

Chapter 15

Insulin Resistance, Metabolic Syndrome, and Therapy

Features of the metabolic syndrome have been described for many years. In the early 1920s, the Swedish clinical investigator Dr. Eskil Kylin described a disorder characterized by the constellation of hypertension, hyperglycemia, and hyperuricemia [1]. Clustering of cardiovascular risk factors, specifically, hypertension, diabetes mellitus (DM), dyslipidemia, and obesity, was further described in the 1960s and 1970s, albeit without elucidation of possible etiologies for the syndrome [2, 3]. In 1988, Reaven termed this constellation of cardiovascular risk factors Syndrome X and posited insulin resistance as its underlying cause [4]. In 1998, the World Health Organization (WHO) provided a working definition for this syndrome and named it “metabolic syndrome” [5].

The metabolic syndrome is also known as the

- cardiometabolic syndrome,
- dysmetabolic syndrome,
- deadly quartet,
- insulin-resistance syndrome,
- metabolic syndrome X,
- syndrome X, and
- Reaven’s syndrome.

Diagnostic criteria for the metabolic syndrome

The metabolic syndrome is a multifactorial condition with considerable heterogeneity. Several standardized diagnostic criteria for the metabolic syndrome are used for its diagnosis.

The metabolic syndrome has been defined not only by the WHO [5, 6], but also by the National Cholesterol Education Program (NCEP) [7], by the American Association of Clinical Endocrinology (AACE) [8], and by the International Diabetes Federation (IDF) [9]. The clinical diagnosis of the syndrome is based on the criteria given in Tables 15.1 and 15.2.

A summary of the revised scientific statement (Table 15.3) from the American Heart Association (AHA)/ National Heart, Lung, and Blood Institute (NHLBI) [11] brings the diagnostic criteria for the metabolic syndrome into alignment with

those from the Joint National Committee (JNC) [12] and the American Diabetes Association (ADA) [13].

The NCEP (or AHA/NHLBI) definition is easiest to use in clinical practice since testing of glucose tolerance, insulin resistance, and microalbuminuria is not required.

Although the definitions of the metabolic syndrome vary slightly between the different organizations, *the stated criteria basically define the same group of individuals presenting with*

- abdominal obesity,
- dyslipidemia,
- hypertension, and
- impaired glucose homeostasis,

each component being a cardiometabolic risk factor in its own right. Beyond the additive effect of these components on cardiometabolic risk, there is a synergism compounding the threat to health.

Importantly, not all individuals with the metabolic syndrome will develop all the clinical features of the syndrome or all their sequelae. Furthermore, the abnormalities or clinical sequelae can develop in any chronological order.

Utility of the definition

The ADA and the European Association for the Study of Diabetes (EASD) have suggested that clinicians should evaluate and treat cardiovascular risk factors without considering whether a constellation of risk factors meets diagnostic criteria for the metabolic syndrome [14]. In their joint statement, the ADA/EASD questioned the clinical utility of the definition because of uncertainty about a unifying etiology, the imprecision of some criteria, variations in the definition of the syndrome, and its questionable utility in risk assessment beyond the established Framingham Risk Assessment tools [7]. The ADA/EASD argued that insulin resistance does not necessarily underlie all causes of the metabolic syndrome, and that the etiology may be related to abnormalities in visceral adipose tissue or an altered inflammatory state [14].

The ADA/EASD concerns are legitimate subjects for ongoing study, and better definitions need to be developed. In truth, the definitions for the metabolic

Table 15.1 Clinical diagnosis of the metabolic syndrome.

Criteria	WHO	NCEP	AACE	IDF
Body mass index (BMI)	BMI >30 kg/m ² - or:			
Waist/hip ratio	Men: >0.90 Women: >0.85			
Waist circumference*	Men: Women:	≥40 in. = 102 cm ≥35 in. = 88 cm	>102 cm=40 in. >88 cm=35 in.	≥94 cm ≥80 cm South Asians/Chinese: ≥90 cm ≥80 cm Japanese: ≥90 cm ≥85 cm
Triacylglycerols or triglycerides (TGs)	≥150 mg/dL	≥150 mg/dL	>150 mg/dL	≥150 mg/dL or therapy for elevated TGs
High-density lipoprotein (HDL)	Men: <35 mg/dL Women: <40 mg/dL	<40 mg/dL <50 mg/dL	<35 mg/dL <45 mg/dL	Therapy for low HDL - or <40 mg/dL <50 mg/dL
Blood pressure (BP)	Antihypertensive therapy, - or BP ≥140/90 mmHg	Antihypertensive therapy, - or BP ≥135/85 mmHg	Hypertension	Antihypertensive therapy, - or ≥130/85 mmHg
Glucose	Type 2 DM, or • impaired fasting glucose (IFG), • abnormal hyperinsulinemic-euglycemic clamp	Fasting glucose ≥110 mg/dL	Fasting glucose >110 mg/dL, or type 2 DM	Fasting glucose ≥100 mg/dL,** or type 2 DM
Other	Microalbuminuria >20 µg/min, or albumin/creatinine >30 mg/g		Insulin resistance -or acanthosis nigricans	
Requirement for diagnosis	Confirmed type 2 DM, or • impaired glucose tolerance (IGT), and • any other two of the above criteria	Any three of the above criteria	Consider also minor criteria such as polycystic ovary syndrome (PCOS), hypercoagulability, endothelial dysfunction, microalbuminuria, and coronary heart disease (CHD)	Central obesity, plus two of the other four criteria

*Waist circumference is measured at the top of the iliac crest horizontally across the abdomen at end-expiration. Individuals of Indian or Asian extraction may have a small waist circumference at baseline and may thus have metabolic syndrome even with a waist circumference of only 27–30 in. African-American women may similarly have small waist sizes. The IDF criteria may be more pertinent than those from the NCEP for screening and estimating risk in Chinese populations [10].

** If >100 mg/dL, an oral glucose tolerance test (GTT) is recommended, but not required, for diagnosis.

syndrome do present an eclectic and very incomplete array encompassing both causes and effects of the underlying pathophysiology.

However, the group of criteria identifying the metabolic syndrome is simple, easy, and inexpensive for healthcare professionals to recognize a population at risk. It brings

Table 15.2 categorical cutpoints for waist circumference in different populations [11].

Criteria	General U.S. population	Non-Asian U.S. adults with strong genetic predisposition to insulin resistance	Asian Americans
Men:	≥40 in.	≥37–39 in.	≥35 in.
Women:	≥35 in.	≥31–34 in.	≥31 in.

Table 15.3 Summary of the criteria for the metabolic syndrome.

Risk factor	Categorical cutpoints
Waist circumference	Men: ≥40 in., ≥102 cm Women: ≥35 in., ≥88 cm
TGs	≥150 mg/dL (1.7 mmol/L), or drug therapy for elevated TGs
HDL	Men: <40 mg/dL (0.9 mmol/L) Women: <50 mg/dL (1.1 mmol/L), or drug therapy for low HDL
BP	Systolic BP ≥130 mmHg, or diastolic BP ≥85 mmHg, or current antihypertensive therapy
Fasting glucose	≥100 mg/dL, or drug therapy for elevated glucose [11]

together the fields of cardiology and endocrinology in a concerted effort to reduce the cumulative, multiplicative risk posed by the clustering of cardiometabolic risk factors arising from that condition.

Several risk factors underlying the metabolic syndrome, such as its prooxidant, proinflammatory, and prothrombotic state, are not addressed in standard risk algorithms, but nevertheless contribute importantly to the future risk of cardiovascular events and metabolic disease [15]. In addition, the metabolic syndrome poses a significant risk not only for cardiometabolic but also for neurodegenerative and neoplastic disease.

The “Dysmetabolic Syndrome X” holds official ICD-9 diagnostic status. This single diagnosis emphasizes the need to identify and “holistically” treat a global risk. It allows the clinician to focus on issues, such as inactivity, lack of fitness, poor diet, visceral obesity, ongoing inflammatory diseases, borderline blood pressure, and many other factors that would be overlooked in a conventional focus on Framingham risk factors alone.

Prevalence of the metabolic syndrome

The metabolic syndrome is diagnosed with increasing frequency world wide. In many individuals, it is associated with obesity and a sedentary lifestyle. Based on the

NCEP/Adult Treatment Panel (ATP) III guidelines, the prevalence of the metabolic syndrome among adults in the U.S. aged ≥20 years is estimated to be 34%, corresponding to 35.1% of men and 32.6% of women. This implies that a little more than one-third of adults in the United States can be characterized as having the metabolic syndrome [16, 17].

Prevalence of the metabolic syndrome rises dramatically as BMI increases, from >6.8% for the underweight- and normal weight population to >56.1% for the obese and extremely obese [17].

