

Dyslipidemia and Glucose Dysregulation in Overweight and Obese Patients

DEREK LeROITH, MD, PHD

Professor and Chief

Division of Endocrinology, Diabetes and Bone Disease

Department of Medicine

Mount Sinai School of Medicine

New York, New York

Inactivity and a sedentary lifestyle contribute to overweight, obesity, and cardiometabolic risk. Overweight and obesity can lead to metabolic abnormalities, insulin resistance, type 2 diabetes mellitus (DM), lipid disorders, and cardiovascular disease. Diet and exercise can effectively reverse overweight and obesity and their related comorbidities. Modest weight loss (5%–10%) and modest physical activity (30 minutes a day) are first-line recommendations for the prevention of type 2 DM. Clinical trials have demonstrated that insulin sensitivity can be improved and type 2 DM can be prevented through lifestyle modification and pharmacologic therapy, including antiobesity drugs, antidiabetic drugs, statins, and antihypertensive drugs. The endocannabinoid system plays an important role in regulating metabolism through its effects on food intake at the level of the hypothalamus and on body composition through peripheral effects on adipose tissue. (*Clinical Cornerstone*. 2007;8[3]:38–52) Copyright © 2007 Excerpta Medica, Inc.

Obesity and overweight are growing health care challenges in the world today. It is estimated that >1.1 billion adults are overweight and 312 million of them are obese.¹ The increasing prevalence of obesity in the United States during the period 1991 to 2004 is shown in the **figure**.² Worldwide, obesity is also an increasing problem in children, with ≥155 million children being overweight or obese.¹ Excess weight in patients should not be ignored by primary care physicians owing to the possibility that these patients might have other cardiovascular risk factors as well, in particular, lipid and/or glucose disorders. This article will review the dyslipidemia and glucose dysregulation that occur in overweight and obese patients and will discuss strategies for reducing these risk factors. Some commonly used terminology is given in **Table I**.

OVERWEIGHT AND OBESITY ARE ASSOCIATED WITH CARDIOMETABOLIC RISK

Overweight, defined as a body mass index (BMI) of 25.0 to 29.9 kg/m², and obesity, defined as a BMI ≥30 kg/m², are both associated with cardiometabolic risk. Other measures used to assess obesity include waist circumference (WC) and waist-to-hip ratio (WHR). WC has been measured at different anatomic locations in various clinical

studies (**Table II**)³; however, it is not known whether one measurement site is preferable to any other. BMI provides information about body volume and mass, while WC provides information about body shape (eg, the presence of central adiposity).³ Although BMI and WC are highly correlated (*r* values range from 0.80–0.95),³ using WC as a surrogate for BMI can produce false positives and is not recommended as the only measurement to be used. For example, in the Third National Health and Nutrition Examination Survey, 14% of women and 1% of men had a high WC measurement (men, >40 in; women, >35 in) but a normal BMI (18.5–24.9 kg/m²).³

The presence of increased cardiovascular risk in obese individuals has been hypothesized to be partly related to the amount and distribution of adipose tissue, although the exact mechanisms are not well understood. The impact of obesity on cardiovascular risk was investigated recently in a study that assessed the association between obesity measurements (BMI, WC, and WHR) and the presence of coronary artery calcium and aortic plaque, 2 measures of subclinical atherosclerosis.⁴ Although WC and WHR were both more strongly associated with subclinical atherosclerosis than BMI, the authors observed that only WHR was independently associated with both measures of atherosclerosis after adjustment for cardio-

