

Intensive Lifestyle Changes Improve CV Risk Profile in Overweight Patients with Diabetes

For overweight patients with type 2 diabetes mellitus (T2DM), a program of intensive lifestyle intervention is more effective in promoting weight loss, improving glycemic control, and reducing cardiovascular (CV) risk factors than standard diabetes education, according to 4-year results from the Look AHEAD: Action For Health in Diabetes trial (NCT00017953).

Look AHEAD is the first prospective trial to evaluate the long-term effects of intentional weight loss on CV outcomes in patients with T2DM. Donna H. Ryan, MD, Pennington Biomedical Research Center, Baton Rouge, Louisiana, USA, presented 4-year results from the Look AHEAD trial.

The Look AHEAD trial randomly assigned 5145 overweight patients with T2DM to treatment programs that included diabetes support and education (DSE) and intensive lifestyle intervention (ILI). Patients in the DSE group (n=2575) attended education sessions 3 to 4 times per year on diabetes management, nutrition, and exercise. Patients in the ILI group (n=2570) attended weekly group sessions for 6 months that focused on developing the behavioral skills that are necessary for weight loss, followed by biweekly sessions for an additional 6 months that focused on how to maintain weight loss. The weight maintenance group sessions continued on a monthly basis for an additional 3 years. The primary composite endpoint of the Look AHEAD trial was time to first CV death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for angina.

Mean body mass index (BMI) was 35.9 mg/k² in the ILI group and 36.0 mg/k² in the DSE group at baseline. Patients in the ILI group lost 8.6% of their body weight after the first year of the program and sustained a weight loss of 4.7% through Year 4. By comparison, those in the DSE group lost a significantly smaller percentage of body weight in the first year (0.7%; p<0.0001) and after 4 years (1.1%; p<0.0001).

At 4 years, the ILI program provided greater improvements in fitness, glycemic control, and CV risk factors, such as blood pressure (BP) and high-density lipoprotein (HDL), than the DSE intervention. Compared with DSE-managed patients, patients in the ILI group had a:

- Higher increase in fitness level: 5.4% vs -0.8%
- Greater change in HbA1C level: -0.20% vs -0.08% (p=0.001)
- Greater likelihood of achieving target HbA1C of <7.0%: 57% vs 51% (p<0.0001)
- Greater improvement in systolic BP: -4.66 mm Hg vs -3.41 mm Hg (p=0.01)
- Greater increase in HDL: 3.95 mg/dL vs 2.58 mg/dL (p<0.0001)

Reflecting greater improvements in glycemic control, patients in the ILI group were less likely than those in the DSE group to use diabetes drugs and insulin throughout the 4-year follow-up period (Table 1).

Table 1. Diabetes Medication Use in Look AHEAD.

No Baseline Use				Baseline Use		
Any Diabetes Drug Use						
Year	DSE (n=348)	ILI (n=354)	p value	DSE (n=2208)	ILI (n=2202)	p value
1	33%	10%	<0.0001	97%	89%	<0.0001
2	46%	17%	<0.0001	96%	88%	<0.0001
3	58%	27%	<0.0001	95%	89%	<0.0001
4	66%	40%	<0.0001	96%	91%	<0.0001
Any Insulin Use						
	DSE (n=2167)	ILI (n=2190)	p value	DSE (n=408)	ILI (n=380)	p value
1	4%	2%	<0.0001	91%	80%	<0.0001
2	7%	3%	<0.0001	85%	76%	0.001
3	9%	4%	<0.0001	85%	77%	0.007
4	11%	7%	<0.0001	87%	77%	0.0008

DSE=diabetes support and education; ILI=intensive lifestyle intervention.

The majority of patients in the ILI and DSE groups achieved target BP levels of <130/80 mm Hg (63% vs 60%; $p=0.08$). Patients in the ILI and DSE groups also had similar improvements in triglyceride levels (-22.90 vs -27.51 mg/dL; $p=0.13$) and, after controlling for statin use, similar improvements in low-density lipoprotein (LDL) levels (-12.71 vs -13.78 mg/dL; $p=0.19$). However, patients in the DSE group were more likely than those in the ILI group to achieve an LDL target of <100 mg/dL (64% vs 61%; $p=0.02$).