The prevalence of the metabolic syndrome varies among ethnic groups. In the U.S., prevalence is highest in Hispanics. For Mexican-Americans, the age-adjusted prevalence of the syndrome is 33.2 and 40.6% for men and women, respectively. Aboriginal people of North America and people who originate from the Indian subcontinent also have an increased susceptibility to develop the metabolic syndrome. The prevalence is lower in non-Hispanic Caucasians and African-Americans and is lowest among individuals of Chinese origin [16].

The incidence of the metabolic syndrome increases steeply with age. The prevalence in 40-year-olds is >37% and rises to >51% for individuals aged 60 years and older. The incidence is higher for women than for men of African-American, Mexican-American, South-Asian and Native-Indian extraction [16–19].

Insulin resistance

Fasting plasma insulin and glucose levels are, in part, determined by a hepatic–pancreatic beta cell feedback loop. With any glucose challenge, three coordinated events preserve normal glucose homeostasis, specifically

- 1 insulin secretion by the pancreatic beta cells,
- 2 suppression of hepatic glucose production by blocking glycogenolysis and gluconeogenesis, and
- 3 stimulation of glucose uptake by the liver, by skeletal muscle, and by adipose tissue.

With insulin resistance, the second and third steps are dysfunctional, as metabolic derangements in muscle, adipose tissue, and liver underlie insulin resistance.

In overt hyperglycemia and type 2 DM, defects in pancreatic beta cells supervene, as all three steps become imbalanced [20].

Hyperinsulinemia with euglycemia

Insulin resistance is a key feature and a hallmark of the metabolic syndrome [4]. Impaired insulin action occurs when target tissues display a diminished capacity of cells to respond to physiologic levels of insulin.

In a compensatory response, the beta cells of the pancreas secrete increased amounts of insulin, and fasting insulin levels are elevated in direct proportion to diminished insulin sensitivity. In the initial stages, insulin

Table 15.4 Plasma glucose values.

Index	Value
Fasting plasma glucose	WHO: <110 mg/dL (<6.1 mmol/L) ADA: 70–100 mg/dL (3.88–5.55 mmol/L)
Plasma glucose 2 hours after a 75 g oral GTT (if measured)	<140 mg/dL (<7.8 mmol/L)
Hemoglobin (Hb)A _{1c}	4 – <6%

secretion and hyperinsulinemia remain adequate to maintain euglycemia [21]. Many individuals with insulin resistance have preserved glucose levels [4].

Normal plasma glucose values are defined in Table 15.4 [22].

The term “insulin resistance” is defined as impaired insulin-stimulated glucose disposal manifested by

- a steady-state plasma glucose level that is in excess of what should be seen with the prevailing plasma insulin level, or
- a plasma insulin level that is in excess of the norm for fasting or for 2-hour postglucose-challenge plasma glucose levels.

The application of the NCEP ATP III criteria to subjects studied at the third National Health and Nutrition Examination Survey (NHANES) showed that IFG criteria were met by only 10% of individuals with the metabolic syndrome [23].

Prediabetes and type 2 diabetes mellitus

Sir Harold Himsworth, a renowned clinician and researcher, was the first to differentiate DM into “insulin-sensitive” and “insulin-insensitive” forms [24]. *Insulin resistance is the fundamental defect and the most important predictor of type 2 “insulin-insensitive” DM* [21, 24]. It predates overt hyperglycemia and type 2 DM by 10–20 years [25]. Insulin-resistance variables are significantly associated with incident type 2 DM [26].

In approximately 80% of insulin-resistant individuals, with the passage of time, functional defects in pancreatic insulin secretion arise. Hyperglycemia reflects the reduction in insulin secretory capacity, causing compensatory hyperinsulinemia to fail and allowing prediabetes and type 2 DM to supervene [21, 27, 28].

Prediabetes is present with any of the following:

- *impaired fasting glucose, IFG, defined as* [22]

Index	Glucose value
Fasting plasma glucose	WHO: 110–125 mg/dL (6.1–6.9 mmol/L) ADA: 100–125 mg/dL (5.6–6.9 mmol/L)

or an alternative to IFG, specifically

- *impaired glucose tolerance, IGT defined as* [8, 22]

Index	Glucose value
Fasting plasma glucose	<126 mg/dL (<7.0 mmol/L)
Plasma glucose 2 hours after a 75 g oral GTT	≥140–199 mg/dL (≥7.78 – <11.06 mmol/L)

or a more convenient and stable measure for this condition

- *HbA_{1c} in the range of*

Index	Value
HbA _{1c}	6.0–6.5%

The presence of the metabolic syndrome increases a person’s risk of progression to type 2 DM approximately five-fold when compared to a person’s risk without the syndrome [15]. In a prospective study of 5,128 men aged 40–59 years with no history of cardiovascular disease or DM, over 20 years of follow-up, the presence of the metabolic syndrome at baseline conferred a relative risk (RR) of 3.57 of developing DM. For those with no metabolic derangements at baseline, the risk was 11.9%. The risk was 31.2% for those with three diagnostic components of the metabolic syndrome, and 40.8% for those with five diagnostic criteria [29], including hyperglycemia. With the advent of hyperglycemia, of the criteria for prediabetic states, IGT poses a greater risk factor for progression to established type 2 DM than the former, IFG. Over 40% of the population in the U.S. over 60 years of age has hyperglycemia [30].

Type 2 DM is diagnosed for the values shown in Table 15.5.

25% of the adult U.S. population has type 2 DM, and the incidence and prevalence of DM have been increasing, together with serious DM-related complications [31]. The estimated economic burden of DM in the U.S. exceeds \$100 billion per year, a substantial proportion of which is due to DM in the elderly [32]. DM is increasing at an alarming rate in all modern societies and is rapidly emerging as one of the greatest global health challenges of the 21st century. Globally, by the year 2030, the WHO estimates that 366 million people will be afflicted with type 2 DM [33].

Table 15.5 Glucose criteria for the diagnosis of type 2 DM.

Index	Value
HbA _{1c}	≥6.5%
Fasting plasma glucose	≥126 mg/dL (7.0 mmol/L)
A nonfasting plasma glucose or symptoms of hyperglycemia	≥200 mg/dL (11.1 mmol/L)
2-hour plasma glucose during an oral GTT	≥200 mg/dL (11.1 mmol/L) [22]

Table 15.6 Insulin resistance manifestations in selected tissues.

Adipose tissue	Decreased adipogenesis, Increased lipolysis, Decreased adiponectin, Increased release of free fatty acids (FFAs)
Skeletal muscle and myocardium	Inappropriate forkhead box (Fox) protein activation [36, 37] Loss of sirtuin expression and activity Increased cell loss Impaired mitochondrial oxidative capacity and biogenesis Intramyocellular fat Reduced disposal of glucose Decreased oxidation of fatty acids Protein catabolism
Liver	Decreased hepatic insulin extraction Inappropriate Fox protein activation [36] Intrahepatocellular fat Decreased glucokinase activity Inappropriate hepatic glycogenolysis and gluconeogenesis Enhanced very low-density lipoprotein (VLDL) synthesis and secretion
Intestines	Enhanced TG-rich lipoprotein (TRL) synthesis and secretion
Central nervous system	Loss of the central weight control functions of insulin and leptin
Vascular endothelium and vascular smooth muscle cells (VSMCs)	Blood vessel endothelial dysfunction Increased vascular inflammation Changes in key regulators of thrombosis

Multiorgan manifestations of insulin resistance

Insulin resistance impairs insulin action in a variety of insulin-sensitive tissues (see Table 15.6). Insulin resistance thus gives rise to multiple metabolic disturbances.

In nondiabetic offspring of diabetic probands, insulin resistance in skeletal muscle and adipose tissue deranges glucose and energy metabolism. Hypoadiponectinemia, as well as high levels of cytokines and adhesion molecules reflecting low-grade inflammation and endothelial dysfunction, are present in subjects with the metabolic syndrome [34]. Of the criteria listed in the NCEP ATP III guidelines for the metabolic syndrome, *hypertriglyceridemia and low HDL levels are most closely associated with insulin resistance* [35].

Selective insulin resistance

The same insulin receptor controls different cellular response pathways (Table 15.7).

Although insulin resistance affects many tissues, some insulin-mediated processes remain sensitive to insulin (Table 15.8). Insulin resistance differentially affects the PI3K and MAPK signaling pathways. Specifically, *in the*

Table 15.7 Insulin response pathways and effectors.

Glucose and lipid metabolic signaling	Phosphatidylinositol 3-kinase (PI3K)
Vascular signaling and nitric oxide (NO) synthase (NOS) regulatory effects	PI3K
Mitogenic signaling with cell growth and proliferation	Mitogen-activated protein kinase (MAPK)

Table 15.8 Selective insulin resistance effect on insulin signaling [39].