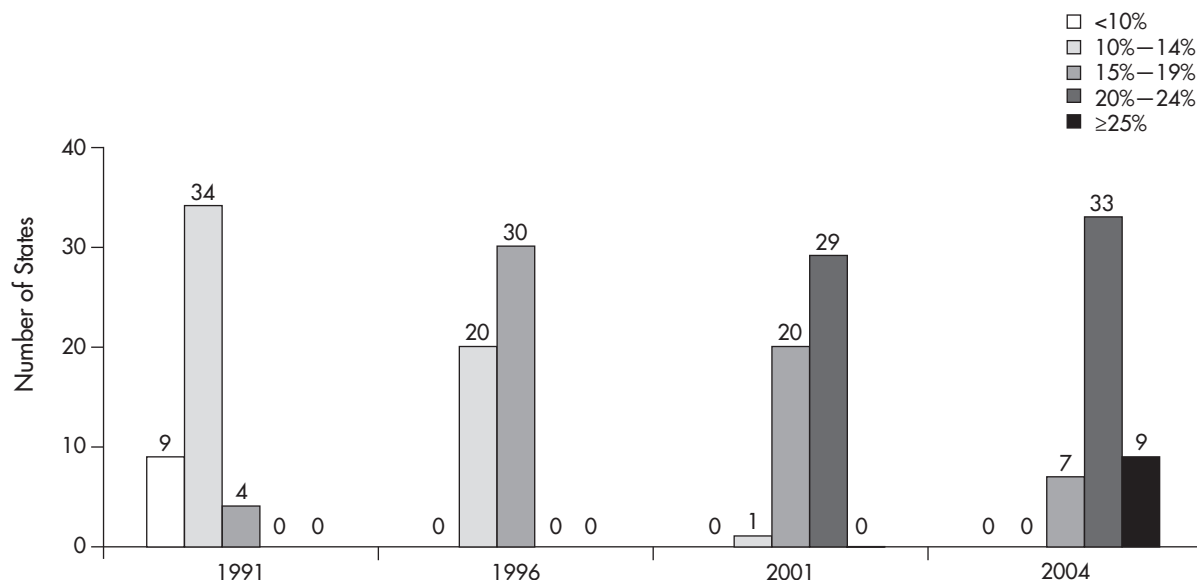


Figure. Increasing prevalence of obesity in the United States, by percentage and number of states. Obesity was defined as body mass index ≥ 30 kg/m². Reproduced with permission from Oxford University Press. Haffner SM. Abdominal obesity, insulin resistance, and cardiovascular risk in pre-diabetes and type 2 diabetes. *Eur Heart J.* 2006;8(Suppl B): B20–B25.

vascular risk factors. Thus, using more than one measurement is recommended.

EXCESS WEIGHT: LIFESTYLE FACTORS LEAD TO LIPID DISORDERS

The increased prevalence of overweight and obesity in the United States has contributed to an increase in mean serum triglyceride (TG) levels. High TG levels in adults also reflect lifestyle factors, such as a high intake of saturated fat and cholesterol, excess weight, and a low physical activity level.⁵ In older adults, the overall trends observed in serum lipids and lipoproteins are steady decreases in both total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) levels⁵; however, these decreases may reflect an increase in the use of lipid-lowering medications such as statins rather than to lifestyle modification (ie, increased exercise or dietary changes).

Physicians should not ignore excess weight in their patients and should routinely screen for cardiometabolic risks, including hyperlipidemia. The management of patients with lipid disorders consists of the following steps: (1) determine whether a patient has a lipid disorder that needs further evaluation and treatment; (2) define the lipid disorder; (3) rule out secondary causes; (4) set treatment goals; (5) initiate therapy based on the treatment goal; and (6) follow-up with the patient.⁶ Disparities

have been observed in the use of lipid-lowering medications among patients with type 2 diabetes mellitus (DM).⁷ Patients less likely to be given lipid-lowering medications include the elderly (aged >75 years), African Americans, and veterans without recently coded heart disease. However, even for patients who are prescribed lipid-lowering medications, up to one third do not reach the target LDL-C goal of <130 mg/dL,⁷ the target for lowering cholesterol in the absence of diabetes or cardiovascular disease (CVD).

KEY POINT

Physicians should not ignore excess weight in their patients and should routinely screen for cardiometabolic risks, including hyperlipidemia.

The National Cholesterol Education Program–Adult Treatment Panel III (ATP III) classification scheme for various lipid levels is shown in **Table III**.⁸ The LDL-C goal is <160 mg/dL for patients at low risk for coronary heart disease (CHD), <130 mg/dL for patients with multiple CHD risk factors, and <100 mg/dL for patients with

TABLE I. DEFINITIONS OF TERMS.

Term	Abbreviation	Definition
Adipokines		Bioactive peptides secreted by adipose tissue; regulate appetite and energy balance, insulin sensitivity, lipid metabolism, blood pressure, and inflammation
Cardiometabolic syndrome		A constellation of maladaptive cardiovascular, renal, metabolic, prothrombotic, and inflammatory abnormalities (visceral obesity and associated insulin resistance/hyperinsulinemia, essential hypertension, diabetic dyslipidemic syndrome, hypercoagulability, hyperuricemia, increased cardiovascular inflammation, and microalbuminuria)
Type 2 diabetes mellitus	Type 2 DM	Fasting plasma glucose level ≥ 126 mg/dL (7.0 mmol/L) or 2-hour 75-g oral glucose tolerance test ≥ 200 mg/dL (11.1 mmol/L)
Impaired fasting glucose	IFG	Fasting plasma glucose level 100 to 125 mg/dL (5.6–6.9 mmol/L); normal: <100 mg/dL
Impaired glucose tolerance	IGT	2-hour 75-g oral glucose tolerance test 140 to 199 mg/dL (7.8–11.0 mmol/L); normal: <140 mg/dL
Insulin resistance	IR	A state in which glucose uptake by adipocytes and muscle cells in response to postprandial insulin secretion is impaired, often with consequent hyperinsulinemia
Metabolic syndrome		A collection of lipid and nonlipid risk factors for coronary artery disease, including abdominal adiposity, hypertension, insulin resistance, atherogenic dyslipidemia (ie, high TG level, low HDL-C level, small dense LDL particles), and prothrombotic and proinflammatory states
Obesity		
Class I		BMI 30.0 to 34.9 kg/m ²
Class II		BMI 35.0 to 39.9 kg/m ²
Class III (extreme)		BMI ≥ 40.0 kg/m ²
Overweight		BMI 25.0 to 29.9 kg/m ²
Prediabetes		Presence of IFG and/or IGT

TG = triglycerides; HDL-C = high-density lipoprotein cholesterol; LDL = low-density lipoprotein; BMI = body mass index.

