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Cardiovascular Effects of Intensive Lifestyle Intervention in Type 2 Diabetes

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Abstract

Look AHEAD (Action for Health in Diabetes) was a randomized controlled trial that examined the impact of long-term participation in an intensive weight loss intervention on cardiovascular disease (CVD) morbidity and mortality in people with type 2 diabetes (T2D). The results from this trial suggest that intensive lifestyle interventions are effective in helping patients to achieve management of cardiovascular risk factors and reducing the need to initiate medication usage to manage these conditions, though the benefits in terms of the prevention of CVD morbidity and mortality beyond those achieved through aggressive medical management of hypertension and dyslipidemia is not clear. Additional benefits of participation in an intensive lifestyle intervention such as lowered chronic kidney disease risk, blood pressure, medication usage, improved sleep apnea, and partial remission of diabetes are discussed.

Keywords

Cardiovascular disease; Look AHEAD trial; Type 2 diabetes; Lifestyle intervention; Weight loss; Risk factors

Introduction

Excess bodyweight is at the core of secondary pathologies including cardiovascular disease (CVD), hypertension, stroke, hyperlipidemia, glucose intolerance, type 2 diabetes (T2D), some types of cancer, sleep apnea, and gallbladder disease [1–3]. Health problems related to obesity are expected to continue to rise at alarming rates. It is projected that by 2030 that the number of deaths caused by CVD will grow to more than 23.6 million [4, 5] and the prevalence of T2D will reach nearly 600 million worldwide by 2035 [6].

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Compliance with Ethics Guidelines

Conflict of Interest Craig A. Johnston, Jennette P. Moreno, and John P. Foreyt declare that they have no conflict of interest.

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The risk of comorbid diseases, such as CVD and T2D, progressively increases as bodyweight rises from a normal range to overweight and obesity [7, 8]. Even moderate increases in weight are related to CVD [7–12] and heart failure [13]. In addition, obesity affects health in various ways. For example, it accelerates the progression of established coronary artery disease [14], increases the risk of heart failure [13], and is associated with atrial fibrillation [15]. Excess bodyweight adversely impacts risk factors of CVD such as hypertension, dyslipidemia, and metabolic syndrome.

People with T2D experience increased rates of morbidity and mortality compared to their non-diabetic counterparts and die on average 8 years before those without diabetes which is, in large part, due to CVD [16, 17]. The triad of hyperglycemia, hypertension, and hyperlipidemia underlie the increased risk for CVD within T2D [16]. CVD risk intervention in individuals with T2D primarily involves achieving optimal care goals in their management [16, 18, 19]. Lifestyle interventions which promote weight loss through diet modification and increased physical activity are recommended as there is evidence supporting their use to improve blood glucose, blood pressure, and lipid levels [19].

Although obesity has been identified as the only central and major modifiable risk factor for CVD [1, 2], there is a paucity of long-term studies that have demonstrated an impact of weight loss on CVD risk factors [20]. Strategies that improve interventions in individuals with T2D include behavioral components and lifestyle management techniques [21, 22]. The Look AHEAD (Action for Health in Diabetes) study examined the long-term impact of weight loss in T2D using a lifestyle management program. This randomized controlled study was conducted for an unprecedented 9.6 years [22, 23]. Overall, the study demonstrated long-term maintenance of clinically significant weight loss in individuals with T2D [24••].

