Metabolic Syndrome and Cardiovascular Disease
Epidemiology, Assessment, and Management

Edited by
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With an Introduction by Scott M. Grundy M.D., Ph.D.
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To all our colleagues in research and healthcare
who have done so much in understanding the causes and
treatments of metabolic syndrome and cardiovascular disease
and to the millions of volunteers who participated in the studies
mentioned in this book. Without all your generosity and efforts,
this book could not exist.

Andrew J. Krentz
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Preface

The term “metabolic syndrome” denotes a clustering of traditional and emerging risk factors for atherothrombotic cardiovascular disease. Moreover, individuals who satisfy the current diagnostic criteria that define the syndrome are also at substantially increased risk of developing Type 2 diabetes—itself a coronary heart disease risk equivalent. Central obesity and insulin resistance are core features of the syndrome, which has come to be recognized as a major global threat to vascular health in the 21st century. The time is optimal for a textbook dedicated to this important issue.

The metabolic syndrome has adverse implications for many aspects of vascular function ranging from endothelial function, the microvascular tree, medium-sized arteries, and large conduit vessels. Furthermore, gathering evidence suggests that interactions between small and large vessel disease may be more important than perhaps has previously been appreciated.

There are fears that the successes in reducing cardiovascular mortality in recent decades may soon be reversed. Fueled by the explosion of obesity, the syndrome is characterized by the clustering of classic and emerging risk factors for cardiovascular disease. No longer is it appropriate to regard obesity, glucose intolerance and diabetes, hypertension, and dyslipidemia as separate entities to be treated in individual clinical settings (e.g. the diabetes clinic, hypertension clinic, etc.). If one of the components of the metabolic syndrome is discovered, then steps should be taken to determine whether others are also present, and for implementing comprehensive approaches aimed toward treating the constellation of metabolic risk factors. This can be accomplished by simple clinical and biochemical tests and a multidisciplinary team approach implementing lifestyle and pharmacologic treatment.

This new paradigm presents challenges for clinicians involved in the assessment and management of individuals with metabolic syndrome. This rapidly moving area is being driven by advances in clinical and basic science. The latter are informing strategies for risk stratification and optimization of nonpharmacologic and drug-based treatment.
Our objective in bringing this book into print has been to present a state-of-the-art account of the salient issues for a clinically-oriented readership. In this endeavor, we are pleased to have been joined by an international team of experts, each recognized in his or her field. Various chapters cover epidemiology, diagnosis, risk assessment, vascular biology, lifestyle measure, management of hyperglycemia, dyslipidemia, and hypertension, and strategies for maximizing compliance to treatment recommendations. We hope that the book will not only be of academic interest but will provide helpful practical guidance to primary care physicians, diabetologists, cardiologists, dietitians, and other healthcare professionals involved in the prevention and treatment of vascular disease.

A better understanding of the mechanisms that cause cardiovascular risk factors to cluster together to the long-term detriment of so many individuals should facilitate more effective measures for prevention and treatment. Scientists working in epidemiology, basic science, drug discovery, and clinical trials each have roles to play in unraveling what is proving to be a major public health crisis.

It has been a pleasure working with colleagues from around the world and with the staff of Informa Healthcare. We welcome feedback from readers in the expectation that the text will require updating in the future, given the rapidly increasing scientific knowledge and developments in the field.

Andrew J. Krentz
Nathan D. Wong
Acknowledgments

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Introduction

Metabolic Syndrome and Cardiovascular Disease is a comprehensive text addressing the cardiovascular risk factors and consequences associated with this important condition, a concept that has evolved over much of the past century, but which has received renewed and heightened attention over the past decade. It has been known for several decades that risk factors for atherosclerotic cardiovascular disease often cluster together. This knowledge is the basis for multifactorial algorithms to predict risk for cardiovascular disease. The Framingham Heart Study produced the first risk-prediction algorithms, but more recently, similar risk engines have been created from other databases of prospective studies. These risk-prediction tools have included all of the established atherosclerotic cardiovascular disease risk factors and provide the basis for estimates of global risk. Only recently have efforts been made to identify particular patterns of risk factors that have a common origin. The metabolic syndrome is one such pattern that has generated much interest in recent years.

Two lines of evidence have merged to produce the metabolic syndrome concept. These different origins have not been fully integrated and account for much of the debate that surrounds the syndrome. The first of these has been the recognition that obesity is strongly associated with multiple risk factors and undoubtedly contributes significantly to them. These include hypertension, hypercholesterolemia, hypertriglyceridemia, low levels of high-density lipoproteins, and hyperglycemia. In spite of much research on these metabolic complications of obesity, researchers in this field never consolidated all of them into a syndrome. But certainly it was recognized that prevention and treatment of obesity is the foundation of management of these risk factors.

