Perspectives in Diabetes

The Metabolically Obese, Normal-Weight Individual Revisited

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Nearly 20 years ago, it was suggested that individuals exist who are not obese on the basis of height and weight, but who, like people with overt obesity, are hyperinsulinemic, insulin-resistant, and predisposed to type 2 diabetes, hypertriglyceridemia, and premature coronary heart disease. Since then it has become increasingly clear that such metabolically obese, normal-weight (MONW) individuals are very common in the general population and that they probably represent one end of the spectrum of people with the insulin resistance syndrome. Available evidence also suggests that MONW individuals could account for the higher prevalence of type 2 diabetes, cardiovascular disease, and other disorders in people with a BMI in the 20–27 kg/m^2 range who have gained modest amounts of weight (2–10 kg of adipose mass) in adult life. Specific factors that appear to predispose MONW, as well as more obese individuals, to insulin resistance include central fat distribution, inactivity, and a low Vo_{2max}. Because these factors are potentially reversible and because insulin resistance may contribute to the pathogenesis of many diseases, it is our premise that a compelling argument can be made for identifying MONW individuals and treating them with diet, exercise, and possibly pharmacological agents before these diseases become overt, or at least early after their onset. One reason for doing so is that disorders such as type 2 diabetes may be accompanied by irreversible consequences, e.g., ischemic heart disease and nephropathy, at the time of diagnosis or shortly thereafter. Another is that MONW individuals in general should be younger and more amenable and responsive to diet and exercise therapy than are obese patients with established disease. That long-term diet and exercise can work is suggested by two large studies in which, over 5–6 years, the incidence of diabetes was diminished in nonobese and minimally obese patients with impaired glucose tolerance. Based on these considerations and the emerging worldwide epidemic of type 2 diabetes, we believe that studies to assess whether therapies aimed at young MONW individuals can prevent the development of type 2 diabetes and other diseases, including perhaps obesity itself, are urgently needed. *Diabetes* 47:699–713, 1998

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FFA, free fatty acid; MONW, metabolically obese, normal-weight; TNF-α, tumor necrosis factor-α.

THE METABOLICALLY OBESE, NORMAL-WEIGHT CONCEPT

> A great many disorders including maturity-onset (type 2) diabetes, hypertension, and hypertriglyceridemia are frequently associated with adult-onset obesity and improve with caloric restriction. It is the premise of this brief review that there are patients with these disorders who are not obese according to standard weight tables or other readily-available criteria; but who would also respond favorably to caloric restriction. It is proposed that such individuals might be characterized by hyperinsulinism and possibly an increase in fat cell size compared to patients of similar age, height, and weight and/or to themselves at an earlier time. The possibility is also discussed that inactivity is a contributing factor in some of these individuals and that for them, the appropriate therapy might be exercise. *Am J Clin Nutr* 34:1617–1621, 1981.

This abstract describes what was referred to in the accompanying article (1) as the metabolically obese, normal-weight (MONW) individual. A second article (2) noted that coronary heart disease was more common in these individuals and raised the possibility that small increases in adiposity—such as those that occur with aging—"may cause endogenous hypertriglyceridemia, maturity onset diabetes" and other disorders "to become manifest in genetically predisposed individuals in the absence of appreciable weight gain." In essence, these articles proposed that the definition of obesity based on height and weight needed to be modified. In the intervening years, a remarkable array of evidence has confirmed that MONW individuals exist, that they are very prevalent in the general population (3,4), and that they may be detectable well before the onset of associated diseases. It has also become evident that together with their more obese counterparts, they have what is now referred to as the insulin resistance or metabolic syndrome or syndrome X (5–7). This

review will reexamine the concept of the MONW individual in light of this information. Its relationship to central obesity and to weight gain in adult life will be stressed, as will some of the factors that could be responsible for insulin resistance in these individuals. In addition, potential approaches for identifying and treating MONW individuals with the intent of diminishing their likelihood of developing diabetes and other disorders will be discussed.

Definitions of insulin resistance and obesity. As originally stated by Berson and Yalow (quoted in 7a), "Insulin resistance may be defined as a state (of a cell, tissue, system or body) in which greater than normal amounts of insulin are required to elicit a quantitatively normal response." In intact humans, it has generally been defined on the basis of high levels of plasma insulin, either fasting or during a glucose tolerance test, or by a decreased rate of glucose disappearance during a hyperinsulinemic-euglycemic clamp (see below for more complete discussion). The notion of the MONW individual was based on the finding of high circulating insulin levels in people with coronary heart disease, type 2 diabetes, and other disorders associated with obesity, who were <115% of ideal body weight (equivalent to a BMI of <28 kg/m^2 [8]). Many of the subjects identified had a BMI in the 23–25 range or even lower (1,2). In part because of such observations, a lowering of the BMI cut points for identifying patients in need of caloric restriction has sometimes been recommended (9,10). On the other hand, recent studies, such as the National Health and Nutrition Education Survey (NHANES III [phase 1]) (11), continue to define overweight as a BMI >27.3 in women and >27.8 in men. Likewise, a BMI of 27 has been suggested on the package inserts of recently popular anorexigenic agents as the lower limit for recommending treatment. In light of this, we will use a BMI of 27 as the anthropometric dividing line between normal-weight and overweight people in this review. As will be evident from subsequent sections, however, MONW individuals often have BMIs far below this level.

Additional patient groups with insulin resistance in the absence of obesity. At the time the concept of the MONW individual was first proposed, it included people with hypertriglyceridemia (12,13), type 2 diabetes (14,15), post–myocardial infarction (16,17), and the offspring of patients with hypertriglyceridemia (18). It was also predicted that some patients with essential hypertension and gallstones and physically inactive individuals would fit this classification (1,2). Since then, the list of associated disorders has grown. Notable additions include certain forms of essential hypertension (19–21), gout (22), polycystic ovary disease (23–25), prior gestational diabetes (26), increased plasminogen activator inhibitor (27), and possibly some types of cancer (28,29) (Table 1).

In addition to the groups noted in the preceding paragraph, hyperinsulinemia and insulin resistance have been found in nonobese offspring and other first-degree relatives of patients with essential hypertension and type 2 diabetes. Thus, it antedates these disorders as well as hypertriglyceridemia (18). Data from a recent study (30), in which 148 young offspring of hypertensive and normotensive parents were compared, are shown in Table 2. The subjects averaged 24 years of age and they were lean; indeed, the mean BMI of each group was <22.5 and no individual had a BMI >25. Despite this, offspring with one hypertensive parent had significantly higher plasma insulin and serum triglyceride levels and a higher systolic blood pressure, and they were insulin resistant. Thus, they had many components of the insulin resistance syndrome (5–7,31–33), but they were not obese, based on their weight and height. Hyperinsulinemia, insulin resistance, and elevated plasma triglyceride levels have also been reported in nonobese, normoglycemic offspring and/or first-degree relatives of patients with type 2 diabetes and hypertriglyceridemia (34–37). As will be discussed later, the offspring and other relatives in some of these studies tended to have higher BMIs (34,36,37) or a greater fat mass (35) than did the control subjects to whom they were compared (Table 3).