Look AHEAD Study Methodology

The Look AHEAD study examined the impact of intentional weight loss achieved through participation in an intensive behavioral lifestyle intervention designed to promote weight loss on cardiovascular morbidity and mortality in overweight and obese individuals with T2D [25]. The principal goal of the Look AHEAD study was to determine the impact of the intensive lifestyle intervention on deaths due to heart attack and stroke as well as non-fatal heart attacks and strokes during the study period of 11.5 years [25]. Due to a lower than expected event rate in the control group, the primary outcome was revised to include hospitalizations for chest pain and the study period was extended to 13.5 years [26]. Secondary outcomes included (1) death from cardiovascular causes, nonfatal heart attacks, or stroke; (2) all cause mortality, heart attacks, stroke, hospitalizations for chest pain, coronary artery bypass grafting, percutaneous coronary intervention, hospitalization due to heart failure, or peripheral vascular disease; and (3) all cause mortality [25]. The trial was conducted at 16 sites across the United States. A total of 5145 overweight and obese participants with T2D were randomized to one of two conditions: (1) Diabetes Support and Education (DSE) or (2) Intensive Lifestyle Intervention (ILI) [27]. Only 14 % of participants had a previous history of CVD [27]. The DSE condition received three 1-h group meetings each year which educated participants on diet, physical activity, and social support; however, behavior change strategies were not taught [28]. Participants in the ILI condition were

encouraged to achieve a sustained weight loss of 10 % of initial weight and to gradually increase physical activity levels to at least 175 min of moderately intense physical activity per week [29]. All participants continued to receive medical care from their physicians, which included management of diabetes and cardiovascular risk factors [25]. A detailed description of study design and the intensive lifestyle intervention and rationale supporting it have been described elsewhere [25, 28, 29]. Look AHEAD is one of the only studies to examine, in a randomized controlled trial, the impact of weight loss on CVD morbidity and mortality in people with T2D.

Primary Outcomes

Despite greater weight loss in the ILI than the DSE group at every annual assessment, the Look AHEAD intervention was ended after 9.6 years due to a lack of significant differences in cardiovascular-related morbidity or mortality between participants in the ILI and DSE [22]. While participants in the ILI did not significantly reduce the rate of CVD morbidity compared with DSE, many other benefits were experienced. For example, participants in the ILI group showed initial improvements in symptoms of sleep apnea [30], cardiorespiratory fitness [31], physical functioning [32], body image [33], and health-related quality of life [34].

It is possible that the benefits resulting from early improvements in CVD risk factors in the ILI will take much longer to appear [35••]. For example, overweight and obese individuals with T2D are at increased risk for renal dysfunction due to poor control of blood glucose levels which also puts these individuals at risk for cardiovascular mortality [36–38]. Improving the control of blood glucose levels in people with T2D is associated with improvements in microvascular complications such as renal dysfunction. Participants in the ILI had a 31 % lower risk of occurrence of chronic kidney disease compared to participants in the DSE [35••]. Improvements in weight, HbA1c, and blood pressure were associated with decreased risk of kidney disease. Because chronic kidney disease is a risk factor for CVD-related mortality, specifically heart failure, reduction in one’s risk of chronic kidney disease may eventually lead to reduced mortality [36, 37]. As a result, it is possible that the Look AHEAD trial was ended before the long-term health benefits of participation in an intensive lifestyle weight loss intervention, and ultimate reduction in mortality due to CVD could be observed. The following is a brief description of some of the additional outcomes associated with the Look AHEAD intervention.

CVD-Specific Risk Factors

Macrovascular Risk Factors for CVD

People with T2D are at increased risk for having hypertension and dyslipidemia [39]. The development of comorbid hypertension or dyslipidemia in people with T2D significantly increases the risk of developing both macrovascular and microvascular complications such as stroke, coronary artery disease, peripheral vascular disease, retinopathy, and nephropathy [40, 41]. There is strong evidence that achieving optimal management of hypertension and dyslipidemia is efficacious in the prevention or slowing of CVD in patients with T2D [16, 42]. Overall, the treatment of hypertension and dyslipidemia in people with T2D and the

frequency of treatment with antihypertensive medications have improved greatly in recent years [39].