CHD or type 2 DM. The ATP III guidelines were first published in 2001, since that time several clinical trials have been conducted with cholesterol-lowering therapy. These studies have resulted in additional recommendations for cholesterol management. One important finding sets a reasonable therapeutic option of targeting an LDL-C goal of <70 mg/dL for very high risk patients.⁹ Of course, using pharmacotherapy to achieve lipid goals is associated with a risk of patient nonadherence or noncompliance with lipid-lowering medications. A prospective survey of 12 months of dispensing data in 138 community pharmacies in Sydney, Australia, found that of the 610 patients included in the study, 60% (366)

discontinued their medication over the 12-month period. Half of the discontinuations (183/610; 30%) occurred within the first 3 months, and a quarter (92/610; 15%) occurred within the first month.¹⁰

PREVALENCE OF TYPE 2 DIABETES MELLITUS CORRELATED WITH OBESITY

There is an emerging epidemic of people with insulin-resistant states, including type 2 DM.¹¹ The number of people with DM worldwide is projected to increase from 171 million in 2000 to 366 million by 2030.¹ The prevalence of type 2 DM in the United States is projected to increase by 72%, from 19.7 million cases in 2000 to

TABLE II. ANATOMIC LOCATIONS USED FOR MEASURING WAIST CIRCUMFERENCE IN DIFFERENT CLINICAL STUDIES.³

- Midpoint between the lowest rib and the iliac crest
- The umbilicus
- Narrowest (minimum) or widest (maximum) waist circumference
- Just below the lowest rib
- Just above the iliac crest

33.9 million cases in 2030.¹ A study of current trends in prevalence data and the US Bureau of Census projections indicates an increase of 165%, from 11 million in 2000 (prevalence of 4.0%) to 29 million in 2050 (prevalence of 7.2%).¹² The fastest growing group with diabetes is projected to be black males (+363% from 2000 to 2050), and the largest percentage increase in DM will be among individuals aged ≥ 75 years (men, +437%; women, +271%).¹²

There are ethnic differences in the tendency to develop type 2 DM. In the United States, the prevalence of DM is 21% in Hispanics compared with 3% in non-Hispanic Americans,¹³ and the prevalence in native Hawaiians is 4 times higher than that of the general population.¹⁴ South Asians are 4 to 5 times more likely to develop type 2 DM than Caucasians,¹⁵ and the incidence of DM in the Pima Indians of Arizona is 19 times higher than that of white Americans (prevalence: 40%–50%).¹⁶ The overall prevalence of diabetes in the United States is expected to increase by 24% in the next 12 to 15 years.¹⁷ The prevalence is expected to increase even more for some minority populations: an increase of >100% is expected among Hispanics in the United States.¹⁷

The increase in the prevalence of type 2 DM is correlated with the increase in obesity; 90% of type 2 DM cases are attributable to excess weight.¹

METABOLIC ABNORMALITIES IN OVERWEIGHT AND OBESE INDIVIDUALS

Overweight and obesity often lead to metabolic abnormalities, insulin resistance, type 2 DM, lipid disorders, and CVD. A study of lipid alterations in young, middle-aged, and older white men found that higher BMI was associated in all age groups with higher TG levels, lower high-density lipoprotein cholesterol (HDL-C) levels, and higher TC and non-HDL-C levels.¹⁸ In young men, the higher TC levels were reflected mainly in the LDL-C fraction; in contrast,

TABLE III. NCEP ADULT TREATMENT PANEL III CLASSIFICATION OF LOW-DENSITY LIPOPROTEIN CHOLESTEROL (LDL-C), TOTAL CHOLESTEROL (TC), AND HIGH-DENSITY LIPOPROTEIN CHOLESTEROL (HDL-C).

LDL-C, mg/dL*	
<100	Optimal
100–129	Near or above optimal
130–159	Borderline high
160–189	High
≥ 190	Very high
TC, mg/dL	
<200	Desirable
200–239	Borderline high
≥ 240	High
HDL-C, mg/dL	
<40	Low
≥ 60	High

*Recent clinical trials suggest a reasonable therapeutic option of targeting an LDL-C goal of <70 mg/dL for very high risk patients.⁹

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the TC levels in middle-aged and older men were reflected in the non-HDL-C fraction. Thus, programs to reduce CHD by improving lipid levels should emphasize achieving and maintaining ideal body weight.¹⁸

KEY POINT

A study of lipid alterations in young, middle-aged, and older white men found that higher BMI was associated in all age groups with higher TG levels, lower HDL-C levels, and higher TC and non-HDL-C levels.

The metabolic risk profiles in men and women were examined in a study conducted in 3001 participants in the Framingham Heart Study.¹⁹ In particular, the association of visceral adipose tissue (VAT) with different pathologic conditions was examined in both men and

women. The prevalence of hypertension, impaired fasting glucose (IFG), and metabolic syndrome increased significantly across increasing VAT quartiles for both overweight and obese patients. There was a tendency for the prevalence of metabolic syndrome to be greater in women than in men. At the same time, the prevalence of IFG was greater in men than in women among normal weight, overweight, and obese individuals.