TABLE 1
Conditions in which hyperinsulinemia and insulin resistance have been observed in nonobese individuals

Condition	Reference
Type 2 diabetes and impaired glucose tolerance	5, 20
Hypertension	5, 19–21
Hypertriglyceridemia/low HDL cholesterol	12, 135, 157
Family history of type 2 diabetes, impaired glucose tolerance, hypertension, or hypertriglyceridema	18, 30, 34–36
Premature coronary heart disease	16, 17
Gout	22
Polycystic ovaries	23–25
History of gestational diabetes	26
Low birth weight	85, 86
Inactivity	107
Central obesity	56, 59
People in general population at increased risk for heart attack in the absence of other identified risk factors	154–157

Hyperinsulinemia and insulin resistance in nonobese individuals in the general population and their association with cardiovascular risk factors. Type 2 diabetes, essential hypertension, and hypertriglyceridemia are common disorders. Thus, the finding of hyperinsulinemia and insulin resistance, both in nonobese patients with these abnormalities and in their relatives, strongly suggests that MONW individuals are very prevalent in the general population. Direct support for this notion was initially provided by two significant studies. In one of them, Hollenbeck and Reaven (3) compared glucose disposal during a euglycemic-hyperinsulinemic clamp and glucose and insulin responses during an oral glucose challenge in 100 nonobese volunteers with normal glucose tolerance. They found that the individuals in the lowest quartile for glucose disappearance during the clamp had the highest insulin response during the glucose tolerance test. This study, which was one of the cornerstones that led to the proposal of syndrome X (5), clearly established that insulin resistance and hyperinsulinemia occur together in a relatively nonobese, normoglycemic population and that they do so very frequently. Subsequently, Zavaroni et al. (4) reported finding modestly higher systolic and diastolic blood pressures and plasma triglycerides and a lower HDL cholesterol level in nonobese male Italian factory workers with hyperinsulinemia (serum insulin >2 SD above the mean of the entire group, i.e., upper decile)

TABLE 2
Metabolic comparison of young adults with and without hypertensive parents

	Parent	
	Normotensive	Hypertensive
Age (years)	24	24
n (M/W)	70/8	64/6
BMI (kg/m^2)	22.3	22.4
Fasting plasma insulin (μU/ml)	8.6	9.9*
Serum or plasma triglycerides (mmol/l)	0.83	1.03*
Plasma glucose (mmol/l)	4.7	4.8
Systolic blood pressure (mmHg)	123	127*
Insulin sensitivity ($10^{-4} \times$ min^{-1}/μU/ml)	13.2	9.4*

Insulin sensitivity is based on minimal modeling of an intravenous glucose tolerance test performed on 38 individuals with normotensive parents and 41 individuals with one hypertensive parent. *$P < 0.05$ vs. subjects with normotensive parents. Adapted from Ferrari et al. (30).

than they did in normoinsulinemic men matched for age and weight (Table 4). In addition, they noted that the hyperinsulinemic individuals had significantly higher plasma glucose levels after an oral glucose challenge. Thus, this important study both confirmed the finding of Hollenbeck and Reaven (3) that hyperinsulinemia and insulin resistance are common in nonobese Caucasian males and established that multiple risk factors for coronary heart disease are more prevalent in such individuals.

MONW individuals are probably mildly obese. Although it remains to be proven definitively, MONW individuals are probably more obese than are individuals of similar height and weight who are not hyperinsulinemic or insulin resistant. Thus, in most, though not all, studies in which nonobese

TABLE 3
BMIs of subjects in studies linking various conditions to insulin resistance in nonobese individuals

Condition	Mean age (years)	BMI (kg/m^2)	
		Control	Insulin resistant and/or with disorder
Studies of patients and relatives			
Type 2 diabetes			
Nondiabetic offspring and relatives			
Ref. 34	46	24.2 (14)	25.9 (13)
Ref. 36	40	24.9 (16)	26.2 (18)
Ref. 35	25	23.6 (20)	23.8 (20)*
Hypertension			
Overt disease			
Ref. 19	36	25.0 (13)	26.0 (11)
Ref. 175	50	27.0 (41)	27.0 (41)
Offspring			
Ref. 30	24	22.3 (78)	22.4 (70)
Polycystic ovaries			
Ref. 25	28	21.3 (8)	22.3 (10)
Ref. 24	29	22.3 (11)	22.9 (8)†
Postmyocardial infarction			
Ref. 16	37	24.3 (10)	24.6 (10)
Ref. 16	54	23.4 (10)	23.6 (10)
General population			
Ref. 3	46	24.1 (75)	26.3 (25)
Ref. 4	39	24.7 (32)	24.7 (32)

Data are means for the number of individuals indicated in parentheses. Control subjects for comparison with patients and their relatives were matched for age, height, and weight. Patients and relatives as a group were insulin resistant compared with control subjects based on plasma insulin measurements (4,16,19,24–30,35,175) and/or rates of glucose disappearance during a hyperinsulinemic-euglycemic clamp (3,19,25,34–36). In the general population studies, insulin-resistant subjects had plasma insulin levels during a glucose tolerance test that were in the upper 10% (3) or 25% (4) for the whole population (see text for details). *From measurements of fat-free mass, it could be calculated that adipose mass of control subjects was 16.3 kg and of insulin-resistant relatives, 18.8 kg. †Intra-abdominal fat mass, measured by CAT scan, was significantly greater in the women with polycystic ovaries.

TABLE 4
Characteristics of Italian factory workers with hyperinsulinemia and normal glucose tolerance

	Normal insulin	Hyperinsulinemia
Age (years)	39	39
BMI (kg/m^2)	24.7	24.7
Insulin (μU/ml)		
Fasting	7	14*
Postglucose (1 h)	35	94*
Glucose (mg/dl)		
Fasting	86	86
Postglucose	94	110*
Triglycerides (mmol/l)	1.2	1.7*
Cholesterol (mmol/l)	4.8	5.1
HDL cholesterol (mmol/l)	1.4	1.2*
Blood pressure (mmHg)		
Systolic	119	126*
Diastolic	78	85*

From 272 men who were studied, a hyperinsulinemic group was defined by having plasma insulin levels 2 SD greater than that of the group as a whole. An equal number of individuals (n = 32) of similar height and weight and with plasma insulin levels within 1 SD of the population mean was used as the normal insulin group. *P < 0.05 vs. normal insulin group. Adapted from Zavaroni et al. (4).

individuals with metabolic obesity were identified, they had a slightly higher BMI or a greater calculated fat mass than did the control subjects with whom they were compared (Table 3). Also, in the one study listed in Table 3 (24) in which it was determined, intra-abdominal fat mass was found to be greater in nonobese insulin-resistant women with polycystic ovaries than in control women. As discussed later (see CENTRALOBESITY), increases in abdominal fat correlate closely with both hyperinsulinemia and insulin resistance in the general population and with the propensity of both obese and nonobese individuals to develop type 2 diabetes and coronary heart disease.

Modest increases in adiposity in adult life and a higher BMI in the subobese range are associated with increased morbidity and mortality. Small increases in adiposity of ~4 kg appear to occur in nonobese men as they proceed from young adulthood to middle age, even in the absence of weight gain (38). Likewise, whatever increase in body weight occurs during this time period is almost always due to an increase in adiposity (38). A relationship between such increases in fat mass in adult life and the development of hypertriglyceridemia (39) and hypertension (40) was proposed more than 25 years ago. Particularly relevant for the MONW concept was a large epidemiological study reported by Abraham et al. in 1971 (40). In it, they noted that individuals who were in less than the 95th percentile for weight as children (9–13 years of age) and who gained sufficient weight to be in the 95–104th percentile as adults (48 years of age) had a 50% greater prevalence of hypertension than did individuals in the 95–104th percentile as children whose relative weight remained the same. More recently, a strong correlation between modest weight gain in adult life (5–20 kg) and the prevalence of type 2 diabetes (41–43) and, to a lesser extent, coronary heart disease (44), gallstones (45), and some forms of cancer (breast and uterus in women; colon in men and to some extent women [28,29,46]) has been observed in both the nurses health study (Fig. 1) and in a cohort of male health professionals. A similar relationship has been found for hypertension (9). The initial weights of the individuals in these studies were not given; nevertheless, it is clear that if they were 5–10% or more below the mean population weight when young, increases in weight in adult life that would have placed them at risk (e.g., 5–10 kg) would not have made them obese based on body weight or BMI criteria. The contribution of even smaller increases in body weight (2.3–4.5 kg) during adult life (after 25 years of age) to the development

