

Chapter 1

The Metabolic Syndrome: A Relevant Concept?

The concept of the “metabolic syndrome” arose from a research perspective. Epidemiologically, the term captures a confluence of clinical risk factors that tend to occur together, raising the question of whether these conditions have a single underlying cause.

Several different definitions of the syndrome have been proposed by various organizations, such as the International Diabetes Federation (IDF), World Health Organization (WHO), European Group for the Study of Insulin Resistance (EGIR), and the U.S. National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP), with various different constellations of risk factors. Although the detailed definitions differ among these organizations, the metabolic syndrome is generally diagnosed when a person presents with any three of the following findings: a generous waist circumference, elevated blood pressure, high triglyceride levels, low high-density lipoprotein (HDL) levels, or elevated fasting blood glucose.

However, beyond minor differences about specific components that make up the various definitions of the syndrome, there are significant disagreements as to the validity of naming this risk factor cluster as a separate condition and using it as a diagnostic tool for treatment. This controversy about the relevance of the metabolic syndrome has pitted diabetologists against cardiologists. In 2005, the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) issued a statement discouraging the use of the term “metabolic syndrome.” In contrast, a few weeks later, the American Heart Association (AHA) and the National Heart, Lung, and Blood Institute (NHLBI) released statements encouraging the clinical use of that term. The controversy continues.

The EASD posits that no additional benefit derives from identifying the metabolic syndrome risk factor cluster over measuring and treating the individual risk factors. The EASD claims that there are no data to confirm that the metabolic syndrome is a true syndrome rather

than a collection of co-aggregating cardiovascular risk factors; and that the collective association with cardiovascular disease is no more than the sum of its parts, much of the risk being linked to obesity, hypertension, glucose intolerance, and hyperglycemia. In short, diabetologists disagree with Aristotle that “the whole is greater than the sum of its parts.”

Since the syndrome may apply to 25 to 33% of the population, the organization also objects to applying a disease label to too many people. The 2005 EASD statement concluded: “There is much fundamental, clinically important, and critically missing information about the metabolic syndrome to warrant a more serious examination of whether medical science is doing any good by drawing attention to and labeling millions of people with a presumed disease that does not stand on firm ground.”

Other criticisms leveled at the concept of the metabolic syndrome are that there is no single therapy for such a syndrome. Rather, each risk factor has to be managed separately.

In truth, the metabolic syndrome concept is intellectually not rigorous and pathophysiologically not logical. One has a risk factor for inflammation (overweight) linked to a single manifestation of endothelial dysfunction (hypertension), associated with a manifestation of hepatic insulin resistance (dyslipidemia), coupled to pancreatic beta-cell failure (hyperglycemia). Furthermore, the Framingham Risk Score will perform better as a predictor of heart disease than the metabolic syndrome.

However, although there may be no synergy among the individual components of the metabolic syndrome on the risk of coronary outcomes, the risk of stroke and all-cause mortality associated with the metabolic syndrome appears to be significant, independent of its components. Also, as cardiologists, we find the metabolic syndrome a helpful concept: it is so readily recognized. How often do we not wonder if a person on the street or in the elevator has the metabolic syndrome? How often can we not just

tell that an individual entering our office has the metabolic syndrome, only to confirm the diagnosis with easy, inexpensive testing? The most common presentation of the metabolic syndrome is in people with visceral fat, who are sedentary, and have poor dietary habits.

The metabolic syndrome is not a disease. It is “individuals” or “people” that have the metabolic syndrome, not “patients.” However, over a lifetime, the metabolic syndrome is itself a powerful predictor for the incidence of chronic disease – not only of vascular disease, for which the Framingham Risk Score would serve well, but also of cardiomyopathy, diabetes mellitus (DM), cancer, renal disease, and dementia, that will turn “people” into “patients.” It is alarming that almost 40 million Americans have DM, that more than twice that number have prediabetes, and that by 2050 one-third of Americans will be diabetic. It is potentially devastating that in the U.S. at least half the population is overweight and 40% will have the metabolic syndrome and be at risk for such diseases. It is, therefore, of tremendous value to be able to easily identify people with this cluster of risk factors. It enables us to target this population for more aggressive lifestyle advice, and for therapy, if needed.

The construct of the metabolic syndrome may not be intellectually pleasing, but it is simple, and it works. Those at-risk individuals who are sedentary, eat unhealthily and excessively, and have visceral and/or ectopic fat, also develop mitochondrial dysfunction, telomere attrition, inflammation, endothelial dysfunction, and insulin resistance. Such individuals typically have elevated triglycerides, and rather than carry a laundry list of diagnoses, many cardiologists prefer to follow Pythagoras: “Do not say a little in many words but a great deal in a few.”

Aside from saying much with little, does it make a difference in clinical practice? We would argue that it does.

Physicians diagnosing only traditional risk factors will likely neglect borderline abnormalities as not relevant or not requiring attention. A slightly generous waist or mildly depressed HDL may not be addressed on a hypertension follow-up visit. Traditional risk factors will fail to capture those at risk in the population.

Physicians treating individual risk factors will prescribe their preferred treatments for each. One might choose a beta-blocker for hypertension; fibrates or ezetimibe might be prescribed for abnormal lipid findings, or a sulfonylurea for hyperglycemia.

In contrast, a physician thinking of the metabolic syndrome will focus on all abnormalities, even if they are of borderline concern. He/she will be aware of the common pathophysiology underlying the individual's presentation: the role that inflammation, oxidative stress, mitochondrial dysfunction, endothelial dysfunction, and insulin resistance all play.

Finding the metabolic syndrome allows the physician to elucidate modifiable factors that contribute to the pathophysiology: Is the person stressed or sleep deprived? Does the individual suffer from some chronic inflammatory process? In this context, overweight is no longer a cosmetic issue but a significant source of systemic inflammation; inactivity or an unhealthy diet are no longer lifestyles but factors that engender endothelial and mitochondrial dysfunction and insulin resistance.

The therapeutic approach chosen will be “holistic,” addressing the underlying pathophysiology. While tailored to an individual's need, interventions will be chosen to synergistically impact on all components. The emphasis will be on aggressive therapeutic lifestyle changes: they do have a major impact on all factors underlying the metabolic syndrome, thus improving all individual risk factors.

With therapeutic interventions, the clinician dealing with the metabolic syndrome will identify therapies that make sense physiologically, that lower inflammation and oxidative stress, that improve mitochondrial and endothelial function, and that reduce insulin resistance. The aim is to have every drug chosen help the entire syndrome: thus a renin–angiotensin–aldosterone system (RAAS) antagonist will be more appropriate than a calcium channel blocker, an HDL-raising statin will be more beneficial than ezetimibe, an AMP-activated protein kinase (AMPK) activator will be more helpful than a sulfonylurea. In the presence of the metabolic syndrome, a clinician may consider prescribing aspirin.

Yes, the metabolic syndrome targets a large segment of the population; however, identifying the many affected individuals is a benefit. These individuals are not diseased. They are simply at higher risk of developing DM, heart disease, cancer, and dementia. The metabolic syndrome allows easy diagnosis and targeting of people for aggressive lifestyle advice. It is an early time in the pathophysiological process when lifestyle interventions are still very effective. Diet and exercise continue to be the cornerstone of any metabolic syndrome prevention-and-treatment strategy, and individuals and society at large will benefit from a timely preventive intervention.