Lemieux et al²⁰ identified a triad of unconventional metabolic risk variables (elevated fasting insulin, apolipoprotein B levels, and small dense LDL particles) that was associated with the risk of developing coronary artery disease. This study, conducted in 185 healthy men, showed that >80% of the men with WC \geq 90 cm and elevated TG levels (\geq 36 mg/dL [2.0 mmol/L]) had the atherogenic metabolic triad associated with CHD. The investigators suggested that patients should be screened routinely for the presence of this triad by measuring WC and fasting TG levels. The same association of WC and fasting TG levels and the presence of the atherogenic metabolic triad was subsequently reported for women²¹ and adolescents.²²

Postprandial hyperlipidemia is a common metabolic abnormality that has been associated with abdominal obesity.²³ During the postprandial phase, atherogenic lipoproteins and their remnants are continually challenging the vascular endothelium.²⁴ It has been suggested that postprandial hyperlipidemia might be more important to the risk of CHD than fasting TG levels^{25–27}; however, measurement of postprandial lipid levels is not readily available to most physicians. A study conducted in 69 men found an association between WC, elevated fasting TG levels, and postprandial hyperlipidemia.²⁸ Thus, the presence of both a WC $>$ 90 cm and an elevated fasting plasma TG level identifies men who have an exaggerated postprandial plasma TG response and an increased risk of developing CHD.

Lipid abnormalities have also been examined in overweight and obese children and adolescents. In a study conducted in 82 obese adolescents, a relationship was observed between lipid levels and insulin resistance (IR).²⁹ The obese adolescents had significantly elevated LDL-C and TG levels and low levels of HDL-C compared with nonobese adolescents. In another more recent study, an abnormal HDL subclass distribution toward smaller particles was observed in overweight children with IR or type 2 DM.³⁰

Obesity is an independent risk factor for CVD, but the conventional BMI classifications and WC cut points that indicate obesity are based on data

from European populations. Studies in South Asians and Chinese populations^{31–33} show an increased risk of type 2 DM and dyslipidemia in these individuals, even with BMI values $<$ 25.0 kg/m². A recent study determined the following BMI cut points of obesity for non-European populations³⁴: South Asian, 21.0 to 28.8 kg/m²; Chinese, 20.6 to 25.9 kg/m²; and aboriginal people, 21.8 to 26.1 kg/m². The International Diabetes Federation also has published WC cut points that indicate central obesity for different ethnic groups (**Table IV**).³⁵ It is important to keep in mind, however, that dyslipidemias do not consistently occur in overweight and obese individuals.³⁶

PREDIABETES CONFERS INCREASED CARDIOMETABOLIC RISK

Prediabetes, defined by the American Diabetes Association³⁷ as the presence of IFG (fasting plasma glucose [FPG] value of 100–125 mg/dL [5.6–6.9 mmol/L]) and/or impaired glucose tolerance (IGT) (2-hour 75-g oral glucose tolerance test [OGTT] value of 140–199 mg/dL [7.8–11.0 mmol/L]), is associated with a substantial risk of progression to type 2 DM. In fact, ~3% to 10% of patients with prediabetes develop diabetes annually.³⁸ The rates of progression to diabetes are similar for patients with either IFG or IGT^{39,40}; however, the combination of IFG and IGT is associated with an even greater risk than either category alone.³⁷ A longitudinal population-based study (n = 3717) found that 26% of subjects progressing to type 2 DM were predicted by their baseline IFG values and that a further 35% who progressed could be identified by their IGT value. The investigators concluded that screening to predict progression to diabetes by IFG alone identifies fewer people than does IGT as assessed by OGTT.⁴¹ Overall, the presence of prediabetes confers a 6-fold increased risk of diabetes compared with normal glucose tolerance.³⁸

Patients with prediabetes also have an increased risk of CVD and cardiovascular and all-cause mortality.^{42,43} In the Australian Diabetes, Obesity, and Lifestyle Study (AusDiab), IFG was associated with a 2.5-fold increased risk of a fatal cardiac event within 5 years, and diabetes or prediabetes accounted for 65% of all heart disease deaths.⁴⁴ In this study, 10,429 individuals (mean age, 51 years) were followed for a mean of 5.2 years. Thirty-four percent of deaths occurring during the follow-up period were due to heart disease. The 5-year

TABLE IV. INTERNATIONAL DIABETES FEDERATION ETHNIC* AND GENDER-SPECIFIC VALUES FOR WAIST CIRCUMFERENCE IN ASSESSING CENTRAL OBESITY.

Country/Ethnic Group		Waist Circumference, cm
Europeans [†]	Male	≥94
	Female	≥80
South Asians (based on Chinese, Malaysian, and Asian-Indian populations)	Male	≥90
	Female	≥80
Chinese	Male	≥90
	Female	≥80
Japanese	Male	≥90
	Female	≥80
Ethnic South and Central Americans	Use South Asian recommendations until more specific data are available	
Sub-Saharan Africans	Use European data until more specific data are available	
Eastern Mediterranean and Middle Eastern (Arab) populations	Use European data until more specific data are available	

*Not country of residence.

[†]In the United States, the National Cholesterol Education Program–Adult Treatment Panel III values (male, 102 cm; female, 88 cm) are likely to continue to be used for clinical purposes.

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death rate for individuals with normal glucose metabolism at baseline was 1.7% versus 12.0%, 5.2%, and 3.9% for those with diabetes, IGT, or IFG, respectively. These results confirm the clinical importance of prediabetes and reinforce the need to target glucose abnormalities to prevent the progression to diabetes.