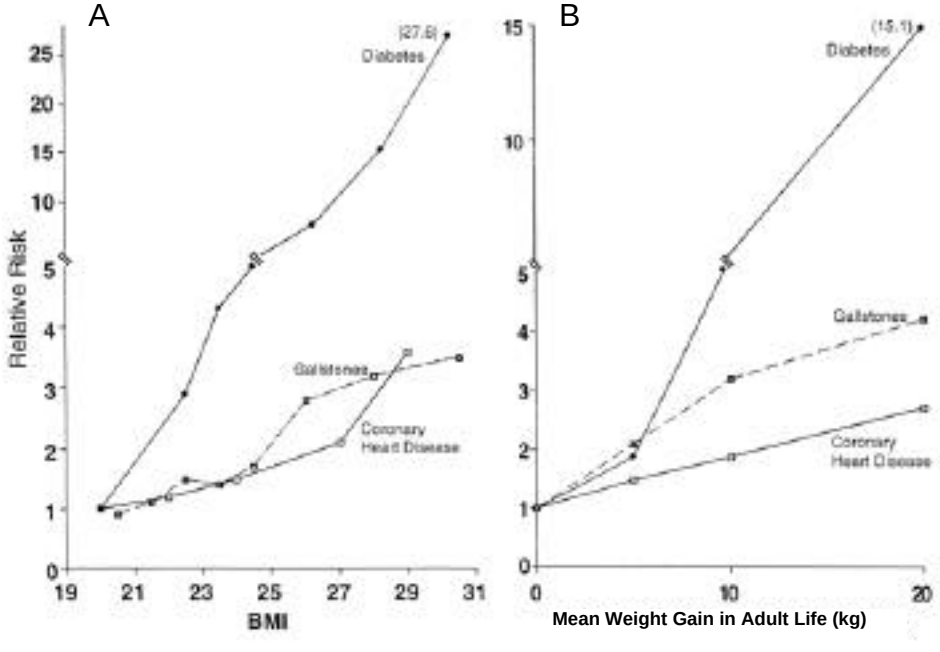

FIG. 1. Relationship of BMI (*A*) and weight gain (*B*) since 18 years of age to relative risks for diabetes, coronary heart disease, and gallstones in the nurses health study. Numbers in parenthesis are relative risks for diabetes if mean weight gain was in excess of 20 kg or BMI was in excess of 30 kg/m^2. Adapted from Refs. 28, 41–43, and 44.

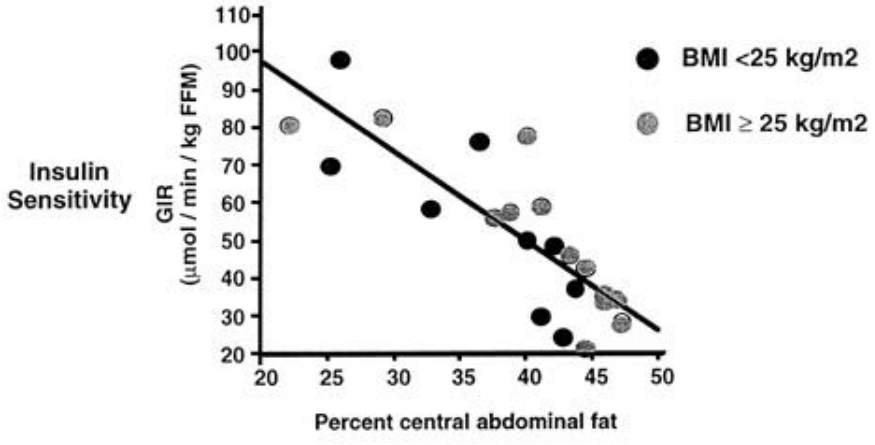

FIG. 2. Relationship between central abdominal fat (measured by dual X-ray absorptiometry), expressed as percent of abdominal tissue, and insulin sensitivity as determined by glucose infusion rate (GIR) during a euglycemic-hyperinsulinemic clamp in subjects with a BMI greater or less than 25. The data show that even normal-weight subjects may have >40% fat in the abdominal area and that this correlates closely with decreased insulin sensitivity. Data from Carey et al. (56).

of an abnormal cardiovascular risk profile has recently been noted in the Framingham project (9).

The relationship between BMI and mortality and morbidity from a variety of diseases was also examined in the nurses health and U.S. male health professional studies. In addition to confirming that morbidity and mortality from coronary heart disease (28,44,47), gallstones (45), diabetes (28,41,43), and some forms of cancer (28,29,46) are increased in men and women who are markedly obese, these studies demonstrated an increased mortality and morbidity from these disorders in individuals with increasing BMIs in the subobese (20–27 kg/m^2) range. As shown in Fig. 1, when smokers are excluded from the analysis, significant increases in risk were evident for all of these disorders in the nurses health study, with the greatest impact of increasing BMI seen on diabetes. Similar findings were observed for men in the male health professional study (42,48) and in a mixed population in the Framingham project (9). Based on the Framingham data, Kannel et al. (9) have suggested that "it may be best to define optimal weight for avoidance of coronary heart disease as that weight that optimizes the cardiovascular risk profile. By this criterion, a healthy body weight would correspond to a BMI of 22.6 in men and 21.1 in women." A final question is whether men and women in the 20–27 BMI range who are at increased risk have experienced a greater increase in adiposity in adult life and are more hyperinsulinemic and insulin resistant than are individuals with a similar BMI who are not at risk. As judged by the very similar relation between BMI and weight gain in adult life and disease morbidity (Fig. 1), these are likely possibilities.

MONW and grossly obese individuals with insulin resistance: a continuum. The data presented in Fig. 1 indicate an increasing prevalence of diseases associated with insulin resistance as BMIs increase from 20 to 27 kg/m^2, with still further increases at higher BMIs. In general, increases in insulin resistance tend to parallel these increases in BMI, although they correlate more closely with increases in adiposity (49). Thus, it is reasonable to consider the relationship between insulin resistance, adiposity, and disease morbidity as a continuum, with MONW individuals at the lower end.

PUTATIVE FACTORS CONTRIBUTING TO METABOLIC OBESITY IN NORMAL-WEIGHT INDIVIDUALS

Over the past 20 years, it has become apparent that a number of interrelated factors are often associated with and may contribute to the pathogenesis of hyperinsulinemia and insulin resistance in both normal-weight and obese individuals. They include central obesity, low birth weight, inactivity, and family history. Apart from their pathophysiological role, the presence of these factors may also be of value in identifying MONW individuals. For this reason, they will be discussed in some detail.

Central obesity. From the foregoing discussion, it appears highly likely that most MONW individuals have some increase in adipose tissue mass compared with normoinsulinemic individuals of similar height and weight, possibly due to weight gain in adult life. How such increases in adipose mass, which are often modest, relate to the metabolic derangements of the insulin resistance syndrome is incompletely understood. One possibility is that they do so because of an increase in adipocyte size (i.e., lipid content/fat cell) (1,2,12), and indeed enlarged fat cells release more free fatty acids and possibly other factors (e.g., tumor necrosis factor [TNF]-α) that could contribute to insulin resistance (49a). Another, and more studied, possibility is that the link between small increases in adiposity and insulin resistance is due to the presence of central obesity.

