Lesson from the Look Action for Health in Diabetes Study

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ABSTRACT

The Look Action for Health in Diabetes AHEAD Study was designed as a long-term randomized controlled clinical trial and powered to detect differences in cardiovascular outcomes, the primary cause of early morbidity and mortality in type 2 diabetes, among subjects randomized to receive an intensive lifestyle intervention or a control group of diabetes support and education. The study was terminated early due to the absence of any difference in the primary outcome, defined as a composite of the first postrandomization occurrence of fatal and nonfatal myocardial infarction and stroke, or angina requiring hospitalization. However, important secondary favorable outcomes were observed in those receiving the intensive lifestyle intervention. This included more weight loss, greater fitness, less disability, less depression, reductions in sleep apnea and urinary incontinence, better glycemic control, and more subjects experiencing diabetes remission. These results underscore the importance of lifestyle interventions as a component of diabetes therapy. Long-term follow-up of Look AHEAD participants is planned, despite discontinuation of the intensive lifestyle program.

Key words: Cardiovascular disease, diet, exercise, type 2 diabetes, weight loss

INTRODUCTION

Therapeutic lifestyle interventions TLSs are recommended as an essential component of the initial and lifelong therapeutic regimen for the majority of individuals with or at risk for type 2 diabetes. TLS interventions consist of dietary and exercise recommendations that promote weight loss in overweight and obese individuals with the ultimate goal of reducing risk for cardiovascular disease CVD, the primary contributor to early morbidity and mortality in type 2 diabetes.

Despite the implied importance of the influence of TLS on promoting glycemic and metabolic control and ultimately reducing risk for CVD events, there were no long-term randomized controlled clinical trials investigating the impact of diet and exercise on CVD outcomes. Until recent publication of the results of the Look Action for Health in Diabetes AHEAD Trial, the majority of intervention studies have focused on achieving strict levels of glycemic control using existing pharmacologic therapies as a way of addressing CVD risk. The failure to observe reductions in CVD outcomes with intensive pharmacologic strategies in several recent large clinical trials supported the need to investigate the contribution of TLS recommendations on amelioration of risk for macrovascular complications.

The primary objective of Look AHEAD Study was to examine the long-term effects of an intensive lifestyle intervention program in overweight subjects with type 2 diabetes when compared with a control group receiving diabetes support and education. The primary outcome was a composite of the first postrandomization occurrence of fatal and nonfatal myocardial infarction and stroke. The study was powered to detect an 18% difference in CVD events between the two groups at 13.5 years of follow-up. Due to the observation of fewer events than anticipated, angina requiring hospitalization was added to this composite measure during the second study year.
Look AHEAD randomized 5145 participants with type 2 diabetes between the ages of 45 and 74 years to an intensive lifestyle intervention or control group. The two groups were well-matched for baseline clinical characteristics. The mean age was approximately 59 years and the mean body mass index was 36 kg/m². Randomized subjects were under reasonable levels of glycemic control with mean baseline A1C values of < 7.5%. Women accounted for 60% of participants and only 16% of subjects were treated with insulin at time of study entry, fulfilling the prespecified recruitment goal of < 30% of insulin-treated subjects. All participants were required to complete a maximal exercise stress test prior to randomization to ensure safety of the exercise intervention.

Retention of participants was high throughout the mean follow-up time period of approximately 10 years, with less than 4% of subjects being lost to follow-up. The ability to maintain retention in the Look AHEAD Study can be attributed in part to the intensive screening process that required candidates to keep detailed records of food intake and physical activity during a 2-week lead in period. This resulted in the inclusion of subjects who were both motivated and willing to perform self-monitoring of caloric intake and physical activity.

The intensive lifestyle intervention was designed to allow participants to achieve and maintain a 10% weight loss through a combination of a decrease in caloric intake and an increase in physical activity [Table 1]. Energy intake was restricted to 1200-1800 calories per day according to body weight. Food choices were limited by use of meal replacement strategies for two meals a day for the first 6 months and one meal a day for the next 6 months. Regular meetings with nutritional support personnel guided participants toward sensible meal planning with encouragement of the intake of fresh fruits and vegetables.