During this same period, researchers in the diabetes field identified a metabolic state called insulin resistance. It was characterized by resistance to the actions of insulin and hyperinsulinemia. Insulin resistance was first recognized as a major contributing factor to Type 2 diabetes. However, in 1998, Dr. Gerald Reaven presented the hypothesis that insulin resistance also can be a cause of risk factors of metabolic origin. Among these risk factors he first identified were
hypothesis, low high-density lipoproteins levels, and hypertriglyceridemia. Although Dr. Reaven called the clustering of risk factors with insulin resistance and hyperinsulinemia tighten by the name syndrome X, others shortly thereafter changed the name to insulin resistance syndrome. Several different names have been used as alternatives for the metabolic syndrome. Besides metabolic syndrome X, and insulin resistance syndrome, there are the dysmetabolic syndrome, metabolic syndrome X, the deadly quartet, CHAOS, and the cardiometabolic syndrome. Often the name chosen is meant to highlight one or another feature of the syndrome. Recently some investigators have raised the question of whether a clustering of metabolic risk factors should be called a “syndrome” at all. This is a semantic issue, but most researchers believe that the term “syndrome” is appropriate for a clustering of risk factors of metabolic origin. For another decade, the metabolic syndrome/insulin resistance syndrome remained a topic of research interest, but did not become an entity for clinical identification. But in 1998, the World Health Organization Working Group on Definition of Diabetes attempted to formulate criteria for the diagnosis of the metabolic syndrome. These criteria were based on the assumption that insulin resistance is the major cause of the syndrome. Subsequently, other organizations have made an effort to reformulate diagnostic criteria both to add simplicity and to include the key features of the syndrome. Over the next eight years, diagnostic criteria have been suggested by the European Group for Study of Insulin Resistance, the United States National Cholesterol Education Program Adult Treatment Panel III, the American Association of Clinical Endocrinology, the International Diabetes Federation, and the American Heart Association/National Heart, Lung, and Blood Institute. The World Health Organization definition was influential in concept but lacking in clinical utilization. The simplicity of the Adult Treatment Panel III definition, however, was attractive to many researchers and clinicians and has sparked great interest. Subsequently, the International Diabetes Federation and American Heart Association/National Heart, Lung, and Blood Institute made minor modifications to the Adult Treatment Panel III criteria. The two are very similar, and use the same risk factors and cut points for diagnosis. This similarity provides enough harmonization to make the two essentially interchangeable for diagnosis.

The metabolic syndrome has been strongly associated with risk for atherosclerotic cardiovascular disease. When Gerald Reaven introduced syndrome X, it identified a clustering of factors related to insulin resistance and predicting risk for atherosclerotic cardiovascular disease. Currently accepted metabolic risk factors for atherosclerotic cardiovascular disease are

- Atherogenic dyslipidemia
- Vascular dysfunction
- Dysglycemia
- A prothrombotic state
- A proinflammatory state
Atherogenic dyslipidemia consists of
- Elevated apolipoprotein B including elevated levels of triglyceride and small low-density lipoprotein particles
- Reduced levels of high-density lipoproteins

There is general agreement that most apolipoprotein B-containing lipoproteins are atherogenic, whether contained in the low-density lipoprotein or very low-density lipoprotein fractions. The relationship between low levels of high-density lipoprotein and atherogenesis is less well understood. Several causative mechanisms have been proposed, e.g., reduced reverse cholesterol transport, loss of protection against low-density lipoprotein oxidation within the arterial wall, and reduction of anti-inflammatory properties. The extent to which a low high-density lipoprotein level contributes to atherogenesis must await controlled clinical trials with high-density lipoprotein-raising drugs. Such trials are currently underway.

Vascular dysfunction is manifest by elevations in blood pressure and by endothelial dysfunction. The former is known to be atherogenic, whereas the latter may be. The role of endothelial dysfunction in the development of atherosclerosis is still under investigation. Finally, some investigators believe that vascular dysfunction may play a direct role in the development of insulin resistance and other metabolic risk factors.