Central obesity and insulin resistance. The relationship between obesity and type 2 diabetes, hypertension, and other disorders associated with insulin resistance has been known for decades (5,32,33,50). Although first suggested more than 40 years ago (51), only since the early 1980s has it been generally recognized that these disorders are even more closely associated with a central (i.e., visceral and subcutaneous abdominal) distribution of adiposity (also referred to as upper-body, truncal, or android [vs. gynoid] distribution of fat) than with general increases in fat mass (52–54). Initially, indirect measures of central obesity showed weak or moderate correlations with insulin resistance and features of the insulin resistance syndrome; however, with the advent of dual X-ray absorptiometry, computerized tomography, and magnetic resonance imaging, which provide more precise measures of central fat, it has become evident that these correlations are very impressive (55–57) (Fig. 2). It has also become clear that central obesity, like hyperinsulinemia and insulin resistance, not only accompanies, but antedates such disorders as type 2 diabetes (58,59), hypertension (60), and coronary heart disease (61). That it may be a very early event is suggested by the finding of the Bogalusa heart study (62,63) that increases in central fat, as reflected by

TABLE 5
Possible factors relating inactivity to insulin resistance

Factors	Reference
Low Vo_{2max}	102, 104–106, 109–116
Decreased muscle capillarity	109, 110, 120
Increased type 2b fibers	109, 110, 120
Central obesity (associated with the above factors)	62, 115, 119, 135, 136
Decrease in GLUT4 glucose transporters in muscle	124
Acute decrease in insulin action in muscle due to inactivity itself	107, 108, 130

TABLE 6
Proposed scoring method for identifying an MONW individual

	Points
Presence of associated diseases or biochemical abnormalities	
Hyperglycemia	
Type 2 diabetes	4
Impaired glucose tolerance (IGT)	4
Gestational diabetes	3
Impaired fasting glucose (110–125 mg/dl)	2
Hypertriglyceridemia (fasting)	
Triglycerides >150 mg/dl/HDL cholesterol <35	3
Triglycerides >150 mg/dl	2
Triglycerides >100–150 mg/dl	1
Essential hypertension	
Blood pressure >140/90 mmHg	2
Blood pressure 125–140/85–90 mmHg	1
Polycystic ovaries	4
Premature coronary heart disease (under age 60 years)	3
Uric acid (>8 mg/dl)	2
Family history (first-degree relatives)	
Type 2 diabetes or impaired glucose tolerance	3
Essential hypertension (under age 60 years)	2
Hypertriglyceridemia	3
Premature coronary heart disease (under age 60 years)	2
Presence of predisposing factors	
Low birth weight (<2.5 kg)	2
Inactivity (<90 min aerobic exercise/week)	2
Evidence of mild obesity or central adiposity (maximum 4 points)	
Weight gain: >4, 8, or 12 kg after age 18 years (W), 21 years (M)	1–3
BMI: 23–25, 25–27 kg/m^2	1, 2
Waist (inches)	
28–30, >30 (W)	1, 2
34–36, >36 (M)	1, 2
Ethnic group at high risk	1–3

MONW individual equals a score of 7 points or greater. Scheme applies to men and women aged 20–55 years with a BMI <27 kg/m^2. The table is constructed primarily on the basis of data from publications listed in Table 1 and presented in Fig. 1. A similar scheme with minor modifications could be applied to individuals with a BMI >27 kg/m^2. In the latter, additional points would be given for greater increases in the obesity-related parameters. W, women; M, men. Ethnic group at high risk includes (in order of ascending risk) black women, Japanese-Americans, Latinos, Melanesians, Polynesians (including New Zealand Maoris), Indians, Australian aborigines, Micronesians (including Naruans), and some American Indian tribes. The risk is especially high in those who have adopted a Western lifestyle.

increases in subscapular, suprailiac, and subcostal skinfold thickness, correlate closely with increases in plasma insulin, blood pressure, and triglycerides in school-aged (6–18 years of age) children.

The correlation between BMI and central obesity can vary considerably from one individual to another. Thus, people with a relatively low BMI, such as MONW individuals, can have gross increases in abdominal fat (Fig. 2) (55,59), and others with a high BMI may have very little intra-abdominal (visceral) fat (64). A striking example of how insulin resistance correlates with the amount of visceral fat in these circumstances are the sumo wrestlers of Japan. As demonstrated by Matsuzawa (65), sumo wrestlers, though generally quite obese, have small amounts of visceral fat (but a very large abdominal subcutaneous fat layer) and are quite insulin sensitive. In contrast, retired sumo wrestlers have large amounts of visceral fat, and they are insulin resistant and have a very high prevalence of type 2 diabetes and cardiovascular disease. Different levels of physical activity in the active and retired groups could have contributed to these findings (see below); however, similar correlations have been described in other studies in which exercise was probably not a confounding factor (64).

Why central obesity correlates so closely with insulin resistance is still unclear. The most widely held view is that central obesity is the initial event and that it leads to insulin resistance by causing free fatty acid (FFA) levels to increase in the portal and peripheral circulations. In support of this notion, a number of studies have shown that increases in plasma FFA levels enhance hepatic gluconeogenesis; diminish the extraction of insulin by the liver, leading to hyperinsulinemia (52,53); and inhibit insulin-stimulated glucose utilization and glycogen synthesis in skeletal muscle of humans (51,53,54,67–69). In addition, FFAs have been demonstrated to increase insulin secretion by the pancreatic β-cell under some conditions (67,70) and to stimulate the synthesis of triglyceride-rich VLDLs by the liver (70a). Visceral fat, from which FFAs are released into the portal circulation, has been shown to be both less sensitive to insulin and more sensitive to the lipolytic effect of catecholamines than is subcutaneous peripheral fat (52–54, 66). Also in patients with central obesity and its associated metabolic complications, the β-3 adrenergic sensitivity of visceral fat is increased (66). In keeping with these observations, fatty acid turnover is significantly greater in grossly obese individuals with a more central than general distribution of adiposity (71). Whether FFA turnover is increased in the normal-weight individuals that we have characterized as metabolically obese is unclear. Plasma FFA levels, which generally parallel their turnover, were not reported by either Hollenbeck and Reaven (3) or Zavaroni et al. (4); and in two small studies in which nonobese, but insulin-resistant, first-degree relatives of patients with type 2 diabetes were evaluated, they were not increased (35,72). On the other hand, in a recent study, somewhat higher plasma FFA levels (582 vs. 470 μmol/l) were observed in 49 lean (BMI 24 ± 3 kg/m^2) offspring of patients with type 2 diabetes than in age- and weight-matched control subjects (72a). Clearly, additional measurements of plasma FFAs and their turnover in MONW individuals are required.

Could central obesity be the result of insulin resistance or a concurrent event rather than its cause? MONW individuals could provide a useful patient group in which to assess whether increased visceral (abdominal) fat is the cause or the result of insulin resistance or a concurrent event. As implied in the preceding section, it is generally held that an increase in central adiposity precedes insulin resistance and plays a role in its pathogenesis. Definitive proof for this is still lacking, however. A contrary view has been proposed by Boyko et al. (73), who found that a high fasting plasma insulin level and insulin resistance precede visceral fat accumulation in Japanese-American men and suggested that visceral adiposity is a secondary event. Likewise, hyperinsulinemia has been shown to be a predictor of obesity in certain populations (74–76). Why hyperinsulinemia should lead to a specific deposition of fat in the viscera is not known; however, Bujalska et al. (77) have recently reported that stromal cells of visceral fat are enriched in 11-β-dehydrogenase (type 1), an enzyme that enhances the conversion of cortisone to cortisol. They also demonstrated that insulin and cortisol induce the activity of this enzyme. Thus, it is possible that by inducing 11-β-dehydrogenase in fat and secondarily increasing local levels of cortisol, insulin could cause a pseudo–Cushing's syndrome (77) in which visceral fat deposition is enhanced.

