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Target Audience

This educational activity is designed for primary care physicians, internal medicine specialists, endocrinologists, diabetologists, cardiologists, and other healthcare professionals involved in the care and management of patients with type 2 diabetes, insulin resistance, and cardiovascular disease.

Learning Objectives

With information from the latest evidence-based studies, participants should be able to:

- Identify patients with insulin resistance, type 2 diabetes, and/or cardiovascular disease
- Select the most appropriate therapeutic regimen for patients with type 2 diabetes and its macrovascular and microvascular complications
- Identify risk factors for cardiovascular disease in patients with type 2 diabetes and select an appropriate therapeutic regimen

Accreditation

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Grantor

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Additional PPS Staff Disclosures

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Diabetes

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Intentional Weight Loss Improves Cardiovascular Disease Risk Factors in Type 2 Diabetes

The long-term effects of intentional weight loss on cardiovascular disease (CVD) risk reduction in the setting of type 2 diabetes are not known. As such, the Look AHEAD (Action for Health in Diabetes) trial, a National Institutes of Health-funded study, investigated the impact of intensive lifestyle intervention (ILI) on the incidence of major CVD events in overweight or obese adults with type 2 diabetes.

This 1-year trial was conducted at 16 centers in the United States and involved 5,145 individuals with type 2 diabetes, aged 45 to 74 years, with BMI >25 kg/m² (>27 kg/m² if taking insulin). Individuals were randomized to either ILI (n=2,570) or diabetes support and education (DSE) (n=2,575). ILI consisted of weekly group and individual meetings (biweekly after the first 6 months) designed to encourage patient weight loss through counseling in behavioral strategies for decreased caloric intake and increased physical activity. The DSE group attended 3 group sessions during the year after the initial sessions and received diet and fitness information but no counseling.

After 1 year, participants assigned to ILI lost significantly more of their initial weight (mean ± standard deviation [SD]) than participants assigned to DSE (8.6% ± 6.9% vs 0.7% ± 4.8%; P<0.001). Additionally, the individual weight loss goal of >10% of initial weight was met by 37.8% of participants in the ILI group versus only 3.2% of participants in the DSE group. Compared with the DSE group, the ILI group also demonstrated greater mean reductions in waist circumference (6.2 ± 10.2 cm vs 0.5 ± 8.5 cm; P<0.001). Mean fitness, as measured by a submaximal exercise test, increased by 20.9% ± 29.1% in the ILI group and 5.8% ± 22.0% in the DSE group (P<0.001). A1C, systolic and diastolic pressure, triglycerides, high-density lipoprotein cho-

lesterol (HDL-C), and urine albumin-to-creatinine ratio ≥30.0 µg/mg improved significantly in the ILI group compared with the DSE group. Mean A1C was significantly reduced from 7.3% to 6.6% in the ILI group but showed little change (from 7.3% to 7.2%) in the DSE group (P<0.001). Systolic blood pressure decreased from 128 mm Hg to 121 mm Hg with ILI vs 129 mm Hg to 127 mm Hg with DSE (P<0.001). Diastolic blood pressure decreased from 70 mm Hg to 67 mm Hg with ILI vs 70 mm Hg to 69 mm Hg with DSE (P<0.001). HDL-C increased from 44 mg/dL to 47 mg/dL with ILI vs 44 mg/dL to 45 mg/dL with DSE (P<0.001). Triglycerides decreased from 183 mg/dL to 153 mg/dL with ILI vs 180 mg/dL to 165 mg/dL with DSE (P<0.001). There were also significant reductions in the ILI group compared with the DSE group in use of diabetes medications (-7.8% vs +2.2%; P<0.001), use of antihypertensive medications (-0.1% vs +2.2%; P=0.02), and use of lipid-lowering medications (+3.7% vs +9.4%; P<0.001).

Look AHEAD is the first large clinical trial comparing ILI with DSE among individuals with type 2 diabetes. This trial demonstrated that clinically significant weight loss in individuals with type 2 diabetes improves diabetes control and CVD risk factors while reducing the use of diabetes, antihypertensive, and lipid-lowering medications. The study investigators noted that continued follow-up is needed to determine whether these changes can be sustained and whether they reduce long-term CVD risk.

The Look AHEAD Research Group. Reduction in weight and cardiovascular disease risk factors in individuals with type 2 diabetes: one-year results of the Look AHEAD trial. *Diabetes Care*. 2007;30:1374-1383.