Metabolic pathway	Defective insulin signaling
Vascular pathway	Defective insulin signaling
Mitogenic pathway	Intact insulin signaling

setting of insulin resistance, insulin has reduced effects only on the PI3K pathways, whereas insulin sensitivity to MAPK signaling is preserved [38].

MAPK signaling may actually be enhanced with insulin resistance.

- Normally, insulin-activation of PI3K negatively regulates the upstream activator for MAPK, Raf-1. With impaired PI3K activation due to insulin insensitivity, insulin-mediated MAPK activity may be enhanced, thus promoting MAPK-mediated mitogenic effects [40].

- Since the insulin/IGF mitogenic pathway is not insulin resistant, tissues susceptible to mitogenic stimulation are fully exposed to elevated levels of insulin/IGF in the setting of compensatory hyperinsulinemia, exacerbating the adverse effects of mitogenic signaling.

Insulin at high concentrations can activate the cognate IGF-1 receptor. Both the insulin and the IGF-1 receptors play overlapping roles in cell growth. A number of side effects of extreme insulin resistance in humans are mediated via insulin activation of IGF-1 receptors [41].

Hyperinsulinemia has adverse effects on those targets that have not become insulin resistant.

- Increased activation of MAPK can greatly stimulate vascular and nonvascular cell growth with vascular remodeling, increase vascular inflammation, and contribute to the pathogenesis of macrovascular complications [42].

- Hyperinsulinemia and its negative effects on FoxO protein activity reduce stress resistance and oxidative stress resistance in tissues. This is compounded by loss of sirtuin activity and further increases in oxidative stress and proinflammatory signaling.

- Hyperinsulinemia stimulates the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system, enhances renal sodium absorption, and contributes to hypertension [43, 44].

- Hyperinsulinemia increases ovarian androgen production, the integral hormonal imbalance observed with PCOS, which affects 1 in 10 U.S. women of childbearing age [45].

- The increased mitogenic milieu of hyperinsulinemia increases the risk of neoplasia.

The multiorgan impact of selective insulin resistance, in concert with mitogenic hyperactivity, ultimately engenders multi-system metabolic and vascular sequelae that characterize the metabolic syndrome.

Other biomarkers of the metabolic syndrome

Insulin resistance and hyperinsulinemia engender dyslipidemia, hypertension, hypercoagulability, impaired fibrinolysis, vascular disease, and a proinflammatory state [39]. As a result, other biomarkers that contribute to the clinical diagnosis of the metabolic syndrome are

- insulin resistance with
 - elevated fasting insulin,
 - high insulin/glucose ratio, or
 - IGT or abnormal 2-hour postprandial glucose;
- dyslipidemia with
 - elevated TGs,
 - small, dense low-density lipoprotein (LDL) particles, and
 - decreased HDL;
- prothrombotic state with impaired fibrinolysis due to
 - elevated serum plasminogen activator inhibitor (PAI)-1,
 - elevated fibrinogen,
 - increased factor VII,
 - platelet aberrations;
- vascular dysfunction with
 - endothelial dysfunction,
 - microalbuminuria,
 - hypertension, and
 - heightened risk of atherosclerotic disease;
- elevated serum uric acid;
- proinflammatory state and mitogenic effects with
 - elevated high sensitivity (hs) C-reactive protein (CRP),
 - elevated insulin-like growth factor-1,
 - elevated tissue angiotensin II levels [46].

The presence of increased systemic inflammation is a defining characteristic of the metabolic syndrome. It has been suggested that CRP become another diagnostic requirement for the metabolic syndrome [47].

Associated clinical findings

Defective insulin signaling is linked to a variety of pathological conditions, and the epidemic rise in the incidence of metabolic syndrome and DM is expected to trigger a steep increase in associated clinical findings and comorbidities, such as

- hypertension,
- a cardiomyopathic process,
- nonalcoholic fatty liver disease (NAFLD) and steatohepatitis,
- atherogenic dyslipidemia,
- coronary, peripheral, and cerebrovascular disease and acute ischemic syndromes,
- calcific vascular and valvular disease,

- a history of gestational diabetes,
- type 2 DM,
- acanthosis nigricans,
- PCOS,
- gallbladder disease,
- frailty,
- depression,
- neuropathy,
- retinopathy,
- dementia and Alzheimer's disease,
- lymphoma, multiple myeloma, or
- cancers of the cervix/endometrium, ovaries, breast, prostate, esophagus, gallbladder, liver, pancreas, kidney, colon/rectum.

Diagnosis of insulin resistance

Since compensatory hyperinsulinemia maintains euglycemia in the setting of insulin resistance for many years, the criteria used in the clinical diagnosis of the metabolic syndrome have low sensitivity for the detection of insulin resistance [23, 34].

Sir Harold Himsworth was the first to measure insulin sensitivity directly via the insulin–glucose test [24]. Various techniques that entail measurement of plasma insulin concentration can diagnose insulin resistance more sensitively:

- The hyperinsulinemic-euglycemic clamp technique is considered the gold standard, but is cumbersome. It entails a prolonged insulin infusion to maintain a constant plasma insulin level and repeated blood sampling. Glucose is then infused and, as the plasma level of glucose falls due to the action of insulin, more glucose is added to maintain a steady level. The amount of glucose infused over time provides a measure of insulin resistance.
- A glucose–insulin tolerance testing-based approach is inconvenient, requiring repeated blood sampling. The 2-hour postglucose challenge glucose and insulin levels are considered a clinically sensitive and simple test.

- Surrogate measures of insulin sensitivity, including
 - the Homeostasis Model Assessment (HOMA) (insulin resistance =
 - fasting plasma glucose mmol/L × fasting plasma insulin μU/mL/22.5, or
 - fasting plasma glucose mg/dL × fasting plasma insulin μU/mL/405,

A HOMA calculator is available at <http://www.dtu.ox.ac.uk/homacalculator/index.php>,

- the insulin sensitivity index (ISI), and
- Quantitative Insulin Sensitivity Check Index (QUICKI), can be applied to single measurements of fasting insulin and glucose. These surrogates have been shown to correlate well with the direct glucose clamp measure [48–53].

In general,

- fasting blood levels of insulin are usually <10 mU/L,
- fasting insulinemia, >15 mU/L, defines hyperinsulinemia, correlating highly with the euglycemic clamp study, and

- the 2-hour postglucose-challenge insulin value may be of even greater utility.

At present, analytic methods for insulin measurement are not yet standardized, and absolute values, in the absence of frequency distributions and norms, are difficult to relate between different assays [54]. The development of standardized insulin assays, or of alternative sensitive biomarkers of insulin resistance, will facilitate the diagnosis of insulin resistance.

Causes of insulin resistance

A multiplicity of genetic and external factors can induce insulin resistance, as shown in Box 15.1. Many have been discussed in detail in the preceding chapters.

Genetics

Insulin resistance can develop in individuals with a genetic predisposition, as determined by family history or population group [55].

Family studies suggest a complex but significant genetic basis to the individual constituents of the metabolic syndrome. A “thrifty genotype hypothesis” implicates the evolutionary selection of metabolic genes in hunter-gatherer societies and during historical periods of erratic food supply. The positive selection of such genetic variants would allow individuals to efficiently deposit calories during brief periods of nutritional abundance and conserve energy stores during prolonged periods of deprivation. In the current setting of perpetual dietary excess compounded by physical inactivity, the expression of such a genetic make-up may devolve into the metabolic syndrome [23] and account for the high prevalence of type 2 DM [56, 57].

The genetic underpinning for insulin resistance is not absolute. *Environmental factors clearly play a major role* [58] that can increase or decrease the expression of this metabolic phenotype.

Physical inactivity

Physical inactivity plays a central role in the development of insulin resistance [59, 60].

Insulin insensitivity develops with inactivity and may occur even after several days of bed rest. With inactivity,

Box 15.1 Predisposing factors for insulin resistance

Genetics		
Physical inactivity		
Aging	→	Insulin resistance
Dysfunctional obesity		
Stress		
Low birth weight		
Medications		

type II fast-twitch, glycolytic, insulin-insensitive muscle fibers are increasingly expressed with reduced fatty acid oxidative capacity, diminished skeletal muscle blood flow, and impaired insulin-mediated capillary recruitment [61, 62].

Federal statistics show that 7 out of 10 adults get too little exercise, and 33% get none [63]. Insulin sensitivity correlates with cardiovascular fitness and is inversely associated with the degree of obesity [64, 65].

Aging

Insulin resistance is associated with aging. All insulin-resistant conditions are, in effect, diseases of physiologic aging, irrespective of chronological age.

With aging, there is a progressive loss of lean body mass, which is replaced by adipose tissue. Muscle loss causes less muscle tissue to be available for glucose disposal. That process, together with the secondary metabolic changes, leads to insulin resistance [66].

