Epidemiology of the Insulin Resistance Syndrome

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The insulin resistance syndrome consists of the co-occurrence of metabolic risk factors for type 2 diabetes and cardiovascular disease, including overall obesity, central obesity, dyslipidemia (characterized by elevated levels of triglycerides and low levels of high-density lipoprotein cholesterol), hyperglycemia, and hypertension. Using criteria proposed by the National Cholesterol Education Program Adult Treatment Panel III, national survey data suggest the insulin resistance syndrome is very common, affecting about 24% of US adults aged greater than 20 years. The syndrome is more common in older people and in Mexican Americans, and will increase in prevalence as populations age and become more obese. Identification of the syndrome warrants aggressive interventions known to prevent type 2 diabetes and cardiovascular disease, including weight reduction, increased physical activity, and control of hypertension and dyslipidemia.

Introduction

Diabetes mellitus and, in particular, type 2 diabetes, is extremely common. Diabetes affects over 8% of the US population between the ages of 20 to 74 years [1]. Its prevalence is rapidly accelerating worldwide, with rates expected to increase more than 165% by 2050 in the United States alone [1]. This epidemic of type 2 diabetes is largely fueled by an epidemic of obesity and physical inactivity [2]. Patients with type 2 diabetes are affected by microvascular complications, but cardiovascular disease (CVD) complications exert the greatest toll. CVD (including coronary heart disease, peripheral vascular disease, and cerebrovascular disease) is more than twice as common among diabetic compared with nondiabetic persons [3]; it is the major cause of morbidity and death in type 2 diabetes [4]. CVD events occur more than twice as frequently as specific microvascular events, and fatal CVD events may be as much as 70 times as common as fatal microvascular events [4]. Diabetes and its complications are extremely costly in terms of both health and dollars. Diabetes causes substantial loss in quality of life, is the fourth most frequent reason for ambulatory physician visits, and incurs greater than $100 billion annually in US health care expenditures [5–7]. Fortunately, our understanding of the precursors of type 2 diabetes and CVD is growing simultaneously with our understanding of the best methods to prevent these conditions.

Over the last quarter century, we have learned that type 2 diabetes and CVD arise over time from a background of adverse levels of diverse metabolic risk factors. In recent years, we have learned that type 2 diabetes and CVD share many risk factors in common, especially obesity, hyperlipidemia, hypertension, and hyperglycemia. These associations gained broader recognition over a decade ago with the postulation of "syndrome X" [8]. Reaven's [8] physiologic research documented that tissue resistance to the effects of insulin was a feature of obesity and a fundamental pathophysiologic precursor of type 2 diabetes, and possibly a precursor of hypertension and dyslipidemia (especially low levels of high-density lipoprotein [HDL] cholesterol and elevated levels of triglycerides). Based on these observations, Reaven proposed that obesity, hyperglycemia, hypertension, and dyslipidemia at least partially arise from insulin resistance and are a recognizable precursor to type 2 diabetes and CVD. The existence of a discrete syndrome has been the subject of controversy, but accumulating evidence lends substantial support for an "insulin resistance" syndrome [9].

Evidence for an Insulin Resistance Syndrome

Early population-based evidence supporting the existence of the insulin resistance syndrome included prospective associations of individual CVD risk factors with the incidence of type 2 diabetes. For instance, data from the San Antonio Heart Study documented a greater prevalence of obesity, hypertension, low levels of HDL cholesterol, hyperglycemia, and hyperinsulinemia among initially nondiabetic subjects who developed type 2 diabetes over 8 years of follow-up compared with subjects who remained nondiabetic [10]. In addition, central obesity, in particular, appeared to be responsible for the role of adiposity conferring elevated metabolic risk [11]. Subsequent data from the San Antonio study have shown that prediabetic subjects with insulin resistance have greater elevations in CVD risk factors compared with insulin-sensitive prediabetic subjects, supporting

Table 1. Definitions of the insulin resistance or metabolic syndrome by the WHO and NCEP ATP III criteria

WHO criteria	NCEP ATP III criteria
(IFG or IGT or diabetes) or insulin resistance plus two or more of the following: Waist:hip ratio > 0.85 (women) or > 0.9 (men) or body mass index > 30 kg/m^2 Triglycerides ≥ 1.7 mmol or HDL cholesterol < 0.9 mmol (women) or < 1.0 mmol (men) Blood pressure ≥ 140/90 mm Hg Microalbuminuria: urinary albumin excretion rate ≥ 20 µg/min or albumin:creatinine ratio ≥ 30 mg/g	Three or more of the following: Abdominal obesity: waist circumference > 88 cm (women) or 102 cm (men) Triglycerides ≥ 1.7 mmol HDL cholesterol < 1.16 mmol (women) or < 0.91 mmol (men) Blood pressure ≥ 130/85 mm Hg Fasting plasma glucose ≥ 6.1 mmol