SEDENTARY LIFESTYLE CONTRIBUTES TO CARDIOMETABOLIC RISK

Inactivity and a sedentary lifestyle contribute to overweight, obesity, and cardiometabolic risk. A prospective study conducted over 5.6 years in 605 middle-aged men found a negative association between energy expenditure during physical activity and progression toward metabolic syndrome independent of aerobic fitness or obesity.⁴⁵ This inverse relationship between physical activity and metabolic risk was also observed in a study conducted in 10-year-old Danish children.⁴⁶ A recent study conducted in >8000 Australian adults found a positive association between television viewing time (as an indication of sedentary behavior) and FPG and 2-hour postchallenge plasma glucose levels.⁴⁷ The strongest associations observed were for the 2-hour postchallenge plasma glucose level and for women. Thus, sedentary behavior appears to be more deleterious in women than in men. Another study

KEY POINT

A study in 173 Australian adults found that sedentary time was positively associated with 2-hour post-challenge plasma glucose levels, while activity of light and moderate to vigorous intensity were negatively associated with glucose levels.

conducted in 173 Australian adults found that sedentary time was positively associated with 2-hour postchallenge plasma glucose levels, while activity of light and moderate to vigorous intensity were negatively associated with glucose levels.⁴⁸ Therefore, even light-intensity physical activity has a beneficial effect on blood glucose levels.

LIFESTYLE CHANGES REDUCE CARDIOMETABOLIC RISK FACTORS

Diet and increased physical activity can effectively reverse overweight, obesity, and their related comorbidities. Modest weight loss (5%–10%) and modest physical

activity (30 minutes daily) are first-line recommendations for the prevention of type 2 DM.³³ Studies published recently^{45,46} provide supporting evidence of the efficacy of both diet and exercise in reversing obesity and obesity-related comorbidities.

A study conducted in 48 overweight patients showed that larger subcutaneous abdominal adipocytes were associated with increased lipid deposition in visceral and hepatic tissues, and this trend promoted the development of IR.⁴⁹ In this study, the trend to IR was reversed both by diet alone and by diet with exercise.

In a 3-month study, 52 obese men were randomized to one of the following groups: diet-induced weight loss, exercise-induced weight loss, exercise without weight loss, or control.⁵⁰ Exercise-induced weight loss without caloric restriction reduced both abdominal obesity and IR. Exercise without weight loss also reduced abdominal fat and prevented further weight gain. The investigators concluded that walking briskly for 60 minutes daily is effective in reducing obesity and IR, even without caloric restriction.

KEY POINT

Walking briskly for 60 minutes daily is effective in reducing obesity and insulin resistance (IR), even without caloric restriction.

In another study,⁵¹ 311 women were randomly assigned to 1 of 4 diets for 12 months: Atkins⁵² (very low in carbohydrate), Zone⁵³ (low in carbohydrate), Lifestyle, Exercise, Attitudes, Relationships, and Nutrition (LEARN)⁵⁴ (low in fat, high in carbohydrate, based on national guidelines), and Ornish⁵⁵ (very high in carbohydrate). Women assigned to the Atkins diet lost more weight and experienced more favorable overall metabolic effects with respect to lipid outcomes at 12 months than women assigned to the other diets. The authors concluded that a low-carbohydrate, high-protein, high-fat diet is a reasonable recommendation for weight loss, at least for the duration of the study.

Four diets with varying glycemic indexes (GIs) were compared in terms of weight loss and cardiovascular risk reduction in 129 overweight or obese young adults.⁵⁶ Participants were randomized to either a high-carbohydrate/low-GI diet, a high-carbohydrate/high-GI

diet, a high-protein/low-GI diet, or a high-protein/high-GI diet. The high-protein and low-GI diets increased body fat loss, but cardiovascular risk reduction was optimized by the high-carbohydrate/low-GI diet.

A clinical trial conducted in 73 obese young adults involved 6 months of intensive intervention followed by a 12-month follow-up period.⁵⁷ The participants were randomized to receive either a low-GI diet or a low-fat diet. Overall, there were no differences in weight loss and body fat changes between the groups. However, in participants with high insulin secretion, the low-GI diet resulted in a greater decrease in weight and body fat, as well as beneficial effects on HDL-C and TG levels. The authors concluded that a low-GI diet may promote a higher degree of weight loss and body fat change than a low-fat diet in obese patients with high insulin secretion.

Finally, a meta-analysis⁵⁸ of 5 randomized, controlled trials that included a total of 447 patients found that, after 6 months, patients assigned to low-carbohydrate diets had lost more weight than those randomized to low-fat diets (weighted mean difference -3.3 kg; 95% CI, -5.3 to -1.4 kg); however, after 12 months, the difference was only -1.0 kg (weighted mean; 95% CI, -3.5 to 1.5 kg). After 6 months, TG and HDL-C levels changed more favorably in patients assigned to low-carbohydrate diets, while TC and LDL-C levels changed more favorably in patients assigned to low-fat diets. The authors concluded that low-carbohydrate, non-energy-restricted diets appear to be as effective as low-fat, energy-restricted diets in inducing weight loss for up to 1 year. However, because of the possibility of unfavorable changes in TC and LDL-C levels, low-carbohydrate diets are not recommended for the prevention of CVD.

KEY POINT

IR is associated with an atherogenic dyslipidemia that confers a high risk of atherosclerosis and CVD.