Exercise prescriptions encouraged 175 min or more of moderate intensity physical activity per week in sessions of at least 10 min duration. All intensive lifestyle intervention participants received pedometers and with a goal of 10,000 steps each day. Group instruction on use of daily activities to increase energy expenditure was provided. All participants were assigned to a lifestyle coordinator. To ensure compliance with both caloric and exercise interventions, meetings with nutritionists, exercise, and behavioral specialists were held on a weekly basis for the first 6 months with a gradual tapering of frequency to at least one in-person or phone contact per month. Periodic refresher courses and national campaigns were introduced to reemphasize the principles of the intensive intervention.

Participants randomized to the control group received three group educational and social support sessions per year. These sessions focused on diet and nutrition, exercise, and issues related to living with diabetes. Control group participants were seen at annual visits and received periodic phone calls to encourage continued participation in this long term clinical trial.

Significant differences were observed between the intensive lifestyle intervention and control groups at 1 year. Weight loss -8.6 vs. -0.7%, \( P < 0.001 \) and fitness levels + 20.9 vs. 5.8%, \( P < 0.001 \) were greater in the intensive lifestyle intervention group. There were associated reductions in A1c and cardiovascular risk factors, providing a clear separation between the intensive lifestyle intervention and control groups in anticipation of meeting prespecified criteria for the primary outcome.

However, these differences in weight reduction and fitness did not translate into long-term reductions in CVD outcomes. The Look AHEAD intensive lifestyle intervention was ended in September 2012, when no group differences were observed in CVD events as the primary composite endpoints. A total of 403 intensive lifestyle intervention and 418 control group participants experienced the primary outcome. These differences were

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**Table 1: Components of the intensive lifestyle intervention in look AHEAD**

| Diet recommendations       |
|----------------------------|
| Caloric intake             |
| 1200-1500 calories/day if <114 kg |
| 1500-1800 calories/day if >114 kg |
| Months 1-6                 |
| Meal replacement shake for 2 meals a day |
| One snack with a food bar  |
| Sensible dinner meal of conventional foods |
| Fruits and vegetable intake encouraged |
| Months 7-12                |
| Meal replacement shake for 1 meal a day |
| Two sensible meals         |
| One snack of conventional foods |
| Fruits and vegetables      |

| Exercise recommendations  |
|----------------------------|
| Physical activity         |
| 175 minutes/week moderate intensity exercise |
| Group instruction on use of daily activities to increase energy expenditure |
| Pedometers provided: goal 10,000 steps/day |
| Group and individual sessions with nutritionists, exercise specialists, and behavior therapists |
| Months 1-6: Weekly meetings |
| Months 7-12: 2 group and 1 individual session/month |
| Years 2-4: One in-person and one phone or email contact/month |
| Each participant was assigned to a lifestyle coordinator for duration of the study |

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not significant as a composite, or when broken down into secondary or other individual CVD events, despite sustained differences in weight loss and fitness levels between the two groups. Subgroup analyses revealed fewer CVD events in intensive lifestyle intervention group participants with no history CVD at baseline, and more events in those with a history of CVD at baseline. However, these trends were not statistically significant. Subgroup analyses based on gender or ethnicity also failed to demonstrate any group differences in outcomes.\textsuperscript{[8]}

The failure to observe differences in CVD events either in all participants or among specified subgroups raises the question as to whether Look AHEAD represents another negative intervention study in type 2 diabetes. This issue is likely to cause debate and commentary in coming years, but it is worth looking at some of the prespecified secondary objectives for Look AHEAD. These secondary objectives included an examination of the effect of intensive lifestyle intervention on diabetes control and complications albuminuria/amputation; measures of physical activity and fitness, dietary intake, body weight, blood pressure BP, lipids, obesity‑related cancers; osteoarthritis symptoms and disability; sleep apnea; urinary incontinence; gall bladder disease; fracture risk and bone mineral density; and quality of life and psychological outcomes.\textsuperscript{[8]}