IFG: FPG 6.1 to 6.9 mmol and 2-hour post-oral glucose challenge plasma glucose < 7.8 mmol. IGT: FPG < 6.1 mmol and 2-hour post glucose 7.8 to 11.0 mmol. Diabetes indicates treatment for hyperglycemia or FPG ≥ 7.0 mmol or 2-hour post glucose ≥ 11.1 mmol. Insulin resistance indicates insulin clamp-assessed glucose uptake below the 25th percentile, or homeostasis-model assessed (fasting insulin and fasting glucose 22.5) insulin resistance above the 75th percentile, as measured among subjects with no metabolic abnormalities [26].
FPG—fasting plasma glucose; HDL—high-density lipoprotein; IFG—impaired fasting glucose; IGT—impaired glucose tolerance; NCEP ATP III—National Cholesterol Education Program Adult Treatment Panel III; WHO—World Health Organization.
(*From* Alberti and Zimmet [27], NCEP [28•].)

a role for insulin resistance in the joint pathogenesis of type 2 diabetes and CVD [12•]. In another study, Finnish men with hyperinsulinemia subsequently developed hypertension and dyslipidemia [13].

A criticism of the insulin resistance syndrome hypothesis is that its constituent traits are very common, and it may co-occur in some subjects independent of any underlying unifying physiology [14]. However, in population studies insulin resistance–related risk factors co-occur to a far greater degree than would be predicted by chance alone. For instance, in the Framingham Offspring Study of primarily white subjects, groupings of three or more of low HDL cholesterol and elevated body mass index (BMI), systolic blood pressure, triglycerides, glucose, and total cholesterol occurred at twice the rate predicted by chance [15]. Similar risk factor clustering was found among white and African-American participants in the Atherosclerosis Risk in Communities Study [16]. In the Italian population-based Bruneck Study, the joint occurrence of all major insulin resistance–related traits occurred over 1000-fold more frequently than expected by chance alone [17]. Results of factor analyses provide additional statistical evidence for an insulin resistance syndrome. Factor analysis is a multivariate correlation method that seeks to identify unifying patterns underlying a large set of intercorrelated variables such as insulin resistance–related metabolic traits. More than a dozen factor analyses of metabolic risk factor data from a wide array of populations have shown that the 10 (or more) individual traits of the syndrome reflect two to four underlying physiologic processes. Many of these analyses are consistent with a central role for insulin resistance or hyperinsulinemia underlying cluster patterns [9,18].

Prospective outcomes data also support the validity of the insulin resistance syndrome hypothesis. Insulin resistance is a fundamental precursor of type 2 diabetes [19], and hyperinsulinemia associated with insulin resistance may be an independent risk factor for CVD [20]. Recently, several studies have shown that the central insulin resistance cluster identified by factor analysis is associated with the incident development of both type 2 diabetes and CVD. Data from Scandinavia show that among initially nondiabetic subjects the insulin resistance cluster increased relative risk for type 2 diabetes by over fourfold [21], and risk for CVD by about 30% [22,23,24•]. Preliminary evidence from the Framingham Study also demonstrates an 11-fold increased risk for incident type 2 diabetes and a 2.4-fold increased risk for incident CVD events associated with the insulin resistance syndrome [25]. In summary, current population-based evidence demonstrates greater than chance co-occurrence of metabolic risk factors linked to insulin resistance, giving rise over time to the joint occurrence of type 2 diabetes and CVD.

Definitions of the Insulin Resistance Syndrome

Despite growing evidence to support its existence, until recently, there has been no uniform definition for the insulin resistance syndrome. Investigators have tended to use idiosyncratic case definitions, impeding uniform analysis of the epidemiology of the syndrome. Even the name of the syndrome has been the subject of wide variation [9,26]. Recently, two expert groups, the World Health Organization (WHO) [27] and the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) [28•] have proposed criteria defining what they call the "metabolic syndrome." These criteria are displayed in Table 1, and suggestions for clinical assessment and management of component traits are listed in Table 2.