At baseline, 84 % of Look AHEAD participants had a history of hypertension or were currently taking an antihypertensive medication, and 56 % of men and 43 % of women reported a history or treatment of high cholesterol [27]. Participants in the ILI significantly improved their systolic and diastolic blood pressure compared to participants in the DSE at 1 year [43] and improvements in systolic blood pressure were maintained throughout the study [22, 44]. No differences in improvements in ankle-brachial index, a marker peripheral artery disease [45], were observed between groups after 4 years of participation in the Look AHEAD trial [46]. However, differences in systolic blood pressure among arterial sites, which is a marker of atherosclerosis [47–49], were smaller for participants in the ILI compared to the DSE suggesting a reduction in the progression rate of localized stenosis [46].

In terms of cholesterol, participants in both the ILI and DSE demonstrated similar decreases in LDL cholesterol at 1 year [43]. Participants in the ILI also demonstrated significant improvements in HDL cholesterol and triglycerides relative to participants in the DSE; however, at year 4, only differences in HDL remained significant between groups and these differences were not maintained at the end of the intervention [22, 43, 44]. Also, at the end of the intervention, LDL levels were actually lower among DSE participants compared to ILI participants [22]. Improvements in blood pressure and lipid levels corresponded with significantly fewer participants initiating the use of antihypertensive and lipid-lowering medications in the ILI compared to the DSE [50].

Despite initial improvements in hypertension, inter arterial systolic blood pressure measurements, and HDL cholesterol, there were no differences in cardiovascular events or CV-related mortality between participants in the ILI and DSE after 9.6 years when the intervention was ended [22]. One possible explanation for this is many patients in the ILI and DSE were being treated with an antihypertensive and/or lipid-lowering medication. The proportion of participants in both conditions meeting ADA treatment goals for the management of hypertension and LDL cholesterol significantly increased in both groups [44]. The results from the Look AHEAD trial suggest that intensive lifestyle interventions are effective in helping patients to manage cardiovascular risk factors and reduce the need to initiate the use of medications to manage these conditions, though the benefit in terms of the prevention of CVD morbidity and mortality beyond the benefits achieved through aggressive medical management of hypertension and dyslipidemia is not clear.

Cardiorespiratory Fitness

Insufficient levels of fitness and physical inactivity are risk factors for CVD events and cardiovascular mortality [51–54]. Increased physical activity reduces cardiovascular risk factors [52] and reduces the need for medical management of T2D by inducing weight loss and improving lean body mass, thereby improving glycemic control, blood pressure, and lipid levels [55, 56]. Specifically, programs that incorporate and combine both aerobic and resistance exercise training have shown the most benefits for the control of T2D [56, 57]. In addition, programs that include behavioral and lifestyle modification have shown reductions

in various CV risk factors in individuals with T2D [43, 44, 58]. In Look AHEAD, participants in the ILI condition were encouraged to incorporate exercise into their daily routines [29]. ILI participants improved fitness levels by engaging in home-based exercises that were designed to progressively increase the amount of physical activity engaged in weekly as well as the intensity level [29]. At the end of year 1, both the ILI and DSE groups demonstrated fitness improvements; however, the ILI group experienced significantly greater fitness improvements compared to the DSE [43]. These improvements were maintained long-term with ILI participants maintaining their fitness levels at 5.1 % above their baseline levels, whereas DSE participants fell below their baseline levels by 1.1 % at year 4 [44]. African American and American Indian/Native American/Alaskan Native participants exhibited smaller improvements in fitness relative to Whites and Hispanics [31].

The observed improvements in fitness levels of the ILI group in years 1 and 4 were also associated with improvements in glycemic control [31] and were independent of changes in weight [31, 43, 44]. These findings suggest that increasing physical activity and cardiovascular fitness levels in individuals with T2D has important health benefits even if individuals are not successful in losing weight. These results are encouraging as weight loss is difficult for many people and may often seem like a daunting endeavor to undertake, but gradually increasing physical activity through the use of progressive goal setting may be a more palatable goal for many people with T2D.

