Too Little Too Late? Lifestyle Intervention for Overweight Adults With Existing Type 2 Diabetes Mellitus

Gregg EW, Chen H, Wagenknecht LE, et al, for the Look AHEAD Research Group. Association of an intensive lifestyle intervention with remission of type 2 diabetes. JAMA 2012;308:2489–96.

Study Overview

<u>Objective</u>. To determine whether intensive lifestyle intervention is associated with remission of type 2 diabetes mellitus (T2DM) in overweight, middle-aged to older adults.

<u>Design</u>. Observational analysis using data from a larger randomized controlled trial.

<u>Setting and participants</u>. The Look AHEAD (Action for HEAlth for Diabetes) trial was a large US-based randomized controlled trial of an intensive lifestyle intervention versus diabetes support and education for overweight patients with known T2DM. The trial took place at 16 centers across the country, with recruitment between 2001 and 2004. The primary outcome of Look AHEAD was to examine the effects of ILI on cardiovascular outcomes. In the fall of 2012, the trial was stopped ahead of schedule by its sponsor due to an observed lack of effect of ILI on cardiovascular outcomes. The ancillary observational analysis reported in this paper aimed to

examine the effect of ILI on the more proximal outcome of diabetes resolution.

Patients were eligible for Look AHEAD recruitment if they had a confirmed diagnosis of T2DM (for this analysis, defined as taking DM medications or having fasting plasma glucose $\geq$ 126 mg/dL or A1c $\geq$ 6.5% AND non-type 1 physiology) and a baseline BMI of 25 kg/m² or greater ($\geq$ 27 if on insulin). Patients with severe hyperglycemia (A1c $\geq$ 11%), hypertension (> 160 mm Hg systolic or > 100 mm Hg diastolic), or triglyceridemia (> 600 mg/dL) were then excluded, as were those who could not comply with a 2-week baseline diet and activity self-monitoring exercise, or those who could not perform a maximal graded exercise test.

The analysis presented in this paper further excluded patients who were missing all DM outcome data or who underwent bariatric surgery during follow-up (n = 287), leaving 4503 adult T2DM patients out of the original 5145 who had been randomized. The diabetes support and education (DSE) arm received 3 group sessions focused on diet,

physical activity, and social support during each year of follow-up. The intensive lifestyle intervention (ILI) arm received frequent individual and group counseling sessions throughout follow-up, ranging from weekly sessions in the first 6 months to twice-monthly sessions in years 2–4. The goals of these sessions were to promote a 1200- to 1800-kcal, low-fat diet and ≥ 175 min/wk of physical activity. In addition to education and counseling, ILI participants were provided with liquid meal replacements to help them achieve caloric restriction.

Once randomized, patients were followed for 4 years with annual study clinic visits. At each visit, study personnel measured patient height, weight, fasting plasma glucose, and A1c. Patients were also asked to report behavioral factors and prescription medications. In addition to the baseline maximal graded exercise test, repeat sub-max exercise tests were administered at the year 1 and 4 visits.

Main outcome measures. The primary outcome of interest for this paper was the prevalence of any T2DM remission (partial or complete). Partial remission was defined as achieving a fasting plasma glucose of 100–126 mg/dL AND an A1c of 5.7%–6.5% without any DM medication, whereas complete remission was defined as achieving fasting plasma glucose < 100 mg/dL AND an A1c of < 5.7%, also in the absence of anti-hyperglycemic medication. Prevalence of complete or partial DM remission was calculated on an annual basis using test results obtained at study visits. Additionally, the duration of DM remission was characterized using the prevalence of remissions that were sustained across 2, 3, and 4 years of follow-up. To statistically analyze the relative prevalence in each study arm, the investigators relied on binary Markov transition models. In order to account for important covariates that were missing during follow-up, they used multiple imputation methods.

Additionally, the investigators examined multivariable associations of covariates that were felt to be likely to impact remission probability (eg, age, sex, race/ethnicity, education level), as well as initial responsiveness to study treatment (as determined by 1-year weight and fitness changes).

Other measures examined in this paper included participant weight loss (% at year 1 and year 4) and change in fitness level, defined as the improvement (or worsening) in metabolic equivalents (METs) achieved during exercise testing (cutoff at 80% of max predicted heart rate or when the participant stopped due to exertion rating of "hard" or "very hard"), comparing baseline test results to those at years 1 and 4.

Results. In considering the results for this study, it is important to note that this paper does not use data from all Look AHEAD patients as they were initially randomized. Over 600 participants who were randomized in the primary trial were eliminated for these analyses. When compared with the original group, the 600 eliminated patients were younger and had less severe disease but were more obese than the subjects analyzed here. Of the 4503 patients in this analysis, a statistically significant difference for measured covariates emerged between the DSE and ILI groups only for the covariate of age, for which the DSE group was slightly older (mean [SD] 59.1 [6.9] years) than the ILI group (mean [SD] 58.6 [6.7] years).