Future follow-up analyses will focus on the effects of intentional weight loss on CV events, Dr. Ryan said.

Measures of Central Obesity Are Better than BMI for Understanding Cardiometabolic Risk

Studying abdominal obesity provides important clues on the pathophysiology and natural history of diabetes and cardiovascular disease. Nick Wareham, MD, University of Cambridge, Cambridge, UK, described recent insights on abdominal obesity and cardiometabolic risk from the European Prospective Investigation into Cancer (EPIC).

EPIC is a multinational cohort study that was designed to evaluate the relationships between dietary intake and health outcomes, including cancer, diabetes, and CVD, among more than 500,000 participants. As part of the EPIC study, the EPIC-Norfolk cohort included 25,633 men and women aged 40 to 74 years. According to Prof. Wareham, data from the EPIC-Europe and EPIC-Norfolk cohorts have demonstrated three main benefits in studying central obesity.

Understanding Disease Etiology

Compared with BMI as an index of obesity alone, measures of central obesity are a better indicator of cardiovascular risk. In one EPIC-Norfolk study, waist-to-hip ratio and waist circumference quintiles were stronger predictors of future coronary heart disease than BMI quintiles, even after adjusting for classical CV risk factors.

Genetic studies have identified collections of single-nucleotide polymorphisms that increase the risk of obesity when considered in aggregate. In one EPIC-Norfolk analysis, individuals who carried up to 4 risk alleles had a mean BMI of 25.5 kg/m², whereas those with 12 or more risk alleles had a BMI of approximately 27 kg/m². However, persons with abundant risk alleles are not necessarily destined for obesity. Indeed, individuals who

are genetically predisposed to obesity appear to benefit even more from having an active lifestyle than those with few genetic markers for obesity.

Cardiometabolic Risk Prediction

One reason for developing risk prediction tools is to be able to rank individual risk profiles and target therapy to those who are at greatest risk. For instance, the Framingham Risk Score is used to identify patients who are most likely to benefit from statin therapy because they are at the highest absolute risk. Incorporating measures of abdominal obesity may improve current tools that are used to predict the development of diabetes and CVD. In an EPIC-Europe analysis, waist-to-hip ratio was a better predictor of future diabetes risk than BMI quintile. A tool that includes both BMI and waist-to-hip ratio may be able to identify a subgroup of high-risk patients who are most likely to benefit from treatment to prevent progression to diabetes, Prof. Wareham said.

Risk prediction tools can also be used to motivate patients to change their behavior. For example, one simple tool allows patients to calculate their “heart age,” which may differ from their chronological age, based on risk factors, such as cholesterol level, blood pressure, BMI, and smoking history. After learning that their “heart age” may be higher than expected, patients may be more motivated to adhere to therapeutic lifestyle changes. We not only need to investigate what risk information is presented, but also how different ways of presenting risk in a numerical format can influence patient behavior. Going beyond the presentation of numbers, it is possible that visual imaging of the harm that an individual is doing to themselves by adverse lifestyles may also play a role. Patients shown images of their own smoking-related harm, such as an arterial scan showing an atheroma, are more likely to cease smoking. It is possible that a similar tool that highlights a patient’s degree of regional adiposity may motivate them to improve adherence to lifestyle interventions.

Demonstrating Response to Interventions

Waist circumference and waist-to-hip ratio may overtake BMI as the preferred tools for demonstrating response to diet, physical activity, and other lifestyle and therapeutic interventions. Another analysis from the EPIC-Europe cohort showed a prospective association between physical activity levels and change in abdominal adiposity (waist circumference) independently of changes in BMI. In several lifestyle intervention trials, including the Hertfordshire Study, decreased waist circumference was an early indicator of success and improved cardiometabolic