Biomarkers Related to CVD Risk

Inflammatory markers and markers of adipose tissue health (e.g., high sensitivity C-reactive protein, adiponectin, plasminogen activator inhibitor-1, and NT-pro brain natriuretic peptide) are associated with increased CVD risk in people with T2D. Participants in the ILI demonstrated improvements in markers of inflammation and adipose tissue health at 1 year suggesting a decreased risk of CVD compared to participants in the DSE [59–62]. Statin therapy and participation in the ILI appeared to have substantial additional benefits in reducing markers of inflammation over statin therapy alone or participation in the ILI alone [63]. These results underscore the importance of lifestyle changes (e.g., weight loss and increased physical activity) and aggressive medical management of CVD risk factors in people with T2D.

Additional Health Issues to Consider

Diabetes Remission

T2D is often considered an incurable condition; however, results from the Look AHEAD trial suggest that participation in an intensive lifestyle intervention focused on weight loss is effective in helping some individuals achieve partial or complete remission of their T2D and maintain these improvements long-term [64•]. Higher remission rates were observed among participants who were more recently diagnosed with T2D, those not prescribed insulin and those with lower initial HbA1c levels. Greater weight loss and increases in physical activity levels were also associated with achievement of partial or complete remission [64•]. Overall, 5.8 and 3.4 % of participants in the ILI achieved complete remission at 1 and 4 years compared to 11.5 and 7.3 % who achieved partial or complete remission at years 1 and 4,

respectively [64•]. Long-term improvements in blood glucose levels to prediabetic or nondiabetic levels are likely to significantly reduce the risk of microvascular complications [65, 66].

Reductions in Medication Usage

Because few people with diabetes are successful in implementing lifestyle changes such as reduced caloric intake and increased physical activity levels on a long-term basis, many people with diabetes require multiple medications to optimally manage their diabetes, hypertension, and lipid levels [67–69]. However, the use of multiple medications is associated with decreased quality of life, greater risk of adverse medication side effects, and increased medical expenses [70, 71].

At the end of year 1, participants in the ILI demonstrated significant reductions in their use of glucose-lowering medications compared to participants in the DSE [43, 50]. Specifically, 52 % of participants in the DSE were taking two or more diabetes medications at the end of year 1 compared to 37 % of participants in the ILI [50]. Additionally, 25 % of participants in the ILI were taking no diabetes medications compared to only 12 % of DSE participants [50]. Use of antihypertensive medications remained unchanged at the end of year 1 for participants who received the intensive behavioral lifestyle intervention, while participants in the DSE increased their use of antihypertensive medications [43]. Both groups increased their use of lipid-lowering medications, though participants in the ILI demonstrated smaller increases than participants in the DSE [43]. Overall, use of diabetic, antihypertensive, and lipid-lowering medications was lower in the ILI compared to the DSE at the end of year 1 with ILI participants taking an average of 3.1 medications compared to 3.6 medications in the DSE [50]. The reduction in medication usage was associated with a significant decrease in total medication costs for the ILI, while costs increased for participants in the DSE [50].

At 4 years, the beneficial impact of the ILI on medication use persisted [44]. Specifically, a greater proportion of participants in the ILI using diabetes and antihypertensive medications at baseline were able to discontinue the use of their medications by year 4 [44]. Of those not using these medications at baseline, a lower percentage of ILI participants required initiation of medication use compared to the DSE. While lipid-lowering medication use increased in both groups, fewer participants in the ILI initiated use of these medications compared to the DSE at 4 years. Overall, participants receiving an intensive behavioral intervention that promoted weight loss and increased physical activity experienced significant improvements in their glycemic control and cardiovascular risk factors which corresponded with a reduced need for medications to manage these conditions, and the beneficial impact on medication use was maintained long-term [43, 44, 50].