Both the DSE and ILI groups in this paper contained more women than men (41.4% and 41.9% male, respectively), were racially and ethnically relatively diverse (62% white in each group, with 13.6% Hispanic), and had a relatively well-educated patient population (> 75% with beyond high school education). Despite the slight age discrepancy between the 2 groups, the median baseline DM duration was equal between them (5 years [IQR 7 for DSE, 8 for ILI]), and the baseline disease severity in terms of glycemic control (mean DSE A1c, 7.37; mean ILI A1c, 7.34), and obesity (mean DSE BMI, 35.9; mean ILI BMI, 35.8) were not statistically different. The use and intensity of diabetes medications was also similar between the 2 groups at baseline. Of the patients included in the baseline measures for this paper, there was a 91% overall retention rate by year 4 of the follow-up period.

Looking at the combined outcome of partial or complete remission of T2DM, absolute rates of any remission were higher for the ILI group (11.5% during year 1, decreasing to 7.3% at year 4) than in the DSE group (2.0% at year 1 and year 4). The prevalence ratios for any T2DM remission, comparing ILI to DSE, were highest in year 1 (5.8 [95% confidence interval {CI} 4.2–7.9]), and also dropped over time due to progressive relapse (reaching 3.4 [95% CI 2.5–4.8] by year 4). Although relapse was common in both groups, there was a greater likelihood of maintaining remission in the ILI group compared with the DSE group.

The complete resolution of diabetes during follow-up was a rare occurrence for both the DSE and ILI groups, but was more likely with ILI. In absolute terms, patients in the ILI group had a 1.3% rate of complete resolution at year 1 (prevalence of remission had shrunk to 0.7% by year 4), compared with a 0.1% rate of complete remission in the DSE group at year 1 (prevalence of remission had grown to 0.2% by year 4). The prevalence ratio of complete remission comparing ILI to DSE across all 4 years of follow up was 6.6 (95% CI 3.3–13.3, $P < 0.001$).

Covariates predictive of any DM remission were, as would be expected, shorter disease duration, lower baseline BMI, and less-severe disease (lower A1c, no insulin use). Testing for interaction between these covariates and the main effect (treatment group) was negative.

As expected, the ILI patients had greater weight loss success after 1 year (–8.6% [95% CI –8.9 to –8.4%]) than the DSE patients (–0.7% [95% CI –0.9 to –0.4%]). Although the ILI group had some weight regain by year 4 (–4.7% [95% CI –5.0 to –4.4%]), it remained more successful at maintaining weight loss than the DSE group (–0.8% [95% CI –1.1 to –0.5%]), relative to baseline. A similar pattern was seen for fitness increases, with years 1 and 4's observed increases being greater in the ILI group than in the DSE group, but not sustained in magnitude for either group by study end. For ILI, year 1 showed an improvement of +20.6% [95% CI 19.5% to –21.8%] in METs, versus year 4 of just +4.9% [95% CI 3.7% to 6.1%], relative to baseline. For DSE, year 1 showed an improvement of +5.3% [95% CI 4.1% to 6.4%] METs, versus a worsening at year 4 (relative to baseline) of –1.5% [95% CI –2.8 to –0.3%]. Participants who were generally more successful at achieving weight loss (those who lost at least 6.5% of body weight) or fitness increases at year 1 did appear to have higher rates of any DM remission (16.4% remission rate in weight loss successes, 15.6% in fitness successes) than those who were unsuccessful, but the subgroup of patients with the highest rate of any DM remission were those who had been diagnosed with DM within 2 years before study enrollment (21.2% rate of any remission).

Conclusion. Intensive lifestyle interventions focused on caloric restriction (to promote a healthier body weight) and exercise (to increase physical fitness) do improve the likelihood of partial T2DM remission for overweight adults. Unfortunately, even with intensive lifestyle intervention, the chances of complete and sustained T2DM remission are low.

Commentary

Along with overweight and obesity, the prevalence of T2DM has risen substantially in the United States over the past few decades [1]. The reasons for this are numerous, but there is a growing sense that our changing lifestyle—becoming more sedentary and consuming high-calorie-dense diets—is a major contributor [2]. The individual and population-level consequences of T2DM are enormous, accounting for significant morbidity and mortality (and resulting medical costs) in affected patients. Medical therapy alone does not address the underlying lifestyle issues, such as diet and physical activity, which fuel the development T2DM. Thus, there has been a considerable amount of study around the use of lifestyle interventions to promote weight loss and physical fitness in an attempt to prevent the onset of this disease [3]. These studies have been promising, with patients who achieve moderate weight loss having significantly lower rates of T2DM onset than those who do not lose weight, even when compared to patients put on medication to slow their progression to overt diabetes [4].