Yet another possibility is that central obesity and insulin resistance are concurrent events due to the presence of a common factor that induces both of them. One such factor could be the aforementioned increase in 11-β-dehydrogenase, if its induction in other tissues, such as muscle and pancreatic β-cell, resulted in hyperinsulinemia and insulin resistance. Another could be inactivity, which by itself appears to cause hyperinsulinemia and central fat accumulation (see below), and still another a primary disturbance in the hypothalamic-pituitary adrenal axis (53,54). Other factors implicated in the pathophysiology of insulin resistance and obesity, such as TNF-α (78) and leptin (79–81a) have not been specifically related to central adiposity, although their role remains controversial.

Weight gain in adult life, abdominal fat deposition, and insulin resistance. Our premise is that small, adult-onset weight gains of the magnitude that increase disease risk (5–10 kg [Fig. 1] or even less [9]) will be associated with increases in both abdominal fat and insulin resistance. We are not aware of longitudinal studies that directly address this notion; however, the demonstration that the weight gain of aging is associated with an increase in abdominal adiposity, even in subjects with a normal BMI (82,83), is consistent with this view, as is the increased prevalence of risk factors for coronary heart disease in such individuals (84). Also consistent with this notion is the strong association of the insulin resistance syndrome with thinness at birth (ponderal index) in individuals who are normal weight or slightly overweight in middle age (85,86). An increased truncal fat or waist-to-hip ratio has been reported in this group by some investigators (85,87); however, precise data on relative changes in total body and visceral fat mass are not yet available.

What is a normal abdominal adipose tissue mass? Insulin resistance clearly occurs in people whose total abdominal or visceral fat mass is increased relative to that of the general population. Whether it also occurs in individuals in whom the size of these fat masses is normal for the population but greater than at an earlier time in their life is not known. Longitudinal studies in people at risk for the insulin resistance syndrome based on family history or birth weight (see below) should almost certainly answer this question. Whatever they reveal, it is highly likely that ethnic differences will have to be taken into account. For instance, African-American women have different intra-abdominal fat volumes than do Caucasian women matched for waist-to-hip ratio (57,88), and Polynesians have been reported to have a lower fat mass, adjusted for weight, height, and age, than do Caucasians (89). Australian aborigines are a population with a high prevalence of type 2 diabetes and a tendency to display insulin resistance (76,90). Evidence has been presented that well-nourished aborigines in their native habitat are very lean, with a BMI generally well under 20 kg/m^2, and that they demonstrate significant insulin resistance at a BMI in the mid-normal range for Caucasian groups (76). Presumably, this insulin resistance is associated with an increased visceral fat mass; however, accurate data on total and regional fat mass in aborigines are not yet available.

Fetal nutrition and low birth weight. Both low birth weight and low weight at 1 year of age have been linked to heart disease, hypertension, type 2 diabetes, and insulin resistance in middle-aged and elderly individuals (85,86), including many whom we would classify as MONW. Likewise, links between birth weight, blood pressure (91), and plasma glucose levels (92) have been documented in adolescents and young adults. These reports were initially based on observations in Caucasians in the U.K.; however, similar results have recently been reported from Sweden (93) and from the San Antonio Heart Study (87). In the latter, normotensive, nondiabetic individuals, primarily non-Hispanic Caucasians and Mexican-Americans, whose birth weight was in the lower tertile had significantly higher levels of fasting serum insulin and a more truncal fat deposition pattern than did individuals whose birth weight was in the highest tertile. The odds of expressing two or more manifestations of the insulin resistance syndrome, such as hypertension, type 2 diabetes, impaired glucose tolerance or dyslipidemia, increased 1.7 times for each tertile increase in birth weight.

Although an increase in weight in adult life further enhances the risk of developing the insulin resistance syndrome in low-birth-weight individuals in middle age (86,87), a low birth weight predisposes to insulin resistance and associated disorders independently of attained BMI (86,87). Thus, many low-birth-weight subjects have BMIs less than 24–26 kg/m^2 when middle aged and would be classified as MONW individuals. As noted earlier, some data suggest that low-birth-weight babies have central adiposity in middle age (85,87); however, definitive measurements of visceral fat are still lacking. Whether this group has abnormalities in FFA turnover or physical activity status is unknown. A delay in the activation of glycolysis/glycogenolysis in exercising skeletal muscle has been detected by nuclear magnetic resonance imaging in these individuals in adult life (86). Also, they have been shown to have high plasma cortisol levels (95), suggesting an abnormality of the hypothalamic-pituitary-adrenal axis or possibly of 11-β-dehydrogenase. Whatever the mechanism, the close relation between birth weight and the subsequent development of insulin resistance and associated disorders suggests that intrauterine nutrition could be a factor in causing susceptible individuals to eventually develop these problems. The fact that the majority of individuals with insulin resistance in midlife were not low-birth-weight infants, however, indicates that it is not the sole factor (96).

Inactivity

Links between inactivity, Vo_{2max}, diabetes, and coronary heart disease. Of the factors potentially operative in MONW individuals, inactivity is one of the most intriguing. In the last four decades, numerous epidemiological studies have shown a strong correlation between a sedentary lifestyle and the prevalence of type 2 diabetes, coronary artery disease, hypertension, and certain types of cancer, as well as a protective effect of physical activity against these disorders (97–103). In addition, an inverse relationship between fitness, as measured by maximal oxygen uptake (Vo_{2max}), and the risk of these diseases has been demonstrated (102,104–106).

If inactivity and a low level of fitness contribute to coronary artery disease, type 2 diabetes, and other disorders, they could do so by predisposing to insulin resistance. Some of the factors linking inactivity to insulin resistance are listed in Table 5 and will be discussed in this and subsequent sections. One of these factors is acute inactivity, which has been shown to cause both glucose intolerance and insulin resistance in a matter of days (107,108). Another is decreased fitness itself. A strong correlation between decreased fitness (low Vo_{2max}) and impaired insulin sensitivity, as assessed by the insulin clamp, has been described in 21 first-degree relatives of patients with type 2 diabetes by Nyholm et al. (109). These nondiabetic subjects were 30–40 years of age; their Vo_{2max} was 15% lower than that of a matched control group; and they were not obese (mean BMI 24.8), suggesting that a low Vo_{2max} may be an earlier indicator of insulin resistance than obesity per se. Central adiposity was not quantified, however. Similar decreases in Vo_{2max} compared with sedentary control subjects have been reported in insulin-resistant individuals with mild type 2 diabetes (110–112) and with impaired glucose tolerance (113,114), in the normoglycemic offspring of patients with type 2 diabetes (115), and in a population of middle-aged Swedish men at high risk for type 2 diabetes (106), although in these groups too the relationship between central adiposity and Vo_{2max} was not clear (see below). Still further evidence for a link between fitness (inactivity) and impaired insulin action is the observation that the cardiovascular risk factor profile that accompanies insulin resistance is often found in poorly conditioned individuals. For instance, in a group of 111 subjects with mild type 2 diabetes, Schneider et al. (112) observed that a low Vo_{2max} was associated with hypertriglyceridemia and hypertension. Likewise, a low Vo_{2max} correlated inversely with elevations in VLDL and blood pressure in nondiabetic offspring in the Framingham project (116).