The reduced insulin sensitivity of aging arises, in part, from physical inactivity, being particularly apparent in sedentary individuals. Muscle loss, and the phenotypic expression of metabolically less active muscle, is accelerated with pursuit of a sedentary lifestyle [66].

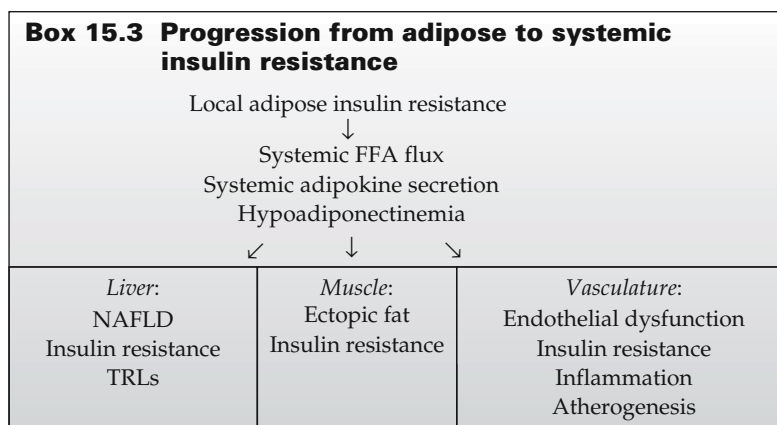
Overweight

Insulin resistance is strongly linked to obesity [67]. In particular, increased dysfunctional obesity, characterized by ponderosity in visceral compartments and ectopic fat, is negatively correlated with insulin sensitivity [68]. Visceral fat is metabolically very active. It is a major factor in the enhanced elaboration of inflammatory cytokines, such as tumor necrosis factor (TNF)-alpha and PAI-1, and in the reduced production of adiponectin. It is instrumental in mediating the systemic release of FFAs.

In the case of dysfunctional visceral obesity, inflammation and insulin resistance may be initiated in adipocytes as a local process [69], as shown in Box 15.2.

Box 15.2 Progression from adipose inflammation to adipose insulin resistance

Inflammatory process
 Endothelial dysfunction
 Adipose macrophage infiltration
 ↓
 Increased adipocyte TNF-alpha/RAAS/adipokines
 Adipose auto/paracrine effects
 ↓
 Adipose insulin resistance
 Antiadipogenesis
 Prolipolysis
 Adipocyte dedifferentiation/apoptosis



Local adipose insulin resistance may, as it progresses, target the metabolism of remote tissues, such as the liver, skeletal muscle, heart, and the vasculature, via the systemic reach of circulating adipokines and FFAs, via the pathways shown in Box 15.3.

Stress

The sensitivity to insulin signaling is decreased by a multiplicity of conditions that are stressful to normal physiology, including

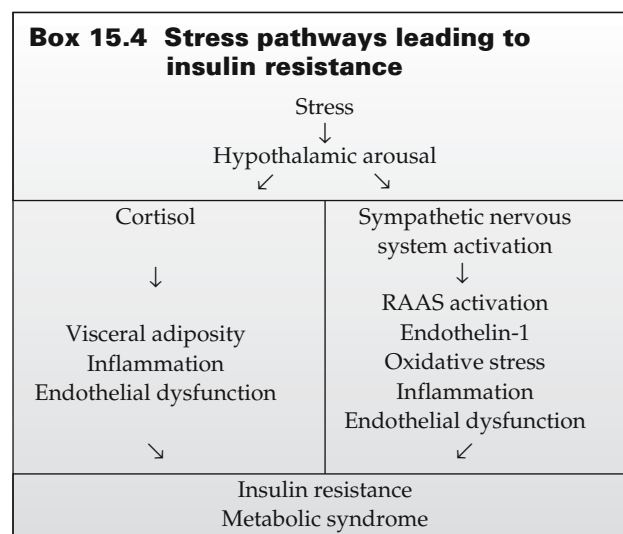
- psychological and mental stress,
- disordered sleep,
- severe protracted injury,
- chronic infection,
- sepsis,
- inflammatory diseases,
- environmental pollutants,
- excessively rich diet,
- elevated iron stores,
- pregnancy,
- impaired estrogen action

and others [70]. These arouse sympathetic hyperactivity, neurohormonal activation, and glucocorticoid excess that divert energy substrate to immune tissues (Box 15.4). The insulin-resistant state is prevalent in hypertension, coronary heart disease (CHD), heart failure, and following myocardial infarction (MI) [71].

Medications

Medications may contribute to insulin resistance. Certain medications, such as glucocorticoids, antidepressants, antihistamines, antipsychotics, antihypertensive alpha or beta-adrenergic blockers, and some protein pump inhibitors, are conducive to adipose tissue weight gain and indirectly increase the risk of insulin resistance.

Glucocorticoids induce resistance to insulin both via direct and indirect mechanisms [72, 73]. Thymidine



analogue reverse transcriptase inhibitor therapy in patients with human immunodeficiency virus (HIV) disease does so by inducing peripheral lipoatrophy via adipose inflammation, severe mitochondrial dysfunction, and increased oxidative stress, leading to adipocyte loss [74, 75].

Low birthweight

Children born prematurely have lower insulin sensitivity when compared with controls [76]. Low birth weight may arise from prenatal stress and is associated with chronic hypothalamic-pituitary-adrenal (HPA) axis hyperactivity. As a result, it may be related to insulin resistance, the metabolic syndrome, depression, and adult type 2 DM [77, 78]. In particular, lower birth weight, followed by accelerated weight gain after 48 months, are risk factors for adult glucose intolerance [78-80]. Adult plasma cortisol levels, albeit in the normal range, decrease with increasing birth weight and correlate with adult systolic blood pressure, glucose and TG levels, waist/hip ratios, and insulin resistance [72].

Pathways toward insulin resistance

Molecular mechanisms underlying insulin resistance

A single common denominator to insulin resistance has been difficult to discern. Given the array of genetic variations, combined with external factors, that play a role in causing insulin resistance, it seems unlikely that there would be only one primary defect in insulin signaling. In fact, multiple biochemical mechanisms have been found to account for the impaired cellular response to insulin. In some individuals, the insulin receptor is abnormal; in others, certain aspects of insulin signaling become dysfunctional [81], including:

1 The insulin receptor autophosphorylation capacity is diminished [82].

2 The normal insulin receptor-mediated tyrosine phosphorylation of insulin receptor substrate (IRS) proteins is prevented by phosphorylation of one or more of the 70 IRS serine or threonine residues known to impair IRS signaling [83]. Serine phosphorylated IRS-1 or IRS-2 may

- lead to dissociation of complexes between the insulin receptor/IRS-1 and/or IRS-1/subunit p85 of PI3K, preventing PI3K activation [84, 85],
- increase Rho kinase/IRS-1 association [84],
- increase the degradation of IRS-1 [85], or
- function as inhibitors for the tyrosine kinase activity of the insulin receptor [86, 87].

3 Tyrosine phosphatases dephosphorylate the insulin receptor and its substrates and terminate the signal generated via tyrosine kinases [88]. Increased expression of several protein tyrosine phosphatases may be seen in obesity [89].

4 In certain circumstances, chronic activation of Akt may induce feedback inhibition of PI3K through proteasome-dependent degradation of IRS-1 and inhibition of IRS-1/PI3K association [90].

5 Reduced expression of IRS-1 is observed in myocytes and adipocytes of obese, insulin resistant persons [91].

6 PI3K activity is impaired.

7 Worsening insulin resistance in primates progressively compromises insulin-stimulated activation of the serine-threonine kinase Akt/protein kinase (PK)B and of the atypical PKC molecular switches needed for inducing glucose transport responses [92, 93].

8 With insulin resistance, atypical PKCs are deficient in muscle, impairing glucose uptake and producing insulin resistance and hyperinsulinemia. The latter, in turn, by activating hepatic atypical PKCs, provoke inordinate increases in lipid synthesis and the typical “metabolic syndrome” features [94].

9 Also in the liver, activated Akt kinase normally inhibits hepatic glucose output when glucose is available. With insulin resistance, overexpression of TRB3, a mammalian

homologue of *Drosophila* tribbles, causes TRB3 to bind to inactive and unphosphorylated Akt, preventing its activation and blocking action [95].

These and other defects may present as primary lesions of insulin resistance. More commonly, they arise secondarily in response to other biochemical disturbances.

Pathways to insulin resistance

Many biochemical paths lead to insulin resistance. Resistance to anabolic insulin signaling is elicited as the metabolic response to basically any adversity that challenges an organism’s physiologic soundness. The mechanisms involved are manifold, multi-tiered, and redundant (Box 15.5). The majority engender positive feedback loops that effectively secure the entrenchment of insulin resistance. The pathways elicited in response to stressors have all been discussed and referenced in detail in the preceding chapters.