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COMMENTARY

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It is well recognized that obesity is associated with cardiovascular (CV) risk, and that even modest degrees of weight loss will improve CV risk factors. However, it is not known whether interventions to lose weight will lead to improvement in outcomes. Furthermore, it may be difficult to achieve and maintain adequate weight loss in a cohort of obese people with diabetes – many of whom are on treatment with drugs that may actually cause weight gain. The Look AHEAD study, funded by the National Institutes of Health, will address this important question. Noted here is the status of the study after 1 year.

The paper reports on the successful recruitment of >5,000 middle-aged people with type 2 diabetes. Those randomized to intensive lifestyle intervention demonstrated significant weight loss that was associated with an improvement in glycemic control, despite reduction in diabetes medications. A wide range of commonly measured CV risk factors improved significantly compared with the control group.

The study, having achieved prespecified goals, will now be allowed to continue. This demonstrated improvement in CV risk bodes well for likely positive outcome in regards to reducing CV events.

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Very Low Birth Weight Is Associated With Impaired Glucose Regulation in Young Adults

Small size at term birth and during infancy has been shown to be associated with increased risks of impaired glucose regulation and cardiovascular disease later in life. Preterm birth is often followed by a postnatal period of prematurity-associated illness, inadequate nutrition, and growth retardation. Preterm birth with very low birth weight (<1,500 g) is also associated with insulin resistance in childhood, yet few studies have examined whether this condition persists into adulthood.

Hovi and colleagues conducted a study to assess the impact of very low birth weight on glucose and insulin metabolism, serum lipid levels, and blood pressure in young adults ranging in age from 18 to 27 years who were born with very low birth weight (600 g to 1,500 g) between January 1978 and December 1985 at Helsinki University Central Hospital, Finland. A matched group of subjects who had been born at term and were not small for gestational age (2,560 g to 4,930 g) was selected for comparison. The 2 groups were similar with regard to age and sex.

A standard 75-g oral glucose tolerance test was conducted in 163 young adults in the very-low-birth-weight group and in 169 controls. Insulin and glucose concentrations were measured at baseline and at 120 minutes after glucose uptake. Cardiovascular events were assessed by measurement of blood pressure and serum lipid levels. Additionally, 150 individuals with very low birth weight and 136 subjects born at term were evaluated for body composition using dual-energy x-ray absorptiometry.

Compared with the term group, very-low-birth-weight subjects were shorter (by 5.3 cm in women and 5.9 cm in men; $P<0.001$). Body mass index was 2.4% ($P=0.29$) and 5.9% ($P=0.02$) lower in women and men with very low birth weight, respectively, than their matched control group. Adjustment for the lower lean body mass, however, did not alter the

relationship observed between the 2 groups for glucose and insulin metabolism.

As compared with the subjects born at term, the very-low-birth-weight subjects had a 6.7% increase in the 2-hour glucose concentration (95% confidence interval [CI], 0.8%-12.9%), a 16.7% increase in the fasting insulin concentration (95% CI, 4.6%-30.2%), a 40.0% increase in the 2-hour insulin concentration (95% CI, 17.5%-66.8%), and an 18.9% increase in the insulin-resistance index determined by homeostatic model assessment (95% CI, 5.7%-33.7%). Subjects with very low birth weight also had an increase of 4.8 mm Hg in systolic blood pressure (95% CI, 2.1-7.4), 4.1 mm Hg in diastolic blood pressure (95% CI, 2.2-6.0), and 2.1 beats per minute (95% CI, -0.9-5.1) in heart rate than those in the term group. Serum lipid levels were similar between the 2 groups.

Hovi and associates concluded that young adults with very low birth weight had significantly higher indexes of glucose intolerance and insulin resistance, and higher blood pressure, compared with those born at term. These differences, however, were not attributable to body size or composition, or fat distribution. The authors suggested that persons with very low birth weight might be more vulnerable to type 2 diabetes and cardiovascular disease later in life, and young adults with very low birth weight might benefit from targeted preventive interventions.

Hovi P et al. Glucose regulation in young adults with very low birth weight. *N Engl J Med*. 2007;356:2053-2063.

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Type 2 Diabetes and Life Expectancy With and Without Cardiovascular Disease

It is known that patients with type 2 diabetes have a greater risk of mortality and morbidity than patients without the disease, including a 2-fold greater risk of cardiovascular disease (CVD). What is not clear is the association of type 2 diabetes with life expectancy with and without CVD.