Dysglycemia can take several forms: high–normal plasma glucose, impaired glucose tolerance, impaired fasting glucose, and clinical hyperglycemia (Type 2 diabetes). A variety of mechanisms have been proposed whereby elevations in plasma glucose can directly promote atherogenesis. In addition, higher glucose levels cause microvascular disease. There is growing evidence that microvascular disease may secondarily cause macrovascular disease. Some investigators question whether the metabolic syndrome and Type 2 diabetes can coexist. According to these investigators, Type 2 diabetes subsumes the metabolic syndrome. Without question, most patients with Type 2 diabetes exhibit current diagnostic criteria for the metabolic syndrome. It must be pointed out, however, that current criterion for the diagnosis of Type 2 diabetes is based entirely on plasma glucose cut points. Further, an alternate view is that Type 2 diabetes is essentially a severe form of the metabolic syndrome. This view is justified by those to point out that it is characterized by multiple metabolic risk factors. Clearly the two conditions have many common pathogenic features.

A prothrombotic state is characterized mainly by elevations of plasminogen activator inhibitor-1. Nevertheless, several other coagulation abnormalities have been reported in patients with the metabolic syndrome. Some of these include
- Platelet dysfunction
- Elevated fibrinogen
- Elevated von Willebrand factor
- Elevated factor VII
- Elevated tissue plasminogen activator antigen
Abnormalities in coagulation and thrombolysis have been implicated both in atherogenesis itself and in propagation of thrombi following disruption of atherosclerotic plaques.

The proinflammatory state associated with the metabolic syndrome appears to have several features. First, circulating levels of inflammatory cytokines are raised. These high levels appear to be derived largely from adipose-tissue beds. Second, in muscle and liver, an excessive influx of fatty acids can elicit the formation of intracellular inflammatory pathways that can induce insulin resistance. Third, the metabolic syndrome is accompanied by increases in acute phase proteins, such as C-reactive protein. Several reports suggest that these proteins may have proatherogenic properties. And finally, there is a cellular inflammatory response in the arterial wall secondary to interaction with the known metabolic risk factors; this inflammatory response may be heightened by increases in circulating inflammatory cytokines.

As indicated above, each of the components of the metabolic syndrome has been implicated in atherogenesis. Because of their colinearity within the syndrome, it has been difficult to dissect the relative contributions of each to atherosclerotic cardiovascular disease events. For this reason, the metabolic syndrome can be considered to be a multiplex cardiovascular risk factor. The metabolic syndrome belongs in the category of causative risk factors similar to individual risk factors of cigarette smoking, hypercholesterolemia, and hypertension. The introduction of a multiplex risk factor is something new to the cardiovascular field, and not surprisingly, the understanding of the place of the metabolic syndrome in cardiovascular risk has been slow in development.

The question has arisen whether the risk for metabolic syndrome as a whole is greater than the sum of the risk factors of its individual components. This is a complex question, but can be addressed in several ways. First, epidemiological studies suggest that multiple risk factors are synergistic in raising risk and not just additive. This synergism has long been called multiplicative risk. Second, several of the risk components, e.g., elevated apolipoprotein B, a prothrombotic state, and a proinflammatory state, are not usually measured in clinical practice. Consequently, their contribution to risk is not identified with the typical clinical measures. Third, some of the measured risk factors, such as low high-density lipoprotein cholesterol, may be predictive but not necessarily causative; thus, the individual risk factors that are used for prediction may be only markers for the true causative factors accompanying the syndrome. And fourth, the metabolic syndrome is a progressive disorder, that is, it worsens over time. Consequently, risk measured at any one time underestimates the long-term risk accompanying the syndrome.

Considerable confusion has arisen regarding the relation of the component metabolic risk factors to the risk surrogates (categorical risk markers) for these
factors that are the basis for clinical diagnosis. In both updated Adult Treatment Panel III and International Diabetes Federation formulations of the risk the following surrogates are included:

- Serum triglycerides <150 mg/dL (<1.7 mmol/L)
- High-density lipoprotein cholesterol < 40 mg/dL (<1.0 mmol/L) in men, and <50 mg/dL (<1.3 mmol/L) in women
- Blood pressure <130 mmHg systolic, and <85 mmHg diastolic
- Fasting glucose <100 mg/dL (<5.6 mmol/L)
- Increased waist circumference (population-dependent thresholds)

The following waist circumference thresholds are recommended:

- Non-Asian <94 cm in men (<102 cm in U.S. men); <80 cm in women (<88 cm in U.S. women)
- Asian <90 cm in men; <80 cm in women

The higher waist circumference in U.S. men and women relates in large part to practicality because of the high prevalence of obesity. However, recent studies have shown that in the United States, a similar prevalence of metabolic syndrome exists by International Diabetes Federation and updated Adult Treatment Panel III criteria.

International Diabetes Federation requires that elevated waist circumference be present for a diagnosis of the metabolic syndrome. Adult Treatment Panel III does not require this when other risk surrogates are present. According to both criteria, when three or more (3+) risk markers are present, a diagnosis of the metabolic syndrome can be made. It has been shown that most persons with 3+ metabolic markers are affected with all of the metabolic risk factors that constitute the metabolic syndrome.