INSULIN RESISTANCE AND DYSLIPIDEMIA

IR is associated with an atherogenic dyslipidemia that confers a high risk of atherosclerosis and CVD. There appears to be impairment in key modulators of insulin-signaling molecules and cascades with IR, resulting in disordered lipoprotein metabolism.¹¹ As mentioned

earlier, the dyslipidemia associated with IR consists of elevated levels of TG, small dense LDL particles and very-low-density lipoprotein, and decreased HDL-C levels, all of which are risk factors for CVD.¹¹

Adipose tissue has an endocrine function that includes secretion of various bioactive peptides called adipokines that are involved in the regulation of biological functions (eg, appetite, energy balance, insulin sensitivity, lipid metabolism, blood pressure, and inflammation). One hypothesis is that changes in the synthesis and secretion of adipokines contribute to the development of obesity and obesity-related diseases.⁵⁹ Altered secretion of adipokines can result in local inflammation, which contributes to the development of IR. Chronic low-grade inflammation and IR may result in vascular dysfunction (ie, atherosclerosis) and metabolic dysfunction (ie, type 2 DM).⁵⁹ It has been further hypothesized that inflammation is the link between IR, obesity, and type 2 DM.⁶⁰ Recent studies show that obesity is a state of chronic inflammation and is associated with elevated levels of various proinflammatory cytokines. It has also been suggested that adipokines secreted by adipose tissue may directly influence vessel walls by influencing the function of endothelial cells and arterial smooth muscle cells.⁶¹

PREVENTION OF INSULIN RESISTANCE AND TYPE 2 DIABETES MELLITUS

Clinical trials have demonstrated that insulin sensitivity can be improved and type 2 DM can be prevented through lifestyle modification and pharmacologic

therapy (Table V^{39,40,62–65}). In the Diabetes Prevention Program,⁶² 3234 patients with IGT and a BMI >24 kg/m² were randomly assigned to 1 of 3 groups: placebo, metformin, or intensive lifestyle modification (counseling regarding a low-calorie, low-fat diet and moderate-intensity exercise for 150 min/wk). After a mean follow-up of 2.8 years, there was a 58% relative risk reduction in the progression to type 2 DM in the intensive lifestyle intervention group compared with the placebo group, while metformin reduced the progression to type 2 DM by 31% compared with placebo. Lifestyle intervention was effective in both men and women and in all ethnic groups. It was most beneficial in patients aged >60 years, who experienced a relative risk reduction in the progression to type 2 DM of 71%. Lifestyle intervention was almost twice as effective as medication in preventing type 2 DM (58% vs 31%).

KEY POINT

Clinical trials have demonstrated that insulin sensitivity can be improved and type 2 DM can be prevented through lifestyle modification and pharmacologic therapy.

TABLE V. SUMMARY OF MAJOR DIABETES PREVENTION TRIALS.

Study	Study Population	Mean BMI, kg/m ²	Type of Intervention	Relative Risk Reduction, %
Diabetes Prevention Program ⁶²	3234 Patients with IGT	34	Lifestyle modification	58
			Metformin 850 mg BID	31
Finnish Diabetes Prevention Study ³⁹	522 Patients with IGT	31	Lifestyle modification	58
Da Qing IGT and Diabetes Study ⁴⁰	577 Patients with IGT	25.8	Diet	31
			Exercise	46
			Diet + exercise	42
STOP-NIDDM Trial ⁶³	1429 Patients with IGT	31	Acarbose 100 mg TID	25
DREAM Study ⁶⁴	5269 Patients with IGT and/or IFG	31	Rosiglitazone 8 mg/d	60

BMI = body mass index; IGT = impaired glucose tolerance; STOP-NIDDM = Study TO Prevent Non-Insulin-Dependent Diabetes Mellitus; DREAM = Diabetes REDuction Assessment with ramipril and rosiglitazone Medication; IFG = impaired fasting glucose. Reproduced with permission from *American Family Physician*. © Copyright 2004, American Academy of Family Physicians. All rights reserved.

In the Finnish Diabetes Prevention Study,^{39,66} 522 obese patients were randomly assigned to a control group or to an intervention group. The intervention group received intensive individualized instruction on weight reduction, food intake, and increasing physical activity. After a mean follow-up of 3.2 years, the intervention group experienced a 58% relative risk reduction in the incidence of diabetes compared with the control group.

In the Da Qing IGT and Diabetes Study in China,⁴⁰ 577 patients with IGT were randomized to 1 of 3 groups: diet only, exercise only, or diet plus exercise. The exercise-only and diet plus exercise regimens resulted in risk reductions in the progression to type 2 DM of 46% and 42%, respectively, compared with 31% for the diet-only regimen.

In the Study TO Prevent Non-Insulin-Dependent Diabetes Mellitus (STOP-NIDDM),⁶³ patients with IGT who were treated with acarbose showed a 25% relative risk reduction in the progression to type 2 DM. Acarbose is an α -glucosidase inhibitor. When acarbose therapy was discontinued at the end of the study, the incidence of diabetes increased, indicating that this drug therapy must be continued to maintain its preventive effects.

The Diabetes REDuction Assessment with ramipril and rosiglitazone Medication (DREAM) trial⁶⁴ was conducted in 24,592 adults with IGT and/or IFG. Rosiglitazone in conjunction with exercise and nutritional counseling reduced the risk of type 2 DM or death by 60% compared with placebo. Furthermore, rosiglitazone increased the likelihood of regression to normoglycemia by 70% to 80% compared with placebo. The effects of rosiglitazone were of the same order of magnitude as the reductions obtained with lifestyle modification described earlier in this section.