Basis for decreased Vo_{2max} in insulin-resistant individuals. The cause of the decreased Vo_{2max} in patients with insulin resistance is unclear. It cannot be explained by inactivity alone, because differences in aerobic fitness persist when insulin-resistant patients with type 2 diabetes and control subjects with apparently similar lifestyles are compared (112,117). A strong genetic contribution to the Vo_{2max} has been reported (118), raising the possibility that the low fitness level in patients with insulin resistance (including MONW individuals) is, in part, genetically determined. Patients with type 2 diabetes (119), their insulin-resistant relatives (109,110,120), and subjects with central obesity with and without diabetes (119) have been demonstrated to have a lower capillary density and a greater white-to-red muscle fiber ratio than do comparable control subjects. To what extent this reflects genetic differences and to what extent it reflects differences in physical-activity status, however, remains to be determined. Another possibility relates to the fact that Vo_{2max} is usually expressed per kilogram of body weight. Thus, lower values might be an artifact resulting from a tendency of insulin-resistant patients at any given weight to have a greater percentage of body fat, especially in the intra-abdominal area. If so, a relatively low Vo_{2max} in a "normal-weight" individual could be an early marker of central obesity as well as the insulin resistance that accompanies it. Whether central obesity itself in some way contributes to inactivity and a decreased Vo_{2max} is not known.

Therapeutic value of exercise. Whatever the etiology of the low level of aerobic fitness in patients with insulin resistance, its presence strongly suggests a therapeutic role for physical activity. Studies initially carried out in rats (121–123) and later in humans (124–126) showed that by a variety of mechanisms, the sensitivity of skeletal muscle to insulin is increased both after an acute bout of exercise and as a result of physical training (Table 5). A considerable body of evidence also indicates that glucose tolerance and insulin sensitivity, as well as various lipid parameters, blood pressure, and fibrinolytic activity, can be improved by regular exercise in insulin-resistant individuals (97,126,127). Interestingly, the exercise need not be intense, considering that long-term walking (128) and jogging (129) programs that produce no or little change in Vo_{2max} have been shown to produce significant improvements in insulin resistance, plasma lipids, and blood pressure. In these and other long-term studies, changes in adiposity make it difficult to isolate the effects of physical activity per se. On the other hand, short-term studies (days) suggest that physical activity can improve insulin sensitivity and glucose disposal in humans, even in the absence of measurable changes in body composition (125,130). In general, improvements produced by regular exercise are greatest in individuals with central obesity and manifestations of the insulin resistance syndrome (131). A near-complete normalization of impaired glucose tolerance, hyperinsulinemia, and hypertriglyceridemia has been observed in subjects with mild type 2 diabetes after a full year of intensive physical training, albeit in association with a modest loss of fat mass (127).

A number of reports are consistent with the notion that regular physical activity, possibly by virtue of its effects on insulin resistance, can also delay or prevent the onset of type 2 diabetes. Thus, in prospective, but not randomized, studies, Helmrich et al. (98) and Manson and co-workers (45,99) have shown a reciprocal relationship between physical activity and the likelihood of developing type 2 diabetes in patient populations with a high incidence of insulin resistance. In addition, in both the Malmo (132) and DaQuing (133) studies, an unstructured exercise program alone or together with diet therapy resulted in a 50% decrease in the progression of impaired glucose tolerance to diabetes over a 6-year period. Both of these studies were randomized prospective trials, and benefits were found in subjects with a normal as well as a high BMI (see below). Finally, a protective effect of physical activity against cancer of the colon (103) and breast (134) has been reported. Whether this is related to its effects on plasma insulin levels or some other factor related to insulin resistance is not known.

Inactivity, exercise, and intra-abdominal fat. A low Vo_{2max} is associated with increased intra-abdominal adiposity in young offspring of patients with type 2 diabetes (115) and with a high waist-to-hip ratio in a variety of patient groups (135,136) (Table 5). As noted above, regular exercise is especially effective in improving cardiovascular risk factors in men and women with a central fat distribution (131). Such regular exercise has been shown to result in a loss of abdominal fat (137,138), and where studied by magnetic resonance imaging in patients with type 2 diabetes, a disproportionate loss of visceral fat (139). Presumably, these changes in abdominal fat mass complement the more direct effects of regular exercise in diminishing insulin resistance and cardiovascular risk factors. They are clearly not the sole basis for them, since enhancement of insulin action can occur after a single bout of exercise (122,125). Also, inactivity can reverse the enhanced insulin sensitivity in muscle of highly trained humans in as little as 3 days (130), presumably well before substantial changes in abdominal fat mass have occurred.

Summary. The interrelationships between insulin resistance, inactivity, and poor aerobic fitness appear to be quite strong, even in normal-weight individuals. The finding of a decreased Vo_{2max} in young patients before the development of disorders associated with the insulin resistance syndrome raises the interesting possibility that decreased fitness and/or physical activity are important factors in their development. It is unclear to what extent central obesity, which often accompanies decreased fitness, contributes to the association between inactivity and insulin resistance. Regular exercise ameliorates the entire cluster of metabolic and hemostatic abnormalities found in patients with insulin resistance. In addition, it tends to reverse the abnormal body composition and fat distribution found in these individuals. A reasonable hypothesis is that the apparent effectiveness of regular exercise in decreasing the incidence of coronary heart disease and type 2 diabetes is due to its effects on insulin action and central adiposity. If so, interventions to increase levels of physical activity, particularly in children, adolescents, and young adults, may be an effective approach to prevent or retard the development of the increasing number of disorders associated with insulin resistance.

Other potential factors. From the foregoing discussion, it is clear that the triad of central adiposity, low birth weight, and inactivity, in concert and perhaps independently, contribute to the pathogenesis of insulin resistance in both normal-weight and overtly obese individuals. Central adiposity (118,140) and level of physical activity (118) may in large part (40–60%) be genetically determined, as is presumably an individual's propensity to develop insulin resistance. The precise nature of the genetic determinants in each instance remain to be established. Candidates under study include genes affecting the synthesis or action of leptin, TNF, and a variety of hypothalamic neuropeptides, as well as genes coding for steps in the insulin signaling cascade or events that determine the composition of skeletal muscle. In addition, recent studies have implicated abnormalities in malonyl CoA and long-chain fatty acyl CoA metabolism in muscle, the pancreatic β-cell, and possibly other tissues, as well as increases in muscle triglyceride content, in the pathophysiology of insulin resistance (141–144). Likewise, the possibility that abnormalities in one or more mitochondrial uncoupling proteins (145) could contribute to obesity and secondarily to insulin resistance requires consideration. Studies in MONW individuals, in whom adaptations associated with generalized obesity should not be present, may help in sorting out the precise role of these factors.

IDENTIFICATION OF MONW INDIVIDUALS

Rationale for treating MONW individuals early in life. As reviewed earlier, hyperinsulinemia, insulin resistance, and some increase in central adiposity antedate and may contribute to the pathogenesis of the disorders with which they are associated (Table 1). For this reason, a compelling argument can be made for treating MONW individuals with diet, exercise, and possibly pharmacological agents (see below) before these disorders become overt or at least early after their onset, i.e., before they produce irreversible changes.

A case in point is type 2 diabetes. Caloric restriction and exercise can improve glucose tolerance, diminish insulin resistance, and improve coronary risk factors in many patients with established type 2 diabetes, especially those who are hyperinsulinemic and insulin resistant (97,126,127). On the other hand, the therapeutic efficacy of diet and exercise in such patients has been limited, because most individuals with this disorder are over 40 years old at the time of diagnosis and many tend to be resistant to lifestyle changes (146). Equally important, 30–40% of patients with type 2 diabetes (147) and a somewhat lesser percentage with impaired glucose tolerance (148–150) already have clinically significant ischemic heart disease at the time of diagnosis, and others have significant microvascular disease and neuropathy (150,151). These considerations do not negate the value of diet and exercise in the treatment of many patients with established type 2 diabetes; however, they strongly suggest that diet and exercise may be more beneficial if instituted earlier in life, i.e., before the onset of overt hyperglycemia (152,153).