Cell senescence

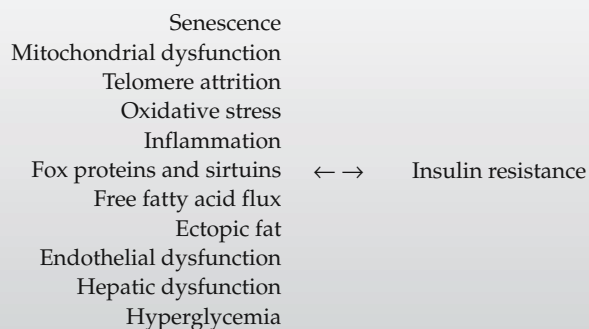
Aging is a physiological degenerative process, the phenotypic expression of cell senescence and drop out on the tissue level. Cell senescence and apoptosis, in turn, arise from a dysfunctional cellular infrastructure, including mitochondrial dysfunction, telomere attrition, and endoplasmic reticulum (ER) stress.

Cell senescence not only impairs normal cellular function, antioxidant defenses, and DNA repair systems; *senescent cells express a proinflammatory phenotype favoring the development of insulin resistance*. The activated oxidative and inflammatory pathways, in turn, feed back to further impair mitochondrial and telomeric function.

Mitochondrial dysfunction

There is a mitochondrial paradigm for insulin sensitivity, as mitochondrial oxidative capacity linearly correlates with insulin sensitivity within skeletal muscle. Barring psychological or physical impediments, muscle mitochondrial number, size, and oxidative capacity are determinants of a person’s degree of fitness, as

Box 15.5 Reciprocal worsening of stress pathways and insulin resistance



measured by exercise tolerance or maximal aerobic capacity [96]. High fitness at any age correlates with insulin sensitivity [97].

This interdependence between mitochondrial function and insulin sensitivity is also the underpinning of insulin resistance and the development of metabolic syndrome and type 2 DM [98]. The decline in mitochondrial density and function, as reflected by reduced exercise capacity, is implicated in the pathogenesis of

- proinflammatory signaling and prooxidant stress [96],
- aberrant insulin signaling and insulin resistance,
- abnormal glucose utilization, and
- the development of type 2 DM, as well as nonfatal cardiovascular events and mortality [97, 99].

In particular, a decline in skeletal muscle mitochondrial function is implicated in age-related loss of fitness and insulin resistance [100]. Fewer and smaller-sized mitochondria are found in skeletal muscle of insulin-resistant, obese, or type 2 diabetic subjects [96]. However, myocardial and hepatic mitochondria are similarly impaired [101, 102].

All risk factors that lead to insulin resistance are associated with impaired mitochondrial function. Aging is a case in point [101]. Overnutrition impairs mitochondrial function [103, 104]. Obesity decreases peroxisome proliferator activator receptor (PPAR) gamma coactivator-1 (PGC-1) activity and mitochondrial gene expression, function, and biogenesis in skeletal muscle and within adipocytes [96, 105]. Genetic factors, inactivity, oxidative stress, endoplasmic reticulum (ER) stress [96], inflammation, and others, are all associated with

- impaired mitochondrial function,
- reduced mitochondrial number and proteins [106],
- decreased energy production via oxidative phosphorylation [107, 108], and
- a decline in insulin signaling [106, 109–112].

Mitochondrial dysfunction not only precedes the onset of insulin resistance; insulin resistance may also impair mitochondrial function, exacerbating it in a vicious circle. Since insulin stimulates the transcription and translation of mitochondrial genes and proteins and increases the mitochondrial ATP production rate, this response becomes blunted with insulin resistance [97]. In addition, the increase in ROS production in insulin resistant muscle impairs mitochondrial function [104].

Telomere attrition

Telomere attrition and a decline in progenitor cell number and function in humans are associated with the aging process. The rise in *insulin resistance is associated with escalated telomere attrition* [113], and insulin resistance and DM associate with telomere shortening and lower telomerase activity [114, 115].

Ultimately all stressors, as diverse as psychological stress or cigarette smoking, devolve into proinflammatory

and prooxidant pathways. When protracted, such signaling ablates vulnerable telomeric DNA and triggers senescence pathways implicated in inflammation and insulin resistance [115, 116].

Oxidative stress

Reactive oxygen (ROS) and nitrogen species (RNS) play a role in the generation of insulin resistance, in its deterioration, and in DM-related sequelae.

Oxidant stress interferes with insulin signaling at various levels. For example,

- ROS and RNS directly oxidize and damage proteins of the insulin signaling pathway, such as IRS-1;
- oxidative stress results in the expression of gene products implicated in impaired insulin sensitivity [117];
- ROS also activate common stress-activated signaling pathways, such as
 - nuclear factor kappaB (NF kappaB),
 - p38 MAPK,
 - JNK/stress-activated protein kinases (SAPKs),
 - PKC,
 - sorbitol/hexosamine stress pathways, or
 - advanced glycosylation end-product (AGE) interaction with AGE receptors (RAGEs),

all of which underlie the development of both insulin resistance and impaired insulin secretion. In turn, insulin resistance increases oxidative stress [81, 87, 117–119].

Inflammation

Inflammation and insulin resistance are intimately interrelated, as insulin resistance is the metabolic manifestation of ongoing inflammation. In general, acute and chronic inflammation trigger insulin resistance, and insulin resistance begets further inflammation. Inflammation variables are significantly associated with incident DM [26].

Serine phosphorylation of IRS

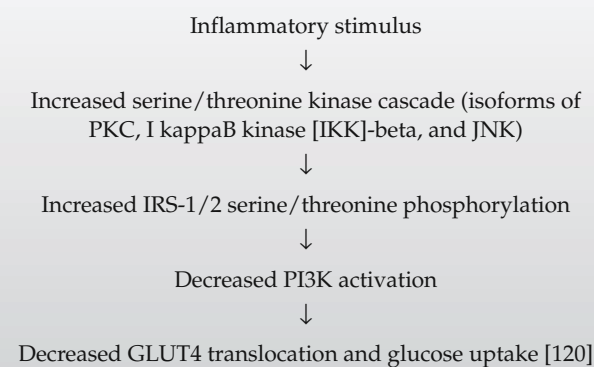
Inflammatory signal transduction pathways mediating insulin resistance (Box 15.6) converge at the level of IRS-1 serine phosphorylation to directly counter-regulate the insulin response by inhibiting IRS-1 activation and suppressing downstream insulin effectors [86, 87].

Inflammation-related activation of NF kappaB, Rho-Rho kinase, TNF-alpha, angiotensin II, and others inhibit IRS-1 tyrosine phosphorylation [83, 121–123].

Indirect mechanisms mediating insulin resistance

Inflammatory mediators also induce insulin resistance indirectly by

- stimulating stress pathways, including
 - ERK-1/2 (p42/p44 MAPK),
 - JNK, or
 - p38MAPK,
- stimulating the expression and activity of inducible nitric oxide synthase (iNOS) [87],
- increasing oxidative stress [124],

Box 15.6 Inflammatory signaling leading to impaired glucose uptake

- impairing mitochondrial function [125],
- reducing nutritive microcirculatory perfusion [126–128],
- stimulating adipose inflammation and circulatory proinflammatory adipokine release,
- inducing antiadipogenesis, lipolysis, and FFA release [129],
- increasing ectopic fat,
- downregulating the expression of PPARs-alpha and -gamma,
- suppressing adiponectin [130],
- activating the HPA axis, and
- activating the sympathetic nervous system.

Forkhead protein and sirtuin deregulation

Fox proteins are components of the insulin signaling pathway. The FoxO transcription factors are key mediators of insulin and growth factor effects on diverse physiological functions, including cell proliferation, apoptosis, metabolism, hepatic glucose production, and longevity [131].

Insulin resistance is associated with FoxO dysregulation and loss of sirtuin expression, impairing mitochondrial oxidative capacity and biogenesis. In turn, the attendant increase in ROS elaboration adversely affects mitochondrial function and telomere biology and creates a proinflammatory milieu, all of which further compromises metabolic homeostasis and feeds forward to worsening insulin resistance. *Fox protein dysregulation and absent sirtuin effects underlie many of the adverse cardio-metabolic sequelae of insulin resistance and the metabolic syndrome.*

Free fatty acid flux

FFAs are a characteristic finding in insulin resistance. *FFAs are an important link between nutrient excess, dysfunctional obesity, inflammation, and systemic insulin resistance* [132], and, in turn, insulin resistance further increases FFA levels. There is an inverse correlation between high fasting

plasma FFA concentrations and decreased insulin sensitivity [133], both acutely and chronically. FFAs are a major cause for peripheral and hepatic insulin resistance, accounting for 50% of insulin resistance in the obese [132]. In particular, dysfunctional visceral-omental adiposity plays a major role in releasing FFAs into the portal vein, delivering FFAs directly and exclusively to the liver [129].

