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The Look AHEAD Trial: A Review and Discussion Of Its Outcomes

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Abstract

The LookAhead trial was a randomized controlled trial comparing an Intensive Lifestyle Intervention (ILI) to a Diabetes Support and Education (DSE) in overweight and obese type 2 diabetes patients to track the development of cardiovascular disease over time. The triaI intervention was stopped for futility after a median follow-up of 9.6 years. While there was a differential effect on weight loss and fitness between the two groups, there was no effect on cardiovascular outcomes. Cardiovascular events were less than half the projected rate per year in the DSE group: thus there was a very low over-all rate of events in both groups. There were many other health benefits of ILI, including improved biomarkers of glucose and lipid control, less sleep apnea, lower liver fat, less depression, improved insulin sensitivity, less urinary incontinence, less kidney disease, reduced need of diabetes medications, maintenance of physical mobility, improved quality of life and lower costs.

Keywords

Randomized controlled trial; type 2 diabetes; overweight; obese; intensive lifestyle intervention; cardiovascular outcomes; diabetic complications; quality of life; cost

INTRODUCTION

Type 2 diabetes (DM2) is a huge global problem. The International Diabetes Federation estimates that 382 million people presently have diabetes and that this number is projected to increase to 592 million by 2035 (1). The financial cost of this is also huge, estimated at $548 billion USD in 2013 (1). At the same time, there has been an increasing prevalence of obesity (2) and since obesity often leads to DM2 (3), it has greatly contributed to the increased incidence of diabetes (4). The side effects of DM2 are many and among the most important is an increased risk of cardiovascular disease (CVD). It is known that DM2 patients have twice the risk of developing CVD than do matched non-diabetic persons (5).

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Conflict of Interest
Xavier Pi-Sunyer declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

As a result, the issue of whether an intensive lifestyle intervention would reduce CVD events in DM2 patients was a question needing an answer.

It was for this reason that the National Institutes of Health sponsored a randomized controlled trial to test whether an Intensive Lifestyle Intervention (ILI) as compared to a Diabetes Support and Education (DSE) in overweight or obese type 2 diabetic patients would lead to cardiovascular benefits. The trial was conducted on 5145 persons in 16 centers in the USA. At the end of a median of 9.6 years of intervention and a maximal follow-up of 11.5 years, the NIH announced that the lifestyle *"intervention was stopped early in NIH-funded study of weight loss in overweight and obese adults with type 2 diabetes after finding no harm, but no cardiovascular benefits"*(6). A report of the results of the trial have been published (7). The ILI led to an 8.6% weight loss the first year and a maintenance of nearly 5% at 4 years and 6.0% at the end of intervention (7). A significant differential of weight loss from DSE was maintained throughout the 11.5 years of follow-up. CVD events were less than half the projected rate in the DSE group (3.13.% per year in DSE vs 0.07% in ILI) (7). Thus there was a very low over-all rate of events in both groups. However, there were many other health benefits that occurred with ILI, including improved biomarkers of glucose and lipid control, less sleep apnea, lower liver fat, less depression, less urinary incontinence, less severe kidney disease, improved sexual dysfunction, reduced need of diabetes medications, maintenance of physical mobility, and improved quality of life. This was achieved with less health care costs (8)

DESIGN OF TRIAL

The design of the LookAHEAD trial has been published (9). The randomization was one to one. Both groups received routine medical care from their own health care providers. All subjects were overweight or obese (mean BMI 36.0) and ranged in age from 45–75. Volunteers had to pass a maximum exercise test to participate in the study. This was done so individuals could be given exercise goals to do throughout this long trial. As a result, patients with more severe cardiovascular disease were excluded. Patients with a past history of heart disease could be admitted into the trial, and 14% of participants gave such a history (10). I The average duration of diabetes was 6.8 years and that HbA1c, blood pressure, and lipids were fairly well controlled at baseline.

n the first year, the ILI intervention focused on behavioral, nutrition and activity themes, while the DSE was invited to 3 group sessions in the first year which reviewed general information of diabetes management. A study goal was set for reduction of baseline body weight in ILI by 7.0%, with each individual person's goal set at 10%. LookAHEAD calorie goals were 1200–1500 Kcal/day with 40–50 gm of fat for initial weights of <250 lbs. and 1500–1800 kcal/day with 50–60 gm of fat for initial weights >250 lbs (11). The diet goals included taking <30% of calories from fat (11). The ILI physical activity goal was to do 175 minutes a week of unsupervised exercise. Most subjects walked, but some jogged, swam, and biked. Some resistance exercise was encouraged.