NEW AGENTS FOR REDUCING RISK

The various pharmacologic interventions that have been used to improve cardiometabolic risk factors include antiobesity drugs (eg, orlistat, sibutramine), antidiabetic drugs (eg, metformin, sulfonylureas, thiazolidinediones [TZDs], acarbose), hypolipidemic drugs (eg, statins), and antihypertensive drugs (eg, diuretics, β -blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers). TZDs, which are peroxisome proliferator-activated receptor- γ ligands, act by sensitizing tissues to insulin action.^{67,68} Metformin, a biguanide, acts on hepatic and muscle tissue and is associated with improvements in IR and β -cell function.⁶⁹

The endocannabinoid system plays an important role in regulating metabolism through its effects on food intake at the level of the hypothalamus, as well as body composition through its postulated effects on adipose tissue (**Table VI**).⁷⁰ Increased activity of the endocannabinoid system affects food intake, energy expenditure, regulation of body weight, and glucose and lipid metabolism.⁷¹⁻⁷³ Increased activity at cannabinoid type 1 receptor sites in the brain is associated with intra-abdominal adiposity (as measured by WC) and increased weight.⁷¹ In peripheral sites, increased activity at cannabinoid type 1 receptor sites is associated with cardiometabolic risk factors, such as dyslipidemia and IR.⁷⁴⁻⁷⁸ Dysregulation of the endocannabinoid system is implicated in abdominal adiposity,⁷⁹ and abdominal obesity is associated with increased levels of circulating plasma endocannabinoids. Thus, the endocannabinoid system may represent a possible target for the treatment of abdominal obesity and associated metabolic changes.

Rimonabant, a selective cannabinoid type 1 antagonist, has been shown to improve several metabolic pathologies associated with type 2 DM and CVD risk and concomitantly reduce weight and WC.⁸⁰ Treatment with rimonabant 20 mg produced greater weight loss and reductions in WC than placebo after 1 year.⁸¹⁻⁸³ Rimonabant therapy was also associated with favorable

TABLE VI. EFFECTS OF CANNABINOID RECEPTOR TYPE 1 BLOCKADE ON FOOD INTAKE AND CARDIOMETABOLIC RISK FACTORS.

Type of Blockade	Effect
Central blockade (Hypothalamus)	↓ Food intake
Peripheral blockade (Adipose tissue)	↓ Abdominal fat (waist circumference)
	↓ Triglycerides
	↓ Small dense low-density lipoprotein
	↓ C-reactive protein
	↓ Insulin resistance
	↑ Adiponectin
	↑ High-density lipoprotein

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changes in serum lipid levels and improved glycemic control in patients with prediabetes and type 2 DM.⁸⁴

CONCLUSIONS

Overweight and obesity often lead to metabolic abnormalities, insulin resistance, type 2 DM, lipid disorders, and CVD. Inactivity and a sedentary lifestyle contribute to overweight and obesity, as well as cardiometabolic risk. Studies have shown that diet and exercise can effectively reverse overweight, obesity, and their related comorbidities. Prediabetes, defined as the presence of IFG and/or IGT, is associated with a substantial risk of progression to type 2 DM. Clinical trials have demonstrated that insulin sensitivity can be improved and that type 2 DM can be prevented by lifestyle modification and pharmacologic therapy.

ACKNOWLEDGMENT

The author would like to thank Carol Lewis for her writing and research assistance in the preparation of his manuscript.

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Address correspondence to: Derek LeRoith, MD, PhD, Division of Endocrinology, Diabetes and Bone Disease, Department of Medicine, Mount Sinai School of Medicine, 1 Gustave Levy Place (1055), New York, NY 10024. E-mail: Derek.leroith@mssm.edu

Dialogue Box

EDITORIAL BOARD

Based on the Australian study reported by Simons et al, up to 60% of patients self-discontinue their medications. Any thoughts as to how to improve compliance?

LEROITH

If the patient is taking 2 medications, prescribing a formulation that combines the 2 agents is a common strategy. The downside, of course, is that it potentially hinders the ability to adjust the dosage of the individual components. In primary care, where time is at a premium, it may also be helpful to focus on one issue at a time. In other words, tell the patient that for this particular visit we will focus on cholesterol and lipids and at the next one, we'll talk about dietary therapy or hypertension. Rather than addressing multiple issues at a time, focus on one. Studies querying patients as they leave their doctors' offices have found that 70% of patients don't remember half of what their doctors say. Focusing on one subject at a time is a practical way of dealing with this.

EDITORIAL BOARD

Serum triglycerides are generally measured while fasting. What about postprandial hypertriglyceridemia?

LEROITH

Postprandial triglycerides are very similar to postprandial glycemia. Although serum triglycerides are usually measured in a fasting state, be aware that a normal fasting triglyceride level does not exclude postprandial hypertriglyceridemia. This is important because high postprandial triglyceride levels have been linked to higher levels of pro-inflammatory cytokines, inflammation, and vascular dysfunction in the cardiovascular system.

EDITORIAL BOARD

How lasting an effect does a weight loss of 5% to 10% provide?