The WHO and NCEP ATP III definitions are similar in their focus on obesity, dyslipidemia, hyperglycemia, and hypertension as constituent traits. However, there are also substantial differences. 1) The WHO considers the presence of elevated postchallenge glycemia as well as insulin

Table 2. Clinical assessment and management of insulin resistance syndrome traits

Clinical assessment	
Glucose tolerance status	
Impaired fasting glucose	Requires an overnight fast of at least 8 hours
Impaired glucose tolerance	Requires an oral glucose tolerance test
Insulin resistance	Not yet recommended in clinical practice; requires (at least) measurement of the fasting insulin level
Body mass index	Weight and height measured with the patient in light clothing
Waist circumference	Abdomen measured with a tape at the level of the umbilicus
Waist:hip ratio	Hip circumference measured at the level of the iliac crest
Triglycerides	Requires an overnight fast of at least 8 hours
HDL cholesterol	Can be performed on nonfasting blood samples
Blood pressure	Most studies use the average of two measurements after the subject has been sitting for 5 minutes
Microalbuminuria	Measured with a timed overnight urine collection or a spot morning urine collection
Clinical management	
Weight loss and increased physical activity	Demonstrated in controlled trials to prevent development of type 2 diabetes [29••,30,31]
Control of elevated blood pressure and lipids	Demonstrated in controlled trials to prevent development of CVD [28•,32]
Insulin-sensitizing drugs	
Metformin	Suggested or demonstrated in controlled trials to prevent development of type 2 diabetes [29••] and CVD in patients with type 2 diabetes [33]
Thiazolidinediones	In the United States, rosiglitazone and pioglitazone; clinical trials show improved insulin sensitivity and reduced levels of CVD risk factors [34,35] One trial underway is testing prevention of type 2 diabetes [36]
Other drug therapies	
3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors ("statins")	Demonstrated in controlled trials to prevent development of CVD; observational data suggest prevention of type 2 diabetes [37]
Angiotensin-converting enzyme inhibitors	Demonstrated in controlled trials to prevent development of CVD; observational data suggest prevention of type 2 diabetes [38]

CVD—cardiovascular disease; HDL—high-density lipoprotein.

resistance, whereas the NCEP ATP III considers only fasting hyperglycemia. Reliance on fasting glucose alone to assess glycemic status may overlook a large proportion of subjects with isolated postchallenge hyperglycemia who may be classified as unaffected by NCEP ATP III criteria [39]. Both criteria explicitly (WHO) or implicitly (NCEP ATP III) include type 2 diabetes as a component trait. There is substantial controversy over this issue: if type 2 diabetes is a consequence of the syndrome then it is not useful to also include it as a component of the syndrome. In addition, assessment of insulin resistance or hyperinsulinemia is not part of usual clinical practice, making this element of the WHO criteria controversial as well [26]. 2) The WHO criteria consider either overall obesity (assessed by BMI) or central obesity (assessed by waist:hip ratio); the NCEP ATP III considers only central obesity (assessed by waist circumference). The effect of this substitution on syndrome prevalence, clinical use of the criteria, or subsequent risk for outcomes is unknown. 3) The WHO criteria assign only one "point" for dyslipidemia; the NCEP ATP III criteria assign up to two "points" for low HDL cholesterol—high triglycerides, potentially overweighting the contribution of dyslipidemia to the insulin resistance syndrome phenotype. The accurate "weight" of each trait contributing to risk for adverse outcomes is uncertain. Regression models predicting the development of type 2 diabetes demonstrate, for instance, that fasting hyperglycemia confers a fourfold greater risk per unit increase than does systolic blood pressure [40]. In addition, it is unlikely that each trait confers truly independent and equivalent risk for outcomes. Thus, weighting each trait equally may distort the risk associated with the insulin resistance syndrome, especially when comparisons are made across populations with substantial differences in underlying trait prevalence. 4) Blood pressure thresholds are higher in the WHO criteria compared with the NCEP ATP III criteria, leaving a lower prevalence, but of more severe, hypertension among those with the insulin resistance syndrome by the WHO criteria. 5) The WHO specify microalbuminuria as a component trait, whereas the NCEP ATP III does not. As for the obesity traits, the marginal effect of this trait difference is unknown.

The presence of these differences and other problems with proposed criteria for the insulin resistance syndrome point out that substantial work to reduce uncertainty about the syndrome remains to be done. In particular, whether proposed criteria identify substantially different subjects or confer differential risk for type 2 diabetes or CVD remains to be determined.