Using data from the Framingham Heart Study (FHS), a cohort of patients in Framingham, Massachusetts who have been examined biannually and followed for more than 46 years, Franco and colleagues built life tables to calculate the association of type 2 diabetes with life expectancy, with and without CVD, in patients aged ≥ 50 years. The following nonoverlapping follow-up periods were selected from the FHS: 1956-1958, 1969-1973, and 1985-1989, to create a period multistate life table stratified by sex and presence of diabetes. The primary outcome of the study was incident or fatal CVD.

In a comparison of baseline characteristics for both cohorts, one with ($n=493$) and one without ($n=8,540$) type 2 diabetes, the diabetes cohort was older (mean age, 68 vs 59 years), predominantly male (51% vs 43%), and contained fewer smokers (27% vs 41%), with a higher mean systolic blood pressure (149 mm Hg vs 137 mm Hg) and body mass index (27.5 vs 26.0 kg/m²), and a more frequent family history of diabetes (30% vs 16%).

After adjusting for age, marital status, smoking, education level, cancer at baseline, physical activity levels, and the starting date of follow-up, results showed that patients of both sexes with diabetes had a significantly increased risk of developing CVD as well as an increased risk of mortality with CVD, and an increased though nonsignificant risk of mortality without CVD. Compared with women without diabetes, women at a similar age with the disease had a hazard ratio (HR) of 2.56 (95% confidence interval, 2.01-3.27) for developing CVD and HR 2.22 (1.74-2.84) for mortality once CVD had developed ($P \leq 0.05$ for both), and HR 1.30 (0.81-2.10, NS) for mortality without CVD. Men with diabetes had similar but

slightly lower risks vs men without the disease: HR 2.40 (1.90-3.03) for incident CVD and HR 1.69 (1.38-2.07) for mortality once CVD had developed ($P \leq 0.05$ for both), and HR 1.27 (0.79-2.03, NS) for mortality without CVD.

Adjusting for the same variables as noted above plus hypertension, women and men in the diabetes cohort aged ≥ 50 years had an average total life expectancy 8.2 and 7.5 years shorter, respectively, and, for those free of CVD, an average life expectancy 8.4 and 7.8 years shorter, respectively, than the women and men in the group without diabetes ($P \leq 0.05$ for all). Differences between the groups for life expectancy with CVD were small and not significant.

Limitations to the study included the historical character of the FHS data that may limit the extrapolation of findings in the present, particularly with the increase in incidence of diabetes, presenting a possible underestimation of the true association of diabetes and CVD with life expectancy. Also, FHS participants were mainly white; so, results may not apply to other ethnic groups who possibly face an even greater health burden with diabetes. It is also possible that not all patients with diabetes were identified from the data presented, adding to the possible underestimation of the negative association of diabetes with CVD and life expectancy risks.

The authors concluded that the analysis of the large, and continuously followed, FHS cohort in a life table perspective demonstrated a dramatic shortening of total life expectancy and life expectancy free of CVD in patients with diabetes, with a greater association among women. These findings emphasize the importance of diabetes prevention in the promotion of healthy aging.

Franco OH et al. Associations of diabetes mellitus with total life expectancy and life expectancy with and without cardiovascular disease. *Arch Intern Med.* 2007;167:1145-1151.

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CME Activity Evaluation/Registration Form

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	Strongly Disagree	Disagree	Agree	Strongly Agree	
1. The activity met the stated objectives in such a way that I am better able to:					
a. Identify patients with insulin resistance, type 2 diabetes, and/or cardiovascular disease	1	2	3	4	5 6
b. Select the most appropriate therapeutic regimen for patients with type 2 diabetes and its macrovascular and microvascular complications	1	2	3	4	5 6
c. Identify risk factors for cardiovascular disease in patients with type 2 diabetes and select an appropriate therapeutic regimen	1	2	3	4	5 6
2. Overall, the activity was presented in a fair-balanced manner.	<input type="checkbox"/> Yes		<input type="checkbox"/> No*		
* If you checked "No," please explain. _____					
3. Overall, the activity was free from commercial bias.	<input type="checkbox"/> Yes		<input type="checkbox"/> No*		
* If you checked "No," please explain. _____					
4. In reflecting on your practice, what type of impact will this educational activity have?					
<input type="checkbox"/> This program has validated my practice in the treatment of type 2 diabetes and its cardiovascular complications.					
<input type="checkbox"/> Need more information before making a change. (Please specify what information you would require.) _____					
5. What is the largest challenge or unmet educational need in your practice?	_____				

6. What other clinical issues are you and your colleagues challenged by that could be addressed in a CME activity? (Please specify.)	_____				

Thank you for your participation.