The ILI patients were seen by individual lifestyle coaches who were registered dietitians, psychologists, and/or exercise physiologists. Sessions were 3 group and 1 individual session

per month for the first 6 months. For the next 6 months they came to 2 group and 1 individual session per month. In years 2–4, they were seen a minimum of once per month and an additional contact by group, phone, mail or e-mail (11). The group sessions were with the same 10–20 participants and lasted 60 to 75 minutes. These included a private weigh-in, group self-reports on weight, self-monitoring and goal setting, presentation of a new topic, discussion of topic and of barriers to success, action plans and homework for the next session (11). The sessions dealt with setting goals for weight, activity, fat and calorie intake. Self-monitoring was stressed, with a fat and calorie counter booklet where food and portion sizes were recorded as well as food portions and physical activity in minutes. These were reviewed with their lifestyle coaches. Effort was placed on strategies to reduce fat and calories. Patients were offered structured menus and up to two meal replacements per day if they wished. The ILI volunteers could choose from four commercial liquid food replacements which were provided free of charge.

A tool-box strategy was used. For subjects having trouble with their weight loss goals, problem solving, motivational interviewing and behavioral contracts were used. For those who did not reach a weight loss of 5% after the first 6 months, an advanced tool box was utilized. These included frozen meals, community classes, exercise items, or use of weight loss medication. Only orlistat was offered. Very few opted to use orlistat and it was not successful in rescuing patients (11).

The characteristics of the patients at baseline were similar in the two groups and have been published (7). There was excellent randomization with risk factors comparable in the two groups.

RESULTS

The results of weight, physical fitness, waist circumference, and glycated hemoglobin throughout the trial have been published (7), as have the cumulative hazard curves for the primary composite end point (7). There was no difference with regard to cardiovascular endpoints between ILI and DSE. The event rate was 1.83 per 100 patient-years for ILI and 1.92 events for patient-years for DSE (HR 0.95, 95% CI 0.83–1.09, P= 0.51). It is for this reason that the DSMB recommended stopping the trial for futility and the NIH agreed to do so.

At 1 year of intervention, the ILI group lost 8.6% of their initial body weight while the DSE group lost 0.7% (12). Fitness levels improved by 20.4% in ILI and by 5% in DSE (13). At study end, ILI still had a 6% weight loss while DSE had 3.5% (7). With regard to fitness, ILI had greater improvement in heart rate recovery after graded exercise testing compared with DSE ($p<0.001$) (14).. The ADA goal of lowering HbA1c <7% was found to have been increased in ILI subjects from 46% to 73%, while in the DSE it increased from 45% to 50%. As for meeting the 3 ADA goals for glycemic control, blood pressure, and lipids increased from 10.8% to 23.6% in ILI and from 9.5% to 16% in DSE ($p<0.001$) (12). At 4 years and 8 years of intervention, even though the weight loss maintenance was attenuated, there was still a significant difference in weight between the ILI and DSE groups (15, 16). This was continued in the weights at the end of intervention (7).

The ILI group showed improved biomarkers of glucose and lipid control (7,12), improved blood pressure (7,14), less sleep apnea (17, 18), lower liver fat (19), less depression (20,21), less urinary incontinence (22), less severe kidney disease and retinopathy (23), reduced need of diabetes medications (24), maintenance of physical mobility (25), improved quality of life (26), less knee pain (27), improved sexual function (28), lowered inflammation (29) and reduced over-all health costs (8).

DISCUSSION

There are a number of issues to review and discuss regarding the LookAHEAD results.

1) Low CVD event rate

As stated previously, there was a much lower CVD event rate than was projected from available data at the time of the start of the trial (0.7%/yr vs 3.125%/yr). In fact, the event rate in DSE was so low that the investigators decided to revise the primary outcome so as to document more events by including hospitalized angina (30). Why did this occur? A number of possibilities could have had an impact. First, the participants' physicians were aware of their patients' participation in the trial. In addition, these physicians were repeatedly reminded by LookAhead sites of the guidelines for treatment of DM2 patients promulgated by the American Diabetes Association. Also, they received results of the biomarkers being followed, so they were well aware if their patients were reaching guidelines or not. This could have affected their interactions with their patients for the better: more advice on behavioral change, more attention to appropriate medications.

Second, while patients were randomized to one of the two groups, all were free to do as they pleased with regard to how they led their life. They could sign up for other weight loss programs or to exercise programs as they wished. These were health conscious individuals who had signed up for a very long study, so they may have been over-all much more careful about health risks than the average person with diabetes.

Thirdly, volunteers could only enter the study if they could perform a maximal exercise test. This was done because part of the intervention was to be increased physical activity and the investigators wanted to be sure that this could be prescribed to the ILI group. But this may have biased towards a "healthier" group of volunteers than the average DM2 patient.