Prevalence of the Insulin Resistance Syndrome

The WHO criteria were proposed in 1998 and the NCEP ATP III criteria were proposed in 2001. To date, there is very little published data on the prevalence of the insulin resistance syndrome in the US population. The best current data were published in early 2002 by Ford *et al.* [41••], based on an analysis of 8814 men and women aged 20 years or older from the Third National Health and Nutrition Examination Survey (NHANES III, 1988–1994), a cross-sectional health survey of a nationally representative sample of the noninstitutionalized US civilian population. Ford *et al.* [41••] used NCEP ATP III criteria to assess prevalence of the syndrome. There are currently no published population-based data on the prevalence of the syndrome by the WHO criteria. According to the NCEP ATP III data, there is substantial heterogeneity in the distribution of insulin resistance syndrome traits. For instance, large waist circumference is more common in women, whereas elevated triglyceride levels are more common in men. Hypertension is relatively common in African Americans, whereas high triglycerides are relatively uncommon. Four of the traits are roughly equally prevalent in white persons, whereas hyperglycemia is relatively uncommon in all groups.

Overall, the prevalence of the syndrome by NCEP ATP III criteria is similar among men and women—about 24%—but increases dramatically with age, from about 7% among people in their 20s to over 40% among people older than 60 years. Racial and ethnic trait heterogeneity give rise to substantial racial and ethnic variation in the prevalence of the syndrome itself. About 36% of Mexican-American women and 28% of Mexican-American men have the syndrome, whereas only about 26% of African-American women and 16% of African-American men are affected. White women (23%) and white men (25%) are equally affected. Overall, 24% of white persons, 22% of African Americans, 32% of Mexican Americans, and 20% of other racial and ethnic groups combined may be classified with the syndrome. Despite these high prevalence rates, they are likely an underestimate of the current prevalence of the syndrome, given the accelerating epidemic of obesity (and its adverse metabolic effects) in the US population over the last decade [42].

Genetics of the Insulin Resistance Syndrome

Like many common chronic diseases, the insulin resistance syndrome is partly determined by modifiable environmental factors, especially obesity and a sedentary lifestyle [43]. However, there may also be a genetic basis for the syndrome. Family studies demonstrate that clusters of metabolic risk factors are transmitted from parents to offspring [44]. Twin studies demonstrate a higher concordance of insulin resistance syndrome traits among monozygotic compared with dizygotic twins, and heritabilities of these traits of 40% to 50% [45,46]. Family studies also demonstrate that a common set of genes may determine not only fasting insulin levels but also lipid and obesity traits [47]. Recent linkage analyses identify loci linked to insulin resistance syndrome traits on chromosomes 3, 6, 7, and 17 [48,49]. The significance of these loci remains to be determined, because translation of linkage information into specific gene discovery has proved enormously difficult. In addition, there are likely to be several genetic determinants for the insulin resistance syndrome, given its underlying trait heterogeneity.

Prevention and Treatment of the Insulin Resistance Syndrome

If insulin resistance is the underlying cause of the insulin resistance syndrome, then interventions to improve insulin sensitivity may constitute an important, specific therapy for the prevention of type 2 diabetes and CVD. Current options for therapeutic management of insulin resistance are listed in Table 2. Because obesity and a sedentary lifestyle are two major modifiable risk factors for insulin resistance, lifestyle changes leading to weight loss and increased physical activity are key therapies to reduce risk factor levels diagnostic of the syndrome. Although there are no data directly addressing the insulin resistance syndrome, data showing that type 2 diabetes can be prevented provide guidance. For instance, the Diabetes Prevention Program (DPP) demonstrated recently that an intensive lifestyle modification program with the goals of at least a 7% weight loss and at least 150 minutes of physical activity per week reduced the incidence of type 2 diabetes to 4.8 cases per 100 person-years, compared with 11 cases per 100 person-years in a standard lifestyle recommendation control group [29••]. This effect translated into an absolute risk reduction of 6.2 cases per 100 person-years, with about seven patients needing treatment for 3 years to prevent one case of type 2 diabetes, and a relative risk reduction of 58% (95% CI: 48% to 66%). The results of the DPP confirm findings of other similar studies, including the Finnish Diabetes Prevention Study and the Da Qing (China) IGT and Diabetes Study [30,31]. The American Diabetes Association advocates counseling patients at risk for type 2 diabetes to lose weight and increase physical activity.