Sleep Apnea

Excess weight gain has been linked with the development of sleep apnea and T2D [72–74] which are also both associated with increased risk for cardiovascular morbidity and mortality [75–78]. Within the Look AHEAD trial, 86 % of participants had obstructive sleep apnea [79]. Greater numbers of nightly apneas and hypopneas were significantly associated with a higher likelihood of having a stroke [79]. However, participation in the ILI

significantly improved symptoms of sleep apneas and led to remission of obstructive sleep apnea in a significant proportion of participants compared to the DSE at 1 year [30]. These results were maintained at 4 years, despite weight regain in about half of participants [80]. Significant weight loss was one of the strongest predictors of improvements in symptoms of sleep apnea at 1 and 4 years [30, 80]. The impact of amelioration of sleep apnea symptoms and the subsequent impact on risk for CVD morbidity and mortality have not been fully explored. These results suggest that participation in an intensive lifestyle intervention is effective in helping participants to lose weight and decrease their symptoms of sleep apnea which may be related to other improvements in cardiovascular-related health outcomes.

Depression

Depression occurs at higher rates in people with T2D and puts individuals at greater risk for adverse CVD outcomes [81–83]. This is concerning as people with T2D are already at increased risk for CVD mortality [16]. Furthermore, some studies have shown that use of antidepressants such as tricyclic antidepressants and monoamine oxidase inhibitors may increase CVD risk [84]. The Look AHEAD trial offered the unique opportunity to examine the association between depression, antidepressant use, and CVD risk factors in people with T2D who were involved in an intensive lifestyle weight loss intervention [85]. Overall, depressive symptomatology and antidepressant use were associated with several risk factors for CVD such as elevated blood pressure and use of antihypertensive medications, smoking, obesity, and lower physical activity levels [85]. Antidepressant use was also associated with elevated lipids and use of lipid-lowering medications [85]. In addition, depressive symptomatology and antidepressant use were predictive of having CVD risk factors (i.e., smoking, obesity status, elevated HbA1c, blood pressure, lipid levels, or use of medications to manage glucose, blood pressure, and lipid levels) in the subsequent year for participants in both the ILI and DSE conditions [86].

While depressive symptoms were indicative of increased CVD risk across groups, participants with depressive symptoms in the ILI experienced significant decreases in their symptoms of depression compared to participants with depressive symptoms in the DSE, especially in year 1 of the study [87, 88]. In addition, the ILI appeared to protect participants without depressive symptoms from developing mild or greater symptoms of depression relative to the DSE [87]. Participants with depression and without depression in the ILI experienced significant weight loss [88]. Overall, these results not only suggest the need for more aggressive monitoring of CVD risk in diabetic patients reporting depressive symptoms but also indicate that participation in an intensive behavioral weight loss program may have a beneficial impact on depressive symptoms and weight loss which may have important implications for the CVD risk of patients with depression and T2D [86–88].

Conclusion

Participants receiving an intensive behavioral weight loss intervention experienced initial improvements in conditions known to increase risk for CVD such as chronic kidney disease [35••], diabetes [64•], hypertension [22, 43, 44], dyslipidemia [43, 44], sleep apnea [30], and depression [87]. Although long-term differences in CVD morbidity and mortality were not

shown [22], it is possible that the benefits associated with initial improvements in these conditions, particularly conditions related to microvascular complications of T2D, may take longer to become apparent [35••]. As a result, it is possible that the Look AHEAD intervention was ended before the long-term health benefits of participation in an intensive lifestyle weight loss treatment could be observed.

The Look AHEAD study is the largest and longest randomized controlled trial for weight loss in people with T2D [23]. The Look AHEAD trial demonstrated that sustained long-term weight loss is possible for people with T2D. Although the differences in weight loss outcomes between the ILI and DSE conditions diminished over time [22], significant initial improvements were demonstrated across multiple areas of health including physical functioning [89], mobility [32, 90], quality of life [34], and medication usage [43, 44, 50], and a significant proportion of individuals experienced partial remission of their diabetes [64•]. The impact that the treatment of obesity has on CVD risk factors and T2D is clearly demonstrated through this study. The challenge is to provide intervention of this type in multiple settings including hospitals, community centers, and rural clinics.

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