Although the metabolic syndrome is multifactorial in origin, the pathogenesis can be simplified into two general categories of causation. The first category can be called metabolic susceptibility. For the syndrome to develop there must be an underlying propensity. Reaven and other workers have suggested that this susceptibility be called insulin resistance. Without question, most people who exhibit the metabolic syndrome also manifest insulin resistance. Even so, the metabolic connection between insulin resistance and the multiple components of the syndrome have not been elucidated. One view holds that insulin resistance, or concomitant hyperinsulinemia, is a direct cause of all of the components of the syndrome. Certainly, insulin resistance contributes directly to the dysglycemia of prediabetes and Type 2 diabetes. On the other hand, the mechanistic link between insulin resistance and other components—atherogenic dyslipidemia, vascular dysfunction, and prothrombotic and proinflammatory states—remains to be clarified. The possibility exists that other causes that are responsible for these abnormalities also produce insulin resistance. If so, insulin resistance may be a marker for the presence of these underlying causes without itself being a direct causative factor. Thus, more research is needed to understand the mechanistic basis of metabolic susceptibility for the metabolic syndrome.
Several factors appear to contribute to metabolic susceptibility. Among these are physical inactivity, advancing age, adipose-tissue disorders, certain drugs, and ethnic, racial, and family propensity. At a more mechanistic level, susceptibility has been related to deficiencies and maldistribution of adipose tissue, loss of muscle mass, genetic defects in insulin-signaling pathways, and other genetic variations. All of these changes are associated with insulin resistance, but whether the latter is a cause or a marker of the several components of the metabolic syndrome is yet to be determined. Certainly, the possibility must be considered that these susceptibilities act on development of metabolic syndrome components in ways that are independent of insulin resistance.

The second large category of causation for syndrome is an excess in body fat. This typically is a manifestation of energy overload. It results in either overweight or obesity. Epidemiological studies show that increases in obesity in a population are accompanied by increases in the prevalence of the metabolic syndrome. Thus, obesity can be viewed as the driving force behind the metabolic syndrome. This is true even for individuals who are metabolically susceptible. Still, obesity is particularly likely to precipitate the syndrome in persons who are susceptible based on other factors. The mechanisms whereby obesity worsens the syndrome is a subject of intense research interest. Recent discoveries show that an excess in body fat is accompanied by abnormalities in release of many factors from adipose tissue. Among these are increased outputs of nonesterified fatty acids, resistin, angiotensinogen, and others. All of these have been implicated in systemic metabolic abnormalities related to the metabolic syndrome. In addition, adiponectin, a putative protective adipokine, is reduced with obesity. Consequently, obesity and its accompanying abnormalities may be a direct cause of several of the metabolic syndrome constituents. The actions of these several adipokines represent an area of great importance in research on the development of the metabolic syndrome.

One of the features of the metabolic syndrome is a tendency to accumulate fat in tissues outside of adipose tissue. This is called ectopic fat. Two prime locations are muscle and liver. In muscle, ectopic fat accumulation is accompanied by insulin resistance. The pathways whereby excess fatty acids in muscle cause insulin resistance are becoming better understood. In liver, ectopic fat accumulation, called fatty liver, is accompanied by insulin resistance and increased outputs of glucose and very low-density lipoprotein triglyceride. The pathways underlying these changes are only partially understood. The reasons for ectopic fat accumulation have not been fully elucidated. One possibility is that patients with the metabolic syndrome may be relatively deficient in adipose-tissue storage capacity. Most of the body fat is normally stored in subcutaneous adipose tissue. If fat storage capacity is limited, caloric overload may result in accumulation of fat elsewhere, hence excess ectopic fat. An example of this phenomenon occurs in patients with lipodystrophy—which is characterized by a loss of body fat, particularly subcutaneous fat. Patients with lipodystrophy typically have large accumulations of ectopic fat and many metabolic complications. One of the features of ectopic
fat accumulation is the presence of excess intraperitoneal (visceral) fat. Thus, visceral obesity can be viewed as a marker of a relative deficiency of subcutaneous fat stores.

The above model of the pathogenesis of the metabolic syndrome provides a rational approach to its management. Highest priority goes to prevention and/or treatment of obesity. Second is modification of metabolic susceptibility. And third is to treat residual risk-factor components of the syndrome. A few comments can be made about each.

