <i>P</i> = 0.002	0.07; <i>P</i> = 0.17	-0.12; <i>P</i> = 0.02
Δ E2				1.00	0.061; <i>P</i> = 0.30	-0.076; <i>P</i> = 0.20	-0.11; <i>P</i> = 0.07	0.008; <i>P</i> = 0.89
Δ Alcohol intake					1.00	-0.012; <i>P</i> = 0.83	-0.083; <i>P</i> = 0.12	0.026; <i>P</i> = 0.63
Δ Total caloric intake						1.00	0.146; <i>P</i> = 0.006	0.008; <i>P</i> = 0.88
Δ Percent calories from fat							1.00	-0.13; <i>P</i> = 0.01

knowledge, changes in FSH were not examined. Serum E2 levels have been believed to be the primary pathway through which weight influences FSH levels in postmenopausal women. In the absence of ovarian E2 production, adipose tissue production of E2 from estrogen and androgen precursors has been believed to be the primary source of serum E2. However, E2 made in most peripheral tissues may be present in relatively small amounts in the circulation. While FSH and E2 levels are not commonly measured in trials of estrogen therapy, at least two randomized trials have reported that estrogen supplementation can triple serum E2 levels (4,5), and FSH levels are subsequently halved (5). The degree of FSH increase was not reported to vary by weight (5), suggesting that exogenous E2 was more influential than weight upon FSH levels in postmenopausal women. The supraphysiologic levels of E2 in postmenopausal women secondary to exogenous estrogen with resulting effects on FSH may not reflect the FSH-E2 relationship at the lower levels of E2 typically observed among women not using estrogen therapy. However, previous observational studies have also reported that higher levels of E2 in the postmenopause are associated with lower FSH levels. Tepper et al. (2) reported that women with low FSH trajectories were most likely to occur with higher E2 levels in the postmenopause, with almost all women who fell into these trajectories having BMIs ≥ 30 kg/m².

While changes in E2 were most strongly correlated with changes in FSH, changes in FSH were still associated with changes in weight even after adjustment for E2. Moreover, changes in anthropometrics and changes in E2 did not have strong correlations in our postmenopausal overweight population. Observational studies of obese women have suggested that correlations between E2 and anthropometrics tend to be reduced among obese women, perhaps due to large amounts of overall body fat (24). This suggests that adiposity-related factors other than E2 may have affected FSH secretion. Therefore, it may be that the prognostic value of FSH for either menopausal staging or other clinical applications might be improved with the measurement of additional markers. Although candidate factors were not examined in this report and are speculative, such factors include other estrogens such as estrone, as well as inhibin B, adiponectin, leptin, and ghrelin, which have been previously reported to be associated with FSH as well as weight (25-29).

Strengths of our report include its randomized design and interventions which successfully induced statistically and clinically significant amounts of weight loss. Our report also had several limitations. Women were overweight or obese and glucose intolerant, and these results may not apply to women who were metabolically healthy. Although it is possible that a larger sample size would have increased the statistical significance of some of the observed associations, such as between changes in weight and changes in E2 production, the sample size was adequate to detect clinically significant changes. Although we used mass spectrometry which is more reliable at lower levels of sex steroid measurement, variance at these lower levels was high and possibly related to unreported estrogen intake. Although change in weight was correlated with change in FSH levels, we were unable to examine other estrogens such as estrone, adipokines (leptin, ghrelin, adiponectin) or inhibin B levels that might have mediated such associations. Because of sample size, we were unable to examine the impact of menopause type upon sex hormone levels in response to randomization. Finally, this study was a secondary analysis of a randomized trial not designed a priori to assess the impact of interventions on FSH concentrations.

We conclude that weight reductions may lead to increases in FSH levels in postmenopausal overweight and obese women, and such changes may result from either reduction in E2 concentrations or other adiposity-linked markers. These results suggest that the gonadotropin axis is sensitive to both serum sex steroids and body composition signaling mechanisms in overweight and obese women even years after the final menstrual period. These results also replicate that finding that even among overweight and obese women, endogenous estrogen production does not suppress FSH production to the extent that FSH levels replicate premenopausal levels. Further investigation of the impact of FSH changes among women with natural and surgical menopause should be conducted. FSH is used as a prognostic marker for success in assisted reproductive technologies as well as supportive diagnostic evidence for conditions of menstrual irregularities including polycystic ovarian syndrome and hypothalamic amenorrhea. While our report did not examine premenopausal or perimenopausal women, our results suggest that weight and weight loss might affect the value of FSH in these applications, and further investigation should be conducted of the relationship between weight loss and FSH in these populations. 

Acknowledgments

The investigators gratefully acknowledge the commitment and dedication of the participants of the DPP. The opinions expressed are those of the investigators and do not reflect the views of the Indian Health Service or other funding agencies. Bristol-Myers Squibb and Parke-Davis provided medication. LifeScan Inc., Health O Meter, Hoechst Marion Roussel, Inc., Merck-Medco Managed Care, Inc., Merck and Co., Nike Sports Marketing, Slim Fast Foods Co., and Quaker Oats Co. donated materials, equipment, or medicines for concomitant conditions.

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