Increased plasma levels of FFAs

- impair mitochondrial function [134],
- induce the innate immune receptor, Toll-like receptor 4 (TLR-4), and downstream NF kappaB [135],
- stimulate the production of cytokines, such as TNF-alpha, interleukin (IL)-1beta, and IL-6 [96],
- activate PKC epsilon [136],
- increase oxidative stress, and
- reduce antioxidant defenses [117],

all of which effects play an important role in compound-ing inflammation and mediating insulin resistance.

In the liver, elevated plasma levels of FFAs impair hepatic insulin extraction, metabolism, and action. FFA-induced hepatic insulin resistance

- enhances glucose output by
 - interfering with insulin suppression of hepatic glycogenolysis, and
 - enhancing hepatic gluconeogenesis, and
- increases hepatic synthesis of TRLs [137].

In the vasculature, increased FFA fluxes impair vascular reactivity and are linked to endothelial dysfunction [117, 138, 139].

High plasma levels of FFAs enhance FFA uptake by pancreatic beta cells and lipotoxicity, leading to progressive loss of beta cell function, an impairment of glucose-stimulated insulin release, and apoptosis [138].

Acute and chronic elevations in plasma FFAs generate insulin resistance in muscle [85, 140]. They reduce oxidative glucose and fatty acid disposal [132].

Ectopic fat storage

For FFAs to induce insulin resistance in nonadipose target tissues, they must first be taken up, reesterified, and accumulated as ectopic intracellular TG. *Ectopic lipid concentrations correlate with insulin resistance* in humans [104, 141–145].

The same factors, encompassing

- adipose inflammation,
 - reduced mitochondrial density [146]/mitochondrial dysfunction [96], and
 - reduced fatty acid beta-oxidative capacity in affected organs [109, 117, 145, 147–158],
- which increase circulating FFA levels, effect the redistribution of lipid to ectopic storage in peripheral, nonadipose tissues. These factors become particularly relevant in the setting of nutritional or adipose excess [159], or, conversely, in the setting of lipodystrophy [160]. The process of aging can sensitize cells to the effects of lipotoxicity

[161]. Ultimately, mitochondrial dysfunction, whether a primary or secondary defect, becomes a feed-forward mechanism for ectopic lipid accumulation and insulin resistance [47].

Although BMI may positively correlate with intramyocellular lipid, there are exceptions:

- high-BMI individuals may have low intramyocellular lipid, and
- low-BMI individuals may have high intramyocellular lipid and, despite being thin, be metabolically obese [162].

Affected tissues include

- skeletal muscle,
- myocardium,
- liver,
- pancreas,
- endothelium, and
- VSMCs [8, 163–165].

Ectopic TG is not only a marker for insulin resistance. Since nonadipose organs have limited TG buffer capacity, excess lipid enters alternative, nonoxidative pathways [166]. Increased cytosolic metabolites resulting from altered intracellular fatty acid metabolism increase oxidative stress [117, 134] and interfere with insulin signal transduction [73, 92, 132, 167–170]. This lipotoxicity contributes substantially to the pathophysiology of insulin resistance, type 2 DM, steatotic liver disease, dyslipidemia, and heart failure [166], which, in turn, worsen insulin resistance.

Endothelial dysfunction

Endothelial dysfunction is present in insulin resistance [138, 171] and is related to the severity of insulin resistance [172], as endothelial dysfunction is the vascular manifestation of ongoing inflammation. The parallels between the metabolic and vascular insulin-signaling pathways imply a coupling of insulin’s metabolic and hemodynamic actions. Insulin resistance thus affects both metabolic and vascular signaling [173]. Endothelial

dysfunction is a link between insulin resistance and cardiovascular disease.

Endothelial dysfunction not only arises with insulin resistance but is implicated in the pathogenesis of insulin resistance and type 2 DM. Dysfunctional eNOS, and/or deficient NO availability, directly and indirectly contribute to insulin insensitivity [84, 174, 175].

Hepatocellular dysfunction

Steatotic liver disease is associated with insulin resistance. The fatty liver is insulin resistant, is related to impaired insulin sensitivity in other tissues, to impaired total body insulin sensitivity, to all components of the metabolic syndrome, and predicts the increased risk of type 2 DM [176, 177]. Fasting serum-insulin concentrations correlate significantly with liver fat content [176].

The hepatic lipid accumulation can cause the development of insulin resistance, and NAFLD is an early predictor of insulin resistance and metabolic disorders [177, 178]. Conversely, insulin resistance contributes to the pathogenesis of NAFLD as insulin resistance plays a major role in the initial accumulation of fat in the liver.

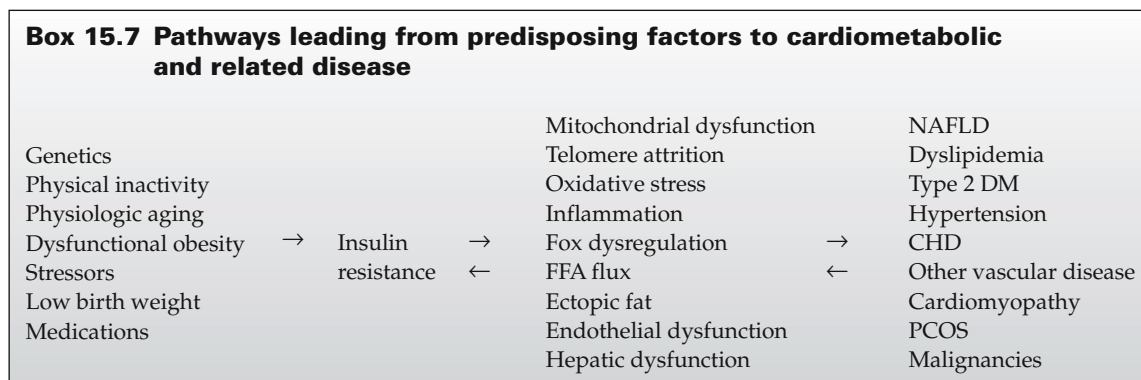
Hyperinsulinemia and hyperglycemia

Progressive hyperinsulinemia and supervening hyperglycemia serve to further impair insulin signaling, insulin-stimulated glucose utilization, and glycogen synthesis [179].

Vicious circles

The various prooxidant, inflammatory, metabolic, and vascular sequelae of cellular insensitivity to insulin interfere with insulin signaling pathways. They become themselves major mediators of insulin resistance, which, in turn, worsens the pathophysiological sequelae. *In a vicious circle, insulin resistance begets more insulin resistance, culminating in the manifestations of the metabolic syndrome and its comorbidities (Box 15.7).*

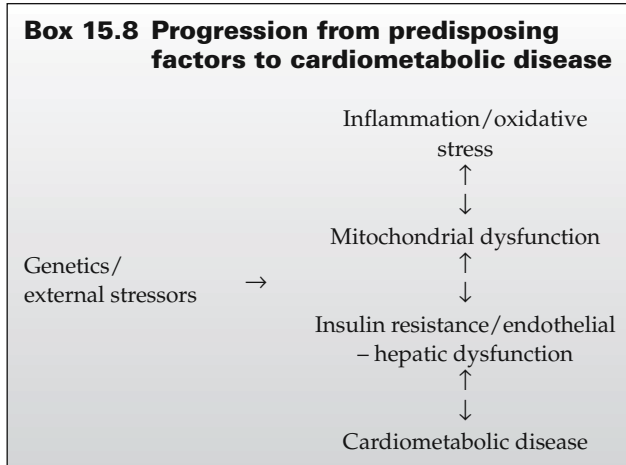
The diagram in Box 15.7 is both too complicated and too simplistic. It might be simplified as shown in



Box 15.8 since all pathways appear to be confluent around inflammation/oxidative stress and mitochondrial dysfunction.

The metabolic syndrome

Upon revisiting the metabolic syndrome, its criteria appear to be a complex mix of causative and effector pathways, all contributing to insulin resistance and the syndrome’s comorbidities, as shown in Table 15.9, or, more simply, as shown in Table 15.10.



Pharmacologic therapy to improve insulin sensitivity

The metabolic disturbance of insulin resistance presents as a reduction in carbohydrate and fatty acid oxidative consumption and metabolic rate. Underlying biochemical abnormalities include Fox protein dysregulation, the impaired expression and activity of sirtuins, constitutional NOS, PGC-1alpha, AMPK, and PPARs-alpha and -gamma. Therapeutic lifestyle changes (TLCs), including

- weight control,
- a healthy diet, and
- physical activity,

are the most important, highly effective, and safest interventions to improve metabolic activity. In the Diabetes Prevention Program (DPP) trial (3,234 individuals, glucose intolerance in the absence of DM), of the three treatment arms (metformin 850 mg twice daily alone versus lifestyle intervention (exercise 150 minutes/week plus 7% weight loss) versus placebo), TLCs reduced the incidence of the DM by 41% (p < 0.001) over 3.2 years [180, 181] with persistent benefits for 10 years [182]. Three-year cumulative DM incidences were 51% versus 34% for placebo versus TLC groups, respectively, with no significant heterogeneity by

Table 15.9 Metabolic syndrome criteria: pathways mediating cause and effect.