Fourthly, while patients could enter the study if they had a history of heart disease, only 14% of the patients did. Thus, again, the cohort may have been healthier than the average diabetic patient.

2) Diet

The nutritional approach in the LookAHEAD trial was based on the success of the DPP (31). Essentially the same diet was recommended, though somewhat more strict with regard to calories. The emphasis was to lower calories by restricting fat to less than 30% of total and also reducing intake of low-quality carbohydrates such as sugar, sugar-flavored beverages, and high calorie snacks. It is impossible to say whether a different dietary

approach would have given different event rates. The investigators opted for an approach that had been found to work.

3) Physical Activity

The recommended increase in activity for ILI was to 175 min per day at least 5 days per week. This was all the investigators felt they could ask from this extremely sedentary and aging population. All documentation of the activity was done by individual diaries, since the exercise was done at or near the home and not at the centers. That the ILI was compliant to an extent was shown by the increase in fitness that was found at 1 and 4 years (13). The DSE also improved somewhat in year 1, suggesting that they also picked up their physical activity, though not as much. Whether a more intensive exercise program in ILI would have had a greater impact is impossible to say.

4) Lifestyle vs medication

The ILI seems to have achieved a lowering of CV events by focusing on nutrition and physical activity. The ILI volunteers were successful in losing weight and maintaining a significant weight loss over the full median 9.6 years of the trial. They were also successful in increasing physical activity. The DSE was also successful in lowering of CV events to the same degree, and they achieved this by taking more medications: for diabetes, for blood pressure, and for LDL cholesterol drop (24). Is one approach superior to the other? ILI had a great number of other positive effects that were enumerated and referenced above. It seems reasonable to suggest that invoking lifestyle change by health professionals and public health agencies is a constructive approach to prevent some of the side effects of DM2.

5) Effectiveness in Relation to Weight

Individuals who were the most severely obese actually lost more weight than patients who were overweight. At 1 year, the severely obese lost 9.04% of initial body weight while the overweight lost 7.43% (32). *"All BMI groups had comparable improvements in fitness, physical activity, LDL cholesterol, triglycerides, blood pressure, fasting glucose, and HbA1c at 1 year. ILI treatment session attendance was excellent and did not differ among weight categories"* (32) This shows that all size individuals can profit from a lifestyle change and all can get equally positive outcomes.

6) Effectiveness in Relation to Age

The ILI was actually more effective for the older volunteers (>65 yrs) than for younger ones. This may be because they were more compliant with diet and physical activity guidelines. They opted for more meal replacements and they came to meetings more regularly (33). Clearly, older age is not a negative with regard to behavioral change.

7) Effectiveness in Relation to Ethnic/Racial Diversity

In LookAHEAD, 35% of participants were from minorities, with BMIs ranging from 25 to 60 kg/m2. All groups were able to lose weight and improve their risk factors. There was little difference among Caucasians, African-Americans, Hispanics. Native Americans did slightly less well. Thus, a preventive approach seems reasonable for everyone.

8) Regression of Diabetes

There was some regression of diabetes in the ILI group (34). This did not occur in the DSE group. This occurred more in patients with a short duration of diabetes diagnosis and who had lost more weight and improved fitness better (34). This is good news since DM2 leads to a host of complications that are costly in terms of quality of life and of dollars spent. It suggests that if one intervenes forcefully early on as soon as diabetes in diagnosed, a chance for remission is there.

9) Duration of Diabetes

The LookAHEAD trial randomized DM@ patient volunteers with an average duration of diabetes of 6.8 years (7). It is possible that an earlier intervention would be successful in reducing cardiovascular risk. It is well-known that the atherogenic process begins long before DM2 is diagnosed (35). It is possible that if only a very recently diagnosed group had been included that a positive effect on CVD events would have been shown.

10) Cost

A crucial issue is the cost/benefit ratio of this preventive approach. A recent publication answers this question. Use and costs of health-care services were recorded across an average of 10 years. *"Compared with DSE over 10 years, ILI had fewer hospitalizations, fewer medications, and lower health-care costs"* (8). So the intervention was carried out without incurring extra health care costs.

CONCLUSION

Overweight and obese DM2 patients are increasing in prevalence is the USA and globally. A majority suffer and die from CVD. The LookAHEAD study was a randomized controlled trial testing whether an ILI would lower the CVD event rate as compared to a DSE group. The event rate was very low in both groups, but there was no difference in CV outcomes between the two groups. The intervention was stopped for futility with a median follow-up of 9.6 years and a maximum one of 11.5 years. Despite no difference in event rates, the ILI profited from a large number of improvements to risk factors and side effects. It raised quality of life at lower cost. Although negative in its primary outcome, it was positive in many other aspects of diabetes morbidity.

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