What is less well known, as these authors point out, is whether similar benefits can be seen in patients who've already gone on to develop disease. In other words, once an adult has diabetes, is their fate sealed? Or, can successful weight loss and physical fitness reverse the course of illness? In an ancillary analysis of RCT data from the Look AHEAD trial, Gregg et al examined whether or not overweight or obese adults with T2DM could achieve partial or complete remission of their disease through an intensive lifestyle intervention. This large, multicenter analysis with up to 4 years of follow-up data from a randomized trial is the first of its kind to report on remission of existing T2DM using a nonsurgical intervention. This is a critically important topic, given the high prevalence and cost of T2DM in the United States. As the authors point out in their comment section, even if full and sustained remission is not achieved, coming off medications and having improved glycemic control is probably important for patient health, quality of life, and could be cost-saving in terms of medical care.

Although the actual dollars saved on drugs for successful patients may not equal the cost of an intensive lifestyle intervention on the overall T2DM population, a cost-effectiveness analysis could shed more light on this topic.

In addition to the large size of the trial, robust design, and a fairly racially and ethnically diverse population, the study had relatively long and intense follow-up given the diet and physical activity nature of the intervention, with an impressive 91% overall retention rate by year 4.

There are a few important limitations to this study, most of which are acknowledged by the authors in the paper. First, this particular study, and therefore the inclusion criteria for it, did not align with the primary aim of the Look AHEAD trial. Because of this, over 600 patients were eliminated from this analysis that were present in the parent study. This left a group that was older (mean age nearly 60 years) and had more severe baseline disease than would have been ideal for a study where DM remission was the primary outcome. Given that the biggest predictors of DM remission had to do with these factors (linked to disease duration and severity), it is possible that the impact of diet and lifestyle changes on DM remission may have been stronger had the trial been performed in younger patients with newly-diagnosed disease. Of course, a group of 35-year-olds with new-onset diabetes would not have been ideal for the parent trial, where the primary outcome of interest was cardiovascular events within 4 years of follow-up. Perhaps counteracting the fact that patients in this study were older and had longer-standing disease, it is important to consider that, for entry into Look AHEAD, patients with severe disease (diabetes, hypertension, or triglyceridemia) were excluded. This means that, despite being slightly older, the group ultimately included in this paper were probably "healthier" diabetics than would be seen in the general U.S. patient population, perhaps biasing the results in favor of a greater likelihood of observing disease remission.

In terms of measuring the outcome of interest, the absolute rates of complete remission were very low, and the authors focus more on the combined outcome of "partial or complete remission," both of which are probably clinically meaningful but perhaps to varying degrees. Furthermore, given the high rates of relapse after an initial remission was achieved, the true impact of an ILI may be small unless patients are able to keep weight off and maintain a high level of physical activity for the long-term, both difficult outcomes to achieve. As the authors acknowledge, the 4-year duration of follow-up may not have captured all of the relapses that will ultimately occur among those with initial remission, again leading to overestimation of the long-term "curative" potential of intensive lifestyle intervention.

The implications of this trial seem to be that, for the majority of overweight adults with T2DM of at least 5 years' duration, the absolute chances of disease reversal are very low. Although the relative remission rates presented in this paper appeared favorable, the absolute rates were very low—only 0.7% of patients in the ILI group had sustained complete remission of disease at 4 years, compared with 0.2% in the DSE group. Taken in conjunction with the incredible resource-intensity needed to implement and maintain this kind of intervention in a large population, this calls into question the general replicability of the intervention in everyday clinical practice. Here, you have the best possible scenario: a large research staff dedicated to careful patient follow-up, money to spend on an intense intervention, even covering liquid meal replacements to help promote weight loss, and a patient population willing to engage in a 5-year randomized controlled trial of lifestyle change. Even with those assets, the absolute effect observed of intensive lifestyle intervention over DSE was relatively small. It's safe to assume that in a busy real-world primary care practice with limited time and money, and a real-life patient population with variable compliance and disease severity, the results of a similar intervention would be even more modest.

Applications for Clinical Practice

In addition to helping prevent progression to T2DM in at-risk patients, intensive lifestyle interventions that successfully help patients lose weight and gain fitness may produce a partial, if not sustained, reversal of T2DM, especially in younger patients with shorter disease duration. Relative to surgical therapy, these effects are modest, and realistic expectations must be set for patients with more severe or long-standing disease at baseline. However, even if disease course is not reversed, there may be other important quality of life or health consequences that occur as a result of lifestyle change, making it nonetheless an important point of discussion for all diabetic patients.

—Kristina Lewis, MD, MPH

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