Criterion	Involved tissues	Causative pathways	Effects
Waist circumference	Adipose tissue Visceral-omental fat	Dietary excess Physical inactivity Stress	Inflammation Oxidative stress Mitochondrial dysfunction FFAs Ectopic fat Hypoadiponectinemia
TGs	Liver Intestines Adipose Muscles	Dietary excess Dysfunctional adiposity Mitochondrial dysfunction FoxO dysregulation Inflammation	Inflammation Oxidative stress Mitochondrial dysfunction Endothelial dysfunction
HDL	Liver Blood	High TGs Inflammation	Endothelial dysfunction Oxidative stress Inflammation
BP	Endothelium, VSMCs Kidney	Endothelial dysfunction Inflammation Oxidative stress Sympathetic and RAAS hyperactivity Mitogenic effects Fluid retention	Atherogenesis Vascular disease Cardiomyopathy Renal disease
Fasting glucose	Pancreas Liver Muscle	FFAs Ectopic fat Mitochondrial dysfunction FoxO dysregulation Inflammation Oxidative stress	Hyperglycemia Type 2 DM Oxidative stress Inflammation

Table 15.10 Metabolic syndrome criteria: cause and effect.

Criterion	Cause versus effect
Waist circumference	Cause
TGs	Effect
HDL	Effect
BP	Effect
Fasting glucose	Effect

ethnic group [181]. The lifestyle modification was exceptionally effective in preventing DM in older individuals [183].

TLCs are more effective than drug therapy in improving insulin sensitivity [180, 181]. Nevertheless, TLC efforts can be complemented, where indicated by comorbidities, such as dyslipidemia, hypertension, vascular disease, or cardiomyopathy, by targeted pharmaceutical interventions that are also insulin sensitizing, as detailed in previous chapters.

There are currently no established guidelines for the use pharmacotherapy with insulin sensitizers purely for the prevention of DM in the setting of insulin resistance or even glucose intolerance.

AMPK-activators

Pharmacologic activation of AMPK improves insulin sensitivity, glucose uptake, lipid profile, and blood pressure in insulin-resistant animal models, making this protein kinase a promising therapeutic target in the treatment of type 2 DM. AMPK appears to be one of the targets of thiazolidinediones (TZDs) and of the insulin-sensitizing adipokine adiponectin [184].

Metformin

AMPK is also the target of the biguanide insulin-sensitizer metformin, which increases the activity of both catalytic subunits of AMPK [185]. In addition to its small peripheral insulin-sensitizing effect, metformin mainly inhibits hepatic gluconeogenesis [186].

When lifestyle modifications fail to achieve or sustain adequate glycemic control, in the absence of contraindications, metformin is the preferred first-line therapy for most patients with type 2 DM, especially for obese diabetics [187]. Unfortunately, monotherapy with metformin is unlikely to maintain adequate glycemic control over the long run, requiring progressive treatment.

Metformin is also used for individuals with PCOS and may show promise for NAFLD [188]. Patients with both IFG and IGT, in addition to any one of the following

- age >60 years,
- BMI >30 kg/m²,
- family history of DM,

- elevated TGs,
- reduced HDL,
- hypertension, or
- HbA_{1c} >6%

may merit consideration of metformin pharmacotherapy (in addition to TLCs).

Metformin decreases cardiovascular risk and delays the onset of type 2 DM [189]:

- Metformin improves endothelial function [189].
- Metformin decreases cardiovascular events in patients with type 2 DM independent of glycemic control. Specifically, in the prospective randomized United Kingdom Prospective Diabetes Study (UKPDS) of obese patients, patients treated with metformin had significant reductions in MI (39% risk reduction, $p=0.01$), as well as in DM-related deaths (42% risk reduction, $p=0.017$), and any DM-related endpoint (32% risk reduction, $p=0.0023$) [190], with benefits persisting up to 10 years after trial completion [191].

- In the DPP trial, over 3.2 years, metformin therapy reduced the incidence of the DM by 17% relative to placebo [180, 181]. Benefits persisted for 10 years [182]; however, there was a complete lack of effect of metformin in women [181], and limited efficacy in persons aged 60–85 years, with the metformin group showing a trend toward higher DM incidence among older participants [183].

As is seen with chronic AMPK activation, lactic acidosis may be a rare complication of metformin therapy [186]. Metformin may cause the malabsorption of vitamin B12, and vitamin B12 levels may decline on therapy [192]. However, overall, metformin has few adverse cardiovascular or other side effects and low costs [187].

Investigational agents

Alternative pharmacological stimulation of AMPK is being explored for the therapy of insulin resistance and DM. 5-Aminoimidazole-4-carboxamide-1-beta-D-ribofuranoside (AICAR) is an analogue of adenosine. It is taken up in skeletal muscle, adipocytes, and hepatocytes and is phosphorylated to form the corresponding monophosphorylated nucleotide, which mimics the allosteric activating effects of 5'-AMP on AMPK. Metabolic effects of AICAR are thus consonant with AMPK activation and entail an increase in GLUT4 translocation and fatty acid oxidation [185].

Currently, excessive amounts of AICAR are required to achieve a pharmacological effect. Rats chronically exposed to AICAR develop hepatic hypertrophy. AICAR causes excessive muscle glycogen accumulation, which may itself impair insulin sensitivity. Excessive uptake of glucose, which, in the absence of exercise, remains unoxidized, induces plasma lactate accumulation and lactic acidosis [193].

Potent and selective AMPK activators have begun to emerge that may be of therapeutic use for patients afflicted with type 2 DM and related metabolic disorders.

PPAR-agonist

Thiazolidinediones, TZDs, were initially developed for their antioxidant properties due to a structural similarity to alpha-tocopherol. They are synthetic ligands, binding to, and partially activating PPAR-gamma [194, 195], a transcription factor that regulates the expression of specific genes predominantly in fat cells. PPAR-gamma ligands increase the transcription of genes coding for

- LPL [196],
- fatty acid transporter protein,
- fatty acyl CoA synthase,
- adipocyte lipid-binding protein 2,
- malic enzyme,
- glucokinase, and
- GLUT4.

The TZDs were the first drugs developed to directly target insulin resistance. Since PPAR-gamma exists primarily in fat cells, TZD action is largely centered on adipose tissue, although TZD use is also associated with antiinflammatory effects that may contribute to restoring insulin sensitivity [197–203]. In addition, TZDs may increase the production of adiponectin in white adipocytes [197, 204, 205] and increase AMPK activity [206].

At the level of adipocytes, TZDs enhance insulin sensitivity primarily via “fatty acid steal.” They potently stimulate adipogenesis and FFA storage in adipose tissue by enhancing subcutaneous adipocyte differentiation and proliferation [196, 197] but may decrease the mass of visceral–omental fat [207].

As a result, TZDs lower the release and circulating levels of FFAs [196]. They reduce ectopic fat deposition in non-adipose tissue, thus sparing other tissues, such as the liver, skeletal muscle, and pancreatic beta cells, from lipotoxicity and decreasing some of the mechanisms leading to insulin resistance [197].

There is also a resulting increase in overall fatty acid oxidation with a secondary enhancement in insulin signaling in skeletal muscle and the liver [195, 197] and improved plasma lipoproteins [208, 209]. Pioglitazone may reduce the risk of conversion of IGT to type 2 DM [210].

Since metformin monotherapy for type 2 DM is likely to fail, TZDs have been among the non-insulin therapeutic choices available as additional treatment, and type 2 DM is currently the only approved indication for therapy with TZDs. TZDs have been tested with variable success in other insulin-resistant conditions, such as NAFLD, PCOS, and lipodystrophies [197].

As with PPAR-alpha agonists, it is important to consider the systemic signaling effects of TZDs rather than

focus on promising but limited metabolic effects [211]. The first TZD, troglitazone, was withdrawn due to hepatic toxicity, including rare cases of hepatic failure and death. There are currently two TZDs in clinical use, although other agents are in development:

1 Rosiglitazone is PPAR-gamma specific. The drug has had a boxed warning regarding the potential risk for myocardial ischemia since 2007 [212], and in 2010, the Endocrinologic and Metabolic Drug Advisory Committee and the Drug Safety and Risk Management Advisory Committee of the FDA deemed rosiglitazone to pose a significant cardiovascular risk. It has been placed under selling restrictions in the U.S. [187], limiting the use of rosiglitazone-containing medicines to

- patients already being successfully treated with the drug,
- patients whose blood sugar cannot be controlled with other antidiabetic medicines and who, after consulting with their healthcare provider, do not wish to use pioglitazone-containing medicines [213].