Similar arguments can be made for treating MONW individuals with or at risk for hypertriglyceridemia, essential hypertension, and polycystic ovary disease, because all of these disorders are associated with premature coronary heart disease. Furthermore, several epidemiological studies (154–157) have suggested that hyperinsulinemia and insulin resistance place an individual at increased risk for coronary artery disease, even in the absence of these disorders. As already noted and will be discussed later, available evidence suggests that diet and exercise can both prevent the transition from impaired glucose tolerance to type 2 diabetes and attenuate the progression of type 2 diabetes (132,133) in patients who were probably MONW individuals.

Present and future approaches to identification. If one accepts the premise that MONW individuals should be treated to prevent or retard the development of associated disorders, they need to be identified when relatively young. Quantitative efforts to define the insulin resistance syndrome both in obese and nonobese (i.e., MONW) individuals are currently under way, using glucose tolerance tests and measurements of plasma insulin, triglycerides, HDL cholesterol, blood pressure, BMI, and waist-circumference as criteria. In one such effort, a preliminary evaluation of offspring (mean age 54 years) of the original Framingham study cohort, 44% of the population had one or more manifestations of the insulin resistance syndrome (158). A longitudinal study of disease outcome in nonobese subjects in this and similarly well-characterized groups (4,93,159) should yield important pre-

dictive information about MONW individuals, as well as provide criteria for their identification.

In the interim, our premise is that most MONW individuals can be identified clinically if one takes into account such factors as family history, birth weight, adult-onset weight gain and central adiposity, physical activity status, and the presence of associated diseases. A somewhat similar conclusion concerning the identification of individuals at risk for type 2 diabetes has recently been drawn by Knowler (149). A tentative scheme for identifying MONW individuals and, for that matter, all insulin-resistant individuals, based on these considerations, is presented in Table 6 and Fig. 3. In essence, a scoring system is proposed in which points are allotted for characteristics associated with insulin resistance, and a score of 7 or greater is considered diagnostic. Thus, a patient with type 2 diabetes, hypertriglyceridemia, and a family history of these disorders would have a score of 13 and be classified as an MONW individual, as would a patient with polycystic ovary disease who is inactive and mildly or centrally obese (7–10 points depending on extent of the obesity). The presence of a strong family history of type 2 diabetes together with an impaired fasting blood glucose (5 points) or the presence of overt type 2 diabetes, hypertension, or central adiposity (waist measurement) by themselves (1–4 points) are not considered diagnostic, because patients fitting this description are not invariably insulin resistant. On the other hand, such individuals are more likely to be insulin resistant than are individuals without these problems (Fig. 3); therefore, a trial (4–12 weeks) of diet and exercise in these and other patients with a score between 3–7 is probably warranted to determine if it produces metabolic improvement (see below).

Direct measurements of insulin resistance are not included in the proposed scheme because they are not practical on a large scale. In addition, it must be emphasized that the proposed scheme is not definitive. It is based on our assessment of the existing literature and will undoubtedly be supplanted once more data are available and the predictive value of each of the listed considerations and of genetic and other factors (e.g., postprandial vs. fasting plasma triglycerides) have been assessed quantitatively. Also, the importance of such factors as age, sex, and ethnic group (160) will have to be evaluated to apply it rigorously to different populations. Needless to say, the initial test of this scheme will be whether patients identified as MONW individuals show significant improvement in biochemical and other parameters as a result of therapy.

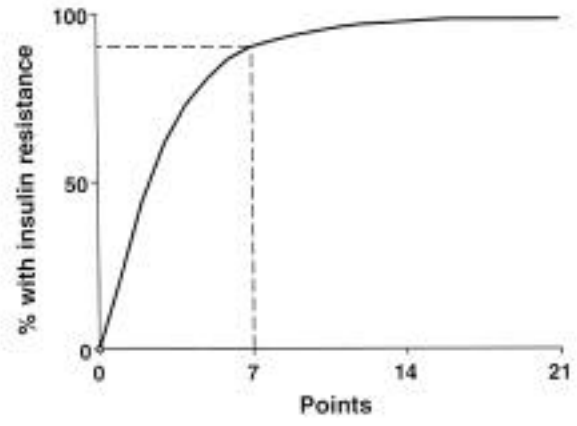

FIG. 3. Hypothetical relation between presence of insulin resistance and points in the scoring system. Figure is based on point scores allotted for the presence of various characteristics of an MONW individual (Table 7) and a "guesstimate" of the percentage of people with a given score who will be insulin resistant. A score of ≥7 is considered diagnostic of the insulin resistance syndrome in a nonobese (MONW) or obese individual. As is evident from the figure, a score of <7 does not rule out the diagnosis; indeed, such individuals are more likely than people with none of the characteristics of an MONW individual to be insulin resistant. For these patients, a therapeutic trial with diet and exercise or possibly pharmacological agents may be diagnostic.

THERAPY

In managing MONW individuals, the goal is to prevent the development of those conditions to which they are predisposed, such as diabetes, hypertension, dyslipidemia, and cardiovascular disease or, if these conditions are already present, to attenuate their progression. The two cornerstones of therapy are diet and exercise.

Diet. We believe that MONW individuals should be placed on a hypocaloric diet, especially if they have experienced some adult-onset weight gain, although no systematic studies of diet therapy in normal-weight individuals have been reported. One could argue that MONW individuals should not be placed on a low-calorie diet because they are at a reasonable weight for their height and it may be difficult for them to maintain a lower weight. On the other hand, it is likely that if accurate body composition determinations are done, they will have disproportionately high total-body and/or abdominal fat, and weight loss will be metabolically beneficial. Furthermore, the required weight loss and dietary restriction should be much less than in more overtly obese individuals, and specific instances of success with diet therapy in such individuals have been noted by the authors (unpublished observations). Finally, if combined with exercise, the chances of maintaining a loss of weight and presumably adipose tissue mass appear to be increased (161). For all of these reasons, we believe that a brief trial of caloric restriction (e.g., 4–12 weeks) is warranted in MONW individuals, and it may be the sole therapy if they are resistant to an exercise program or exercise alone has not been successful. Even if not designed to produce weight loss, diet therapy is probably needed to prevent an additional increase in weight, which could in turn further increase insulin resistance (49). We believe the diet should be a prudent one, with no more than 30% of calories from fat (10% saturated, 10% monounsaturated, 10% polyunsaturated) and no more than 300 mg of cholesterol. A hypocaloric version of the American Heart Association type 1 diet is an appropriate choice (162). It is also reasonable to ensure an adequate intake of folic acid and B12 to keep homocysteine levels low (163) and an adequate intake of antioxidants as protection against cardiovascular disease (164).