It is in through an examination of these secondary outcomes that Look AHEAD offers important information that supports efforts to promote intensive lifestyle intervention among individuals with type 2 diabetes. Participants randomized to ILS had greater reductions in A1C, lost more weight, had greater reductions in waist circumference, a greater increase in fitness levels, and more mobility with less disability than those receiving diabetes support and education. Similar to what has been observed in earlier studies, these favorable changes were most marked at 1 year but differences were maintained for the duration of the study.\textsuperscript{[8]} For example, the initial 8.6% weight loss in the intensive lifestyle intervention group at 1 year was followed by a period of weight regain through year 5, following which there was a gradual decline with a sustained weight loss of 6.5% at the end of the study. Fitness levels also peaked at 1 year followed by a decline over the next 4 years; however, fitness levels remained above baseline values in the intensive lifestyle intervention group, while a decline was observed in the control group.

Other benefits observed with the intensive intervention in Look AHEAD included favorable changes in sleep apnea, urinary incontinence, and health‑related quality of life HRQL. The Sleep AHEAD study enrolled 264 subjects from four centers who were representative of the overall Look AHEAD population.\textsuperscript{[12]} Subjects in this substudy had evidence of obstructive sleep apnea (OSA) with a baseline mean apnea–hypopnea index AHI of 23.2 ± 16.5 events per hour. Participants receiving the intensive lifestyle intervention experienced a decrease in AHI events of 9.7 ± 2.0 events per hour when compared with the control group. Remission of OSA occurred in more intensive lifestyle intervention than control group participants. These improvements were directly related to weight loss with greatest improvements observed in participants losing ≥ 10 kg body weight.

In women, the prevalence and incidence of urinary incontinence was reduced among those receiving the intensive lifestyle intervention at 1 year.\textsuperscript{[13]} Changes in HRQL using the 36‑Item Short‑Form Health Survey and Beck Depression Inventory II BDI‑II scale demonstrated improvements in the physical component measures of HRQOL and BDI‑II scores in the intensive lifestyle intervention group. These changes were also associated with changes in weight and fitness.\textsuperscript{[14]}

An investigation into adverse events was conducted to determine in these may have been affected by the intensive lifestyle intervention. Although medical management was relegated to a participant's physician, adjustments were made to diabetes medications to offset risk for hypoglycemia in the intervention group. There were no observed group differences in the frequency of hypoglycemia, fractures, amputations, congestive heart failure, or occurrence of gallstones. These findings support the safety of interventions that promote weight loss through caloric reductions and increased physical activity in obese and overweight individuals with type 2 diabetes.

The focus on CVD events as the primary outcome can blur the benefits that were observed with the intensive lifestyle intervention program in Look AHEAD. The intensive lifestyle intervention was associated with improvements in glycemic control, mobility, OSA, HRQL, and urinary incontinence in women. More participants in the intensive lifestyle intervention group experienced remission of their diabetes, which may have accounted for higher levels of low‑density lipoprotein cholesterol and the less frequent use of ace inhibitors and angiotensin receptor blockers in this group. Remission of diabetes was more likely in those with a shorter disease duration and lower baseline A1C, suggesting that the presence of residual beta cell function may be necessary to maximize the effects of exercise on glycemic control.\textsuperscript{[15]} Greater reductions in systolic BP and increases in high‑density lipoprotein cholesterol were observed with intensive lifestyle intervention. Waist circumference, a measure of central obesity, was reduced,
as was the incidence and prevalence of depression. While these changes do not satisfy the requirements for a positive study, they do provide validation of including TLS as a major component of therapy in type 2 diabetes.

In summary, an intensive lifestyle intervention focused on weight loss did not reduce the rate of cardiovascular events in overweight or obese adults with type 2 diabetes. However, significant improvements were observed in CVD risk factors, sleep apnea, depression, and quality of life. One important aspect of therapy in individuals with type 2 diabetes is to promote well-being as those who live with this disorder deal with the multicomponent therapy required to achieve metabolic control. Although the intensive lifestyle intervention has been discontinued, Look AHEAD participants continue to be followed to determine the long-term effects of the intervention on health outcomes. It is likely that we will learn more about these effects in the coming years.