Eligibility criteria for the DPP included age ≥ 25 years, a BMI of ≥ 24 kg/m^2, a fasting plasma glucose level of 5.3 to 6.9 mmol, and 7.8 to 11.0 mmol 2 hours after a 75-g oral glucose tolerance test. Other features of the insulin resistance syndrome were not included in eligibility criteria, although it is likely that many DPP participants would be classified as having the syndrome. The prevalence of the insulin resistance syndrome among people otherwise meeting DPP eligibility criteria will provide evidence of the expected benefit of applying the DPP results to insulin resistance syndrome management, which is the subject of ongoing research.

The DPP also demonstrated that treatment with the insulin-sensitizing drug metformin (850 mg twice a day) reduced the incidence of diabetes to 7.8 cases per 100 person-years compared with placebo. This effect translated into an absolute risk reduction of 3.2 cases per 100 person-years,

with about 14 patients needing treatment for 3 years to prevent one case of type 2 diabetes, and a relative risk reduction of 31% (95% CI: 17% to 43%). Metformin therapy was less effective in subjects older than 60 years and those with a BMI less than 30 kg/m^2. Metformin may also reduce CVD events in patients with type 2 diabetes [33]. The other major class of insulin-sensitizing drugs, the thiazolidinediones (of which rosiglitazone and pioglitazone are currently available in the United States), also improve metabolic risk factor levels [34], and may reduce the progression of atherosclerosis [35]. One clinical trial underway is testing whether troglitazone prevents the development of diabetes in women with gestational diabetes [36], but currently there is no direct evidence that the thiazolidinediones are useful for diabetes or CVD prevention.

3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (or "statins") and angiotensin-converting enzyme inhibitors have also been suggested to prevent not only CVD, but type 2 diabetes. In post-hoc analyses of randomized controlled trials to prevent CVD, the statin pravastatin [37] and the angiotensin-converting enzyme inhibitor ramipril [38] were found to reduce the relative risk of diabetes by about 30%. Both these drugs may have beneficial effects on vascular endothelial function; their antidiabetic effect is consistent with the hypothesis that insulin resistance, type 2 diabetes, and CVD share endothelial dysfunction as their ultimate common antecedent [50]. On the basis of relatively weak effects, scant experimental data, and the potential for adverse drug effects, the American Diabetes Association currently does not advocate the routine use of any drug therapy to prevent type 2 diabetes. By extension, the same argument can be made for the prevention of the insulin resistance syndrome.

Therapeutic lifestyle changes have broad benefits on health and can safely be recommended for most subjects. However, it must be emphasized that we do not know whether treatment aimed at the insulin resistance syndrome will reduce the risk for adverse outcomes to an equal or greater degree than treatments aimed at individual metabolic traits. There is solid experimental evidence that therapies directed specifically at hyperlipidemia, hypertension, and hyperglycemia significantly reduce risks for type 2 diabetes and CVD events and should be considered for patients with any of these conditions [28•,29••,32]. Perhaps the greatest value in recognizing the insulin resistance syndrome is not that it suggests specific treatment for insulin resistance, but that it identifies a patient with an extremely adverse metabolic state warranting aggressive intervention for specific risk factors.

Conclusions

Over the last decade we have learned that type 2 diabetes and CVD share many risk factors in common. Even mild elevations in blood pressure, plasma lipids, and blood glucose, when they occur in combination, confer substantial excess risk for type 2 diabetes, CVD, and death. The co-occurrence of these risk factors is linked to obesity (especially central obesity) and insulin resistance; this co-occurrence constitutes the insulin resistance syndrome. Recently proposed case definitions enable epidemiologic analysis of the insulin resistance syndrome, although specific details of the definition, including which traits (especially diabetes), trait thresholds, and trait weightings are appropriate, remain to be resolved. Emerging prevalence data suggest that the insulin resistance syndrome is very common, especially among older people and in Mexican-American populations. The syndrome will undoubtedly become even more common over time, paralleling the exploding epidemic of obesity and type 2 diabetes in the United States and worldwide.

Weight loss and increased physical activity are important treatments to reduce insulin resistance, but recognition of the syndrome in an individual patient should trigger aggressive intervention to reduce levels of specific traits. The etiology, prevention, and treatment of the insulin resistance syndrome are currently the current focus of intense research activities. We can expect our understanding of the public health and clinical importance of the syndrome to have a much stronger evidence base within the next few years.

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