Exercise. The value of exercise in the therapy and prevention of insulin resistance and associated disorders has already been reviewed. We would only add here that it may be the most important aspect of therapy for many MONW patients because it enhances insulin sensitivity and helps to achieve and maintain a decrease in adiposity (161). In addition, it may be a very acceptable lifestyle change, particularly for young and some middle-aged individuals. Perhaps the best advice that can be given to most MONW subjects is to develop a consistent habit of physical activity that will continue throughout life. As reviewed elsewhere (165,166), vigorous exercise programs in patients with established type 2 diabetes and possibly other disorders associated with insulin resistance must be initiated

TABLE 7
Effects of 6 years of diet and exercise therapy on progression to type 2 diabetes in lean and overweight patients with impaired glucose tolerance (DaQuing study)

	Control	Diet	Exercise	Diet and Exercise
Lean				
n	50	55	57	46
Initial BMI (kg/m^2)	22.4	21.8	21.7	22.3
% diabetic (6 years)	30	21	15*	16*
Overweight				
n	83	75	84	80
Initial BMI (kg/m^2)	28.5	28.3	27.9	28.6
% diabetic (6 years)	60	36*	43*	42*

Roughly equal numbers of men and women, aged 44–46 years at the onset of the study, were followed in each group. Results are means for indicated number of subjects. Diet consisted of a decrease in ethanol and refined sugar intake and an increase in vegetables in the lean young group and a similar diet with reduced calories in the overweight subjects. Exercise consisted of an increase in daily leisure physical activity of varying intensity. Lean and overweight groups experienced small increases and decreases in BMI respectively over 6 years. Body fat and its distribution were not measured, nor were plasma insulin or triglyceride levels. Blood pressure was measured but not reported. *$P < 0.05$, significantly different from control group. Adopted from Pan et al. (133).

with caution, because of the high prevalence of ischemic heart disease and risk of foot problems (if there is neuropathy or peripheral vascular disease) in these individuals.

Diet and exercise: long-term studies. A number of long-term studies suggest that diet and exercise are very likely to work in many MONW individuals. In one of these, the DaQuing study (133), men and women with impaired glucose tolerance were placed on diet therapy, an exercise program, or the two in combination. As shown in Table 7, all three therapeutic approaches diminished progression to overt type 2 diabetes by 30–50%. Of particular note, these beneficial effects were observed in both lean (BMI ~22) and overweight (BMI ~28) subjects, albeit the fraction of lean individuals progressing to diabetes was somewhat lower. Plasma insulin and triglyceride levels, central adiposity, and other indexes of insulin resistance were not reported; however, on the assumption that the lean patients of DaQuing are similar to Caucasians with glucose intolerance, most of them would presumably be classified as MONW individuals. A second report suggesting the utility of long-term diet and exercise in patients with insulin resistance is the Malmo study (133). Here 181 patients with impaired glucose tolerance (mean age 48 years) were placed an a diet and/or physical training program and followed for 5–6 years. Body weight (initial BMI ~26.6 kg/m^2) was reduced by 2.3–3.7% among participants, and $V_{O_{2max}}$ increased by 10–14%. In contrast, a 0.5–1.7% increase in weight and a 5–9% decrease in $V_{O_{2max}}$ was observed in matched individuals (initial BMI, 26.7) who did not participate. In >50% of the treated patients with impaired glucose tolerance, glucose tolerance was normalized and progression to type 2 diabetes was diminished, whereas glucose tolerance tended to deteriorate in subjects not on the diet plus exercise regime. In addition, decreases in plasma lipids and hyperinsulinemia were observed in the patients with impaired glucose tolerance treated with diet plus exercise, but not in the matched control group. Of equal interest, 50% of a subgroup with early type 2 diabetes was in remission after 6 years. Unlike the DaQuing study, a breakdown of patients into lean and overweight groups was not reported. What is clear from Malmo, DaQuing, and other studies (127–129,167) is that diet and exercise can be remarkably effective in treating large groups of patients with impaired glucose tolerance, early type 2 diabetes, and various dyslipidemias. Although insufficient information is available to state definitively that many of the patients in these studies were MONW individuals, it seems highly likely.

Pharmacological therapy. Whether the MONW individual is a candidate for pharmacological treatment to prevent subsequent disease is an interesting question. It is reasonable to assume that if diet and exercise do not work, the early use of agents that diminish insulin resistance should be considered. Thus, it has been reported that therapy with metformin can reverse abnormalities in nonoxidative glucose metabolism in nonobese relatives of patients with type 2 diabetes (168), and thiazolidinediones have been shown to enhance insulin sensitivity in both experimental animals and humans (169,170). Further studies are required, however, to ascertain the risk/benefit ratio of these and other pharmacological therapies, when used both intermittently and chronically. Anorexigenic drugs, such as dexfenfluramine, that decrease an individual's weight by 5–10% at one time seemed a promising therapeutic alternative, because they concurrently diminish many manifestations of the insulin resistance syndrome in patients with type 2 diabetes (171). Because of the development of primary pulmonary hypertension and valvular heart disease (172), the use of these agents is no longer feasible until safer drugs are available. Hopefully, more definitive information concerning the use of metformin and troglitazone in MONW individuals and their value in disease prevention will be provided by the Type 2 Diabetes Prevention Trial (159) and by the Stockholm Diabetes Prevention Program (93).

Prevention. As noted earlier, 25–50% of a middle-aged U.S. population of Caucasian descent has one or more manifestations of the insulin resistance syndrome, and many of these individuals will not be overweight. Current medical practice patterns do not usually result in the early identification of these individuals unless patients have diabetes, hypertension, or other associated diseases or are overtly obese. A basic premise of this review is that once established, these dis-

orders often have irreversible consequences; therefore, individuals at risk for them should be treated with diet, exercise, and possibly pharmacological therapy much earlier (i.e., adolescence to young adulthood). A scheme for identifying MONW individuals and others with insulin resistance that partially fulfills this need is presented in Table 6 and Fig. 3. In the future, the use of genetic markers may provide both earlier and more definitive identification.

Hypothetically, genetic and other markers could enable us to identify people at risk for developing both insulin resistance and central obesity, as well as the diseases that become manifest in their presence. With respect to identifying individuals at risk for developing insulin resistance, Bouchard and Perusse (118) have demonstrated in identical twins that 40–60% of an individual's propensity to central obesity, as well as his or her level of physical activity, are genetically determined. Intuitively, it seems highly likely that once specific genes (or lack of them) that predispose to central obesity and inactivity (or decreased $V_{O_{2max}}$) are identified, it will be possible to select those individuals for whom a lifestyle characterized by dietary discretion and regular physical activity is especially desirable.

It is also likely that in the near future it will be possible to genetically identify individuals at risk for disorders that become manifest when insulin resistance/central obesity occurs. One such disorder for which the gene may already have been identified is "nonmodulated" hypertension (21,173). Patients with this problem account for 30% of subjects with essential hypertension and are characterized by normal-to-high renin levels and abnormal responses to angiotensin when placed on low- and high-salt diets. They differ genetically from other individuals with hypertension and nonhypertensive subjects by the presence of homozygosity for threonine in codon 235 of the angiotensinogen gene. Most interestingly, they are not obese (BMI ~23), but they are hyperinsulinemic and hypertriglyceridemic and have a large increase in the thickness of their subscapular skinfold (21). Thus, they may represent a group of individuals in whom genetic factors predisposing to insulin resistance and a form of hypertension work in tandem. Whether they have central obesity and/or will benefit specifically from diet/exercise therapy remains to be determined. If such a lifestyle change proves beneficial, the next question will be whether it should be recommended for normotensive young people who present with the genetic abnormality.

CONCLUDING REMARKS

We believe that there now exists a strong rationale for identifying MONW individuals and assessing whether their treatment prevents or at least retards the development of diabetes, some forms of hypertension, and a number of other diseases, possibly including obesity itself. It is our premise that MONW individuals are the patients with insulin resistance most likely to benefit from interventions because they are generally younger and less obese than their counterparts with overt disease. As a consequence, they should be more amenable and responsive to diet, exercise, and possibly pharmacological therapy. Equally important, if associated diseases are present, they will presumably be less advanced. In light of the emerging worldwide epidemic of type 2 diabetes and other diseases associated with insulin resistance/central obesity (100,173), as well as the already existing high prevalence of MONW individuals in many societies, a randomized prospective study to assess this premise is urgently needed.

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