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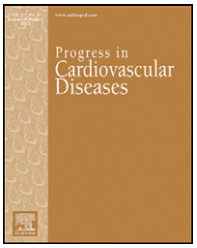

The Look AHEAD Trial: Implications for Lifestyle Intervention in Type 2 Diabetes Mellitus

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ABSTRACT

Given the array of adverse health consequences of obesity, including increased risk for type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD), the Look AHEAD trial (N = 5145) was conducted to test the hypothesis that an intensive lifestyle intervention (ILI) for weight loss would achieve significantly greater reductions in CVD morbidity and mortality than a control condition of diabetes support and education (DSE) among participants with T2DM. A number of significant and long-term improvements were observed for ILI, including body weight, physical fitness and physical function, glucose control, quality-of-life (QoL), and healthcare costs. However, ILI did not significantly reduce CVD-related morbidity/mortality (i.e., CVD death, non-fatal MI, non-fatal stroke, hospitalized angina) after nearly 10 years of follow-up. There was a suggestion of heterogeneity of response based on the history of prior CVD at baseline ($p = 0.06$). Despite the overall lack of CVD risk reduction, ILI remains important for care of patients with T2DM, particularly when accompanied by medication management. In particular, ILI may be an appealing option for patients wanting to minimize medication intensification. Also, ILI carries with it other potential benefits important to patients (e.g., improvements in physical functioning and QoL). Based on data from other trials, intensive medication management, such as tight glycemic control, is not without potential risks, which should be weighed in making treatment decisions. Future research is needed to determine if results observed in this trial would be replicated among younger patients, those without established T2DM, and/or those with no pre-existing CVD.

Obesity, cardiovascular disease (CVD), and type 2 diabetes mellitus (T2DM)

Obesity is associated with increased risk factors for CVD, including hypertension (HTN), dyslipidemia, and T2DM.[1] In addition, obesity is associated with a variety of other clinical conditions and psychosocial outcomes, such as osteoarthritis, certain types of cancers, sleep apnea, depressive symptoms, diminished physical functioning, and reduced quality-of-life (QoL).[2–7] Obesity is related to increased overall mortality that is primarily driven by deaths attributable to CVD, cancers, and diabetes/kidney diseases.[8] Finally, obesity is one of the key

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Abbreviations and Acronyms

BMI = body mass index

BP = blood pressure

CVD = cardiovascular disease

DSE = diabetes support and education

HTN = hypertension

ILI = intensive lifestyle intervention

LDL-C = low-density lipoprotein cholesterol

MI = myocardial infarction

PA = physical activity

QoL = quality of life

$SPPB_{exp}$ = expanded short physical performance battery

T2DM = type 2 diabetes mellitus

risk factors, along with poor diet, physical inactivity, and others, for the highly prevalent and expensive chronic disease burden in the United States.[9]

There are numerous benefits of weight loss for the prevention and control of T2DM and other CVD risk factors.[1] Modest reductions in body weight are associated with significant reductions in the incidence of HTN and T2DM.[10–14] Results from the Diabetes Prevention Program (DPP) demonstrated a 58% reduction in T2DM risk with modest initial weight losses of approximately 7 kg.[10] Modest weight loss is also associated with improvements in low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol, triglycerides, insulin level, and glycemic control.[1,15] Given the documented benefits of modest weight loss for the prevention and management of chronic health conditions and CVD risk factors, current clinical guidelines recommend 5%–10% weight reduction for overweight and obese patients.[1] In particular, the guidelines identify lifestyle modification targeting dietary changes, physical activity (PA), and other behavioral strategies to promote weight loss as an appropriate initial intervention for most overweight and obese patients.[1]

However, long-term data on weight loss, especially from controlled trials, are scarce. A recent systematic review and meta-analysis of lifestyle interventions for patients with or at risk for T2DM, including major results from Look AHEAD, concluded that there was no evidence of benefit on all-cause mortality, and insufficient evidence on CVD and microvascular outcomes.[16] The authors noted that improvement in some secondary outcomes did not persist beyond the intervention phase and the clinical significance of findings was not clear. The secondary outcomes considered in this analysis were limited to body composition, metabolic variables, PA, and dietary intake. Other outcomes important to patients, such as QoL, were not examined.

The Look AHEAD trial of weight loss in T2DM

Rationale

When the participating centers in Look AHEAD were initially funded in 1999, relatively short-term lifestyle interventions had been shown to improve CVD risk factors and obesity-related metabolic abnormalities. It was unknown whether these improvements could result in reductions in CVD-related morbidity or mortality, or whether long-term weight loss interventions could have adverse consequences.[17] This was, and is, particularly relevant to patients with T2DM, who experience elevated CVD risk. To address this gap in the literature, the Look AHEAD trial was designed and conducted to examine the effects of weight loss through behavioral means on CVD morbidity and mortality.[18] Look AHEAD was designed to test the hypothesis that an intensive multi-component lifestyle intervention compared to diabetes support and education would reduce the incidence of CVD outcomes and improve other health parameters, including CVD risk factors, mortality, diabetes-related metabolic risk factors and complications, safety of interventions, indices of general health, QoL, and economic consequences among participants with T2DM.[18]

Description

Participants

Details of the Look AHEAD protocol, intervention protocol, and sample characteristics have been described previously.[18–20] Briefly, participants had T2DM and could be using any type of glucose-lowering medication, although the proportion of participants using insulin was limited to <30%. Participants with a history of certain types of CVD, including uncomplicated myocardial infarction (MI), coronary artery bypass surgery, percutaneous coronary intervention, and chronic stable angina pectoris, were included if the diagnosis or condition occurred at least 3 months prior to screening, in order to increase generalizability and to increase the expected event rate. There were extensive eligibility criteria, which are summarized in Table 1.

The study sample included 5145 participants randomized to either an intensive lifestyle intervention (ILI) or diabetes support and education (DSE). The average age of participants was 58.7 years, 60% were women, 37% were racial/ethnic minorities, and the mean body mass index (BMI) was 36.0 kg/m^2.[20] The median duration of T2DM was 5 years, mean baseline A1c was 7.3%, and 14% of patients reported a history of CVD at baseline.

Outcomes

The primary outcome was a composite variable of CVD morbidity and mortality consisting of CVD death, non-fatal MI, non-fatal stroke, and hospitalized angina.[21,22] When the intervention was stopped in September 2012, the median follow-up was 9.6 years. In addition to the primary outcome of CVD events, Look AHEAD included additional composite CVD outcomes as well as numerous additional clinical outcomes, including body weight, physical fitness, glycated hemoglobin, lipids, BP, medication use, diabetes complications, and health care cost, among others.

Treatment conditions

The intervention protocol has been described in detail elsewhere.[19] ILI aimed at achieving and maintaining at least a 7% weight loss by focusing on reduced caloric intake and increased PA. The program included frequent contact throughout the trial, with both group and individual sessions, a calorie goal of 1200–1800 kcal/day (<30% of calories from fat and >15% from protein), use of meal replacement products, and at least 175 min per week of moderate intensity PA. A toolbox of