Rosiglitazone has been withdrawn from the market in Europe due to the increased risk of cardiovascular events [187, 214–218].

2 Pioglitazone appears to bind to both PPAR-gamma and PPAR-alpha and is metabolized via the hepatic P450 CYP3A4 enzymes. There is no FDA warning on the risk of CHD for pioglitazone [187], which may protect against MI [219]. Its sale has been suspended in France and Germany due to the potentially increased risk of bladder cancer.

In addition, preclinical studies have suggested that TZDs are tumor-producing, and TZD use increases the risk for colonic carcinoma in the setting of familial adenomatous polyposis coli [220]. Due to their adipogenic effect, TZD-induced adipose mass accretion may amount to 1–4 kg/year, 2–3 kg for every 1% reduction in HbA_{1c} [195, 197]. TZDs can cause fluid retention, which manifests primarily as peripheral edema due to plasma volume expansion with dilutional cytopenia, particularly in users with systolic or diastolic ventricular dysfunction [197, 221]. TZD therapy may cause cardiac hypertrophy [195, 222] and may increase the risk of heart failure and bone fracture [215]. TZDs may enhance atherogenesis [223].

Dual PPAR-alpha and -gamma agonists would be expected to be superior insulin sensitizers than isolated PPAR-gamma agonists. Although dual PPAR-alpha and -gamma agonists, called glitazars, have been developed [217, 224, 225], several have been withdrawn in late-stage clinical development due to safety concerns in humans [226, 227].

Dual PPAR-gamma/PPAR-delta and PPAR-alpha/PPAR-delta agonists are under investigation as hypolipidemic, hypoglycemic, and antiatherogenic agents, as are agonists combining the effects of the three PPARs. Selective PPAR modulators that retain beneficial

drug effects without the adverse effects are in development [227].

Another investigational venue is the development of compounds that induce conformational changes in the PPAR-gamma protein in order to fully remove its phosphorylation mark and enhance insulin sensitization [228].

Conclusion

A profusion of pathways leads to insulin resistance. For any individual, a diverse set of genetic, environmental, and nutritional factors apply, and different aspects may assume primary versus secondary importance. In some, the process may be initiated locally, later to become systemic. In others, it may present systemically.

The redundancy of mechanisms that impair anabolic insulin signaling suggests a potential physiologic benefit to insulin resistance. Insulin resistance occurs in response to adverse physiologic or psychologic stressors. Aspects of inflammatory and oxidative stress pathways appear to underlie most, if not all mechanisms of insulin resistance. Insulin resistance is effectively a part of the inflammatory response, its metabolic expression. Over the course of evolution, mammals have had to weather innumerable hardships, such as repetitive starvation, injury, infection, illness, and other stressors. The ensuing stress-inflammatory responses terminate anabolic pathways and engender an insulin-resistant catabolic state to secure a ready supply of fuel to immune system cells and the brain during stressful periods. Insulin resistance pathways may provide an organism with the capacity to successfully survive repetitive deprivation in a hostile environment. For example, dolphins appear to have a “diabetic switch” that renders them insulin resistant and keeps their brains supplied with glucose even when they have not fed for a while. Like humans, dolphins have big brains. A similar diabetic “switch” may have evolved in humans to allow them to survive food scarcity and a high-protein diet during the ice-age [229].

As is true for most aspects of physiology, the survival benefit of insulin resistance pathways is lost when, what should be a temporary, compensatory fix, is sustained over the long term. Once insulin resistance becomes protracted, its redundant, complementary, and synergistic mechanisms, compounded by present-day nutritional excess and sedentary life, impair mitochondrial dysfunction and engender pathophysiological vicious circles. In the absence of a reversal of precipitating factors, or effective intervention, insulin resistance, once established, begets further insulin resistance.

Whereas anabolic and vascular insulin signaling is compromised by insulin resistance mechanisms, insulin’s mitogenic signaling remains immune to such constraints

and is, in fact, enhanced. The combination of insulin resistance and hyperinsulinemia engenders a multiplicity of significant adverse effects, compounded by related Fox protein dysregulation, absent sirtuin activity, and mitochondrial dysfunction. These and other mechanisms increasingly erode the integrity of subcellular structures and intracellular/intramitochondrial biochemical pathways. This process appears at first to be reversible but then becomes irreversible. The degradation of the cellular infrastructure entails cell senescence, which further contributes to proinflammatory activation and insulin resistance, and evolves into cell drop-out, tissue and organ failure, organismal aging, and age-related chronic disease. As a result, the progression to metabolic syndrome, vascular disease, type 2 DM, and other comorbidities bespeaks physiologic aging, irrespective of an individual’s chronological age. This is a very major concern given the growing present-day epidemic of childhood obesity and carbohydrate intolerance.

In view of the redundant mechanisms of insulin resistance, it is not surprising that a multifaceted approach is needed for its prevention and/or reversal. Antioxidant, antiinflammatory, stress-relieving interventions will be of benefit, comprising lifestyle measures that aim to improve the balance between energy intake and expenditure by

- decreasing energy intake,
- enhancing fatty acid oxidation in muscle and liver, and
- ensuring adequate fatty acid storage in subcutaneous adipose depots.

TLCs, specifically

- identification and correction of physiologic stressors, such as cigarette use, inadequate sleep, mental stress, or periodontal disease,
 - high-quality antiinflammatory diet, such as the Mediterranean diet, rich in fiber, n-3 fatty acids, and sirtuin activators,
 - weight control or loss, if indicated, and
 - daily >30–60 minutes of moderately intense aerobic exercise and resistance training,
- are the safest, least expensive, easiest, and most successful measures to address insulin resistance, safer and more

Table 15.11 Targeting of metabolic syndrome pharmacotherapy.

Risk factor/Comorbidity	Intervention
Hypertension	RAAS antagonism
Vascular disease	Vasodilating beta-blocker
Cardiomyopathy	
Dyslipidemia	“Broad spectrum” statin Fibrates
Hypercoagulability	Aspirin (clopidogrel for aspirin intolerance)
Hyperglycemia (IFG plus IGT)	Consideration of metformin, particularly in the obese

	Antioxidant	Anti-inflammatory	Anticoagulant	Endothelial protection	Antiproliferative	Antihypertensive	Antiatherogenic	Cardiovascular events	Insulin sensitivity	Adiponectin
"Broad spectrum" statins	+	+	+	+	+	?/+	+	+	+	n/a
Fibrates	n/a	n/a	n/a	n/a	n/a	n/a	n/a	?/+	+	n/a
ACE inhibitors	+	+	+	+	n/a	+	n/a	+	+	+
ARBs	+	+	n/a	+	n/a	+	+	+	+	+
Vasodilating beta-blockers	+	n/a	n/a	n/a	n/a	+	+	+	+	n/a
Metformin	n/a	n/a	n/a	+	n/a	n/a	n/a	+	+	n/a
Aspirin	+	+	+	n/a	+	n/a	n/a	+	n/a	n/a

+ = beneficial; n/a = not available.

effective than current pharmacotherapy. Just like overnutrition induces mitochondrial dysfunction, calorie restriction can restore mitochondrial function. Bariatric surgery has shown promise in instances of morbid dysfunctional obesity resistant to TLCs, albeit at significant risk and expense.

In conjunction with TLCs, pharmacotherapy targeting specific comorbidities is key to patient management (see Table 15.11).

The pharmacotherapies chosen (Table 15.12) should embrace established secondary prevention strategies. In many instances, their beneficial effect on cardiometabolic outcomes derives not only from their efficacy in correcting a specific physiologic derangement (e.g. hypertension, dyslipidemia) but also from their pleiotropic effects that comprehensively address the underlying derangements of the metabolic syndrome.

Pharmacotherapy, underpinned by the disciplined pursuit of TLCs, will reverse insulin resistance and delay or prevent the devastating consequences of the metabolic syndrome.

Future research directions may focus on therapeutic strategies to limit mitochondrial dysfunction and radical production and increase fatty acid oxidation in muscle. Attractive therapeutic targets might be NO and/or sirtuin signaling to increase mitochondrial biogenesis, Fox proteins like FoxC2, PGC-1alpha, AMPK, or even antisense therapy.

Ultimately, an aggressive, comprehensive, multifaceted therapeutic approach will benefit not only cardiovascular and metabolic health, but will aid in the prevention of other related medical problems, such as cancer, frailty in aging, and dementia.

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Table 15.12 Pleiotropic properties of metabolic syndrome pharmacotherapy.

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