To reduce the burden of metabolic syndrome in society, obesity prevention deserves a high priority for public health. This is true for all nations of the world. Changing lifestyles can largely account for the rising prevalence of the syndrome throughout the world. For much of the world, life is becoming more sedentary and food is increasingly available. Both lead to energy overload and obesity. Society is ill prepared to reverse this trend. But both governments and society at large must recognize the consequences of allowing obesity to develop unchecked. Greater national commitments to modifying the structure of daily life habits will be required to reverse this unfortunate trend.

For individuals who have developed obesity, management requires intervention by the healthcare community. Priority in clinical management should go to persons in whom obesity has elicited the metabolic syndrome. A major challenge to the healthcare system is to develop more efficient lifestyle interventions. This may require creation of clinical management structures that do not currently exist in most medical settings. In overweight/obese subjects with the metabolic syndrome, the primary goal is to reduce body weight by 10% in the first year. If this can be achieved, a secondary goal is to reduce weight to the desirable range, e.g., a body mass index less than 25 kg/m². To achieve these goals, a combination of caloric restriction, behavior modification, and increased physical activity will be required.

The second aim in management of the metabolic syndrome is to reduce metabolic susceptibility. The most practical means for achieving this aim is to enhance physical activity. Regular exercise will lower insulin resistance, improve cardiovascular risk factors overall, and reduce risk for cardiovascular events through multiple mechanisms. Further any secondary causes of metabolic susceptibility should be appropriately treated. Drug treatment of metabolic susceptibility is problematic. However, insulin sensitizers are promising. Included in this list are metformin and thiazolidinediones. The pharmaceutical industry is engaged in intensive research to develop new agents for reducing susceptibility to the metabolic syndrome; but at present, this field of research is in its infancy.

The third therapeutic approach is to favorably modify each of the risk-factor components of the syndrome with drug therapies. It is appropriate to use absolute risk estimates to guide choice and intensity of drug therapy. Several risk-assessment tools are available for estimating absolute risk. Among these are Framingham and PROCAM risk scoring. Others are under development.
Eventually, population-based risk scoring will be available so that absolute risk can be estimated from equations that factor in the baseline risk of the population. Some investigators have attempted to estimate absolute risk from the components of the metabolic syndrome alone. This is a mistake. The components of the syndrome do not incorporate all of the contributions to global cardiovascular risk.

Recently, the American Diabetes Association has introduced a multiple-component risk algorithm called Archimedes. This algorithm estimates what is called cardiometabolic risk. This term can be taken to refer to all cardiovascular diseases of atherosclerotic origin plus all other diseases of metabolic origin. Among the metabolic diseases are prediabetes, diabetes, fatty liver, cholesterol gallstones, polycystic ovarian syndrome, and obstructive sleep apnea. The current Archimedes algorithm includes multiple risk factors but at present only predicts absolute risk for cardiovascular disease and diabetes. Presumably as it is developed it will extend to predict other metabolic diseases. This ambitious program currently is a work in progress, and it will have to be validated with a variety of databases.

First-line therapy for atherogenic dyslipidemia is to reduce apolipoprotein B levels. Statin drugs are the most effective apolipoprotein B-lowering drugs. Other drugs that lower apolipoprotein B levels in patients with elevated triglycerides are ezetimibe, fibric acids, and nicotinic acid. The latter two also raise high-density lipoprotein-cholesterol levels, which may provide additional risk reduction. Currently, other drugs are under development that raise high-density lipoprotein concentrations. Whether these drugs produce incremental risk reduction awaits on-going clinical trials.

The primary target of vascular dysfunction is an elevated blood pressure. Many investigators favor use of drugs that dampen the renin-angiotensin system in patients with the metabolic syndrome. This is particularly the case for those patients who have Type 2 diabetes. Calcium-channel blockers are effective blood-pressure lowering agents, and generally are devoid of metabolic side effects. Beta-blockers and diuretics both can worsen insulin resistance, but may be required to achieve blood pressure goals in some patients.

The major unresolved question about glucose elevations in the prediabetes range is whether glucose-lowering drugs are indicated to prevent progressive hyperglycemia. Without doubt clinical hyperglycemia is a risk factor for both macrovascular and microvascular diseases. But is it enough just to treat hyperglycemia when it reaches the level of Type 2 diabetes? Ongoing clinical trials are discussing this question.

At present, there are no specific therapies for a prothrombotic state other than antiplatelet drugs, notably aspirin. If patients with the metabolic syndrome have reached a level of risk high enough, the benefits of aspirin therapy outweigh the potential side effects—particularly bleeding complications. Further, there is currently no specific treatment for a proinflammatory state other than a reduction through lifestyle changes.

In summary, the metabolic syndrome as a multiplex cardiovascular risk factor is growing in importance as the world’s population becomes increasingly