LEROITH

If a patient loses 5% to 10% of their weight, within 3 to 6 months, a favorable impact on blood pressure, blood glucose, and lipids is seen. With sustained weight loss, the benefit is maintained for the next year. The problem is that at the 2-year point, many patients regain the lost weight. Some studies have shown, however, that drug treatment of hyperlipidemia and hypertension is easier in these patients, even after they regain the lost weight. There appears to be a prolonged effect over and above the initial reduction in weight.

EDITORIAL BOARD

Do you find it surprising that the elderly are less likely to be prescribed a lipid-lowering agent?

LEROITH

That finding comes from studies which suggest that older patients aren't prescribed the medication they should be getting because physicians seem nervous to push too hard. Statistics also show that older patients don't achieve target cholesterol levels even when started on a lipid medication—this is likely because their physicians say “what is the point?” I remember when I trained, it was felt that for patients 65 or 70 years of age, life expectancy was limited. As a result, we tended not to push medications because of concerns regarding side effects to which older people were felt to be more prone. Since older patients stand to benefit from more aggressive lipid lowering, this attitude really needs to change.

EDITORIAL BOARD

Do you favor a low-carbohydrate, high-protein diet or a high-carbohydrate, low-protein, low-fat diet for weight loss?

LEROITH

In addition to being small, studies comparing these different diets have not looked at patient outcomes in the long term. Many of them have looked at impact on lipid levels, a surrogate marker which may not necessarily correlate with cardiovascular outcomes. For patients

Dialogue Box

with insulin resistance, a low-carbohydrate diet would be expected to favorably impact high-density lipoprotein cholesterol (HDL-C) and triglyceride levels but increase low-density lipoprotein cholesterol (LDL-C) and total cholesterol. When people first started doing these high-fat diets (such as the Atkins diet), the concern was that if a patient with diabetes or metabolic syndrome was given a high-fat diet, they would start to lose weight but their cholesterol and triglycerides would go out of whack. In reality, this didn't really happen to a marked degree because when they lost weight, their insulin resistance improved. To answer your question, I don't prefer any of them because when you go high protein, you can't go too high without including fat. And if you go high carbohydrate and they have metabolic syndrome, then you run into problems with triglycerides. Suffice it to say that the most important thing is reducing caloric intake. I tell our nutritionist to work with the patient on reducing calories and keeping the diet balanced. I never liked rapid weight-loss diets because of rebound—up to 95% of patients regain the weight they lose. Instead, I favor gradual weight loss through lifestyle changes grounded in regular exercise and a reduced intake of calories.

EDITORIAL BOARD

How do you instruct patients to exercise?

LEROITH

First of all, one needs to be careful and make sure the patient doesn't have heart problems. For some patients, an exercise cardiac stress test will be required. Once this issue is resolved, I tell patients to use a treadmill with a monitor, or if they are going to walk in the street, to get a heart rate monitor. Patients need to get their pulse up, depending on their age. I encourage them to get to 75% or 80% of their maximum predicted heart rate. You don't start them at the maximum; rather, you want them to build up to it gradually and work their way up to the target heart rate.

EDITORIAL BOARD

Do patients have to lose weight for exercise to be beneficial?

LEROITH

No. Even without weight loss, if they achieve a high level of aerobic exercise—what we call treadmill fitness—where they get their pulse and oxygen consumption up, they will reduce abdominal fat and prevent further weight gain. Patients who really exercise have a better outcome, which is independent of weight loss.

EDITORIAL BOARD

Do you favor fibrates or niacin for lowering elevated triglycerides?

LEROITH

At the moment, I'm leaning more toward niacin for a number of reasons. First of all, niacin lowers both LDL-C and triglycerides, and raises HDL-C. Second, Niaspan® (KOS Pharmaceuticals, Inc., Cranbury, New Jersey) and some of the newer niacin formulations appear well tolerated. Furthermore, they don't have an adverse effect on glycemic control as we used to think. Finally, I have less concerns adding niacin to a patient already on a statin as I would with adding a fibrate.

EDITORIAL BOARD

Which lipid-lowering drug would you favor in a patient with metabolic syndrome, whose LDL-C level is <100 mg/dL but whose serum triglycerides and non-high-density lipoprotein (HDL) are high?

LEROITH

I would put them on a statin. The evidence in my mind suggests that statins not only have cholesterol-lowering effects but also other positive effects on the cardiovascular system still not completely understood.

EDITORIAL BOARD

Let's say the patient's low-density lipoprotein level on a statin drops to <70 mg/dL but their triglycerides and non-HDL-C remain above. Would you push the dose of the statin higher?

Dialogue Box

LeROITH

No. The statin is not going to raise the HDL level. At that point, I'd add niacin.

EDITORIAL BOARD

What would be your approach to a thin, hypertensive middle-age male with an LDL-C level of 70 mg/dL but a low HDL level in the 20s and elevated triglycerides >200 mg/dL, who doesn't meet the criteria for metabolic syndrome?

LeROITH

Although this patient does not demonstrate the metabolic phenotype in terms of visceral adiposity, he would still meet the criteria for insulin resistance. Such a profile is particularly common among Southeast Asians, Indians, and other Asians—despite having abdominal visceral adiposity, these people are often slim. This patient would have high fasting insulin levels, which are responsible for the hypertension and the high serum triglycerides, and low HDL-C levels. I would be most concerned about the low HDL-C level and the hypertriglyceridemia and likely start the patient on niacin.