REFERENCES

1. American Diabetes Association. Standards of medical care for patients with diabetes mellitus. Diabetes Care 2013;36:S11-166.
2. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. American Diabetes Association (ADA); European Association for the Study of Diabetes (EASD); Management of hyperglycemia in type 2 diabetes: A patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2012;35:1364-79.
3. Brooks MM, Frye RL, Genth S, Detre KM, Nesto R, Sobel BE, et al. Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) Trial Investigators Hypotheses, design, and methods for the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) Trial. Am J Cardiol 2006;97 (12A):9-19G.
4. Look AHEAD Research Group, Wing RR. Long-term effects of a lifestyle intervention on weight and cardiovascular risk factors in individuals with type 2 diabetes mellitus: Four-year results of the Look AHEAD trial. Arch Intern Med 2010;170:1566-75.
5. Duckworth W, Abraira C, Moritz T, Reda D, Emanuele N, Reaven PD, et al. VADT Investigators. Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med 2009;360:129-39.
6. Action to Control Cardiovascular Risk in Diabetes Study Group, Gerstein HC, Miller ME, Byington RP, Goff DC Jr, Bigger JT, Buse JB, et al. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008;358:2545-59.
7. ADVANCE Collaborative Group, Patel A, MacMahon S, Chalmers J, Neal B, Billot L, Woodward M, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 2008;358:2560-72.
8. Look AHEAD Research Group, Wing RR, Bolin P, Brancati FL, Bray GA, Clark JM, Coday M. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. N Engl J Med 2013;369:145-54.
9. Skyler JS, Bergenstal R, Bonow RO, Buse J, Deedwania P, Gale EA, et al., American Diabetes Association, American College of Cardiology Foundation; American Heart Association. Intensive glycemic control and the prevention of cardiovascular events: implications of the ACCORD, ADVANCE, and VA diabetes trials: A position statement of the American Diabetes Association and a scientific statement of the American College of Cardiology Foundation and the American Heart Association. Diabetes Care 2009;32:187-92.
10. Ryan DH, Espeland MA, Foster GD, Haffner SM, Hubbard VS, Johnson KC, et al., Look AHEAD Research Group. Look AHEAD (Action for Health in Diabetes: design and methods for a clinical trial of weight loss for the prevention of cardiovascular disease in type 2 diabetes. Controlled Clinical Trials 2003;24:610-28.
11. The Look Ahead Research Group, Pi-Sunyer X, Blackburn G, Brancati FL, Bray GA, Bright R, Clark JM, et al. Reduction in Weight and Cardiovascular Disease Risk Factors in Individuals With Type 2 Diabetes: One-year results of the Look AHEAD trial. Diabetes Care 2007;30:1374-83.
12. Foster GD, Borradale KE, Sanders MH, Millman R, Zammit G, Newman AB, et al., Sleep AHEAD Research Group of Look AHEAD Research Group. A randomized study on the effect of weight loss on obstructive sleep apnea among obese patients with type 2 diabetes: the Sleep AHEAD study. Arch Intern Med 2009;169:1619-26.
13. Phelan S, Kanaya AM, Subak LL, Hogan PE, Espeland MA, Wing RR, et al. Look AHEAD Research Group. Weight loss prevents urinary incontinence in women with type 2 diabetes: Results from the Look AHEAD trial. J Urol 2012;187:399-44.
14. Williamson DA, Rejeski J, Lang W, Van Dorsten B, Fabricatore AN, Toledo K, Look AHEAD Research Group. Impact of a weight management program on health-related quality of life in overweight adults with type 2 diabetes. Arch Intern Med 2009;169:163-71.
15. Gregg EW, Chen H, Wagenknecht LE, Clark JM, Delahanty LM, Bantle J, et al. Look AHEAD Research Group. Association of an intensive lifestyle intervention with remission of type 2 diabetes. JAMA 2012;308:2489-96.

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