

LETTER TO THE EDITOR

Individual variation in the metabolic syndrome: a new perspective on the debate

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Dear Sir:

Recently, the question of whether a diagnosis of metabolic syndrome is clinically useful was debated by 2 of the most preeminent scientists in the field, Reaven (1) and Grundy (2). The authors present opposing views on the matter. Reaven argues that a diagnosis of metabolic syndrome has no clinical utility and that the risk factors—atherogenic dyslipidemia, high blood pressure, insulin resistance, and obesity—that predispose individuals to an increased risk of heart disease and diabetes should be treated separately and aggressively. Grundy, on the other hand, recognizes that this clustering of metabolic risk factors is indeed useful because it directs physicians toward prescribing lifestyle therapies that address all of the risk factors simultaneously.

Reaven further points out that it is difficult to diagnose the metabolic syndrome because the World Health Organization, the National Cholesterol Education Program, and the International Diabetes Foundation all have different criteria for diagnosis. Moreover, he makes a convincing argument that, in fact, all of these different risk factors have one common cause—insulin resistance. Conversely, Grundy argues that it is not yet clear that insulin resistance is the only causal factor involved in the development of the syndrome, pointing out that obesity itself may play a causal role. He argues, therefore, that it is more prudent to diagnose the clustering of risk factors that represents the metabolic syndrome as a separate disease entity to emphasize a need for lifestyle therapies in clinical practice.

Of course, both viewpoints are well thought out, and the debate is timely in light of the growing number of American adults and children who have this syndrome. We would like to introduce an additional perspective to the debate—that of individual variation.

Whereas people may be remarkably similar to one another at the DNA level, gene expression is affected by many different factors, including diet and lifestyle, and is modified by single nucleotide polymorphisms (SNPs) in key regulatory genes. The end product is a highly unique person with a unique metabolic profile that changes in response to diet, lifestyle, and other conditions. Not only are people different from one another, they are different from themselves at different points in time.

Metabolism viewed from the perspective of systems theory

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The human metabolic landscape is a complex web of interplaying components, effectors, regulators, inputs, and outputs, with each organ system working both individually for its own benefit and also together for the overall maintenance of health of the whole organism. For example, in peripheral insulin resistance, the muscle and adipose cells reduce their responsiveness to insulin's stimulation of glucose uptake, despite the fact that increased concentrations of insulin are being secreted by the pancreas, which senses increased concentrations of glucose in the blood.

When such metabolic dysregulation occurs, few symptoms manifest initially because other systems in the body are able to compensate for the changes. However, over time, the continued imbalance begins to exert a sustained influence on metabolic regulation, and various consequences of altered metabolite concentrations, regulatory failures, and gene expression lead to partly or irreversible damage at multiple sites.

Systems theory can teach us much about the management of such complex systems. For instance, the notion that the whole is greater than the sum of its parts is a basic tenet of systems theory, arguing that because all the components of a system are related, any changes in one component will affect all the others. Likewise, changes in one metabolic organ affect all the others through shared pathways, such as common signaling molecules and availability of precursors for metabolic reactions. To the complex but general predictions of systems theory must be added the divergent genetic and metabolic backgrounds of individuals that can and do lead to variations in individual responses to metabolic variation.

In obesity, the proinflammatory messenger tumor necrosis factor is produced at the site of the adipose tissue, which induces signaling cascades locally and at different sites, such as the liver. Conversely, an increased availability of acetyl CoA in the liver induces the de novo synthesis of fatty acids, which in turn are transported to the adipose tissue for storage in some individuals but, in others, cannot be successfully exported and develop into fatty liver disease.

Another basic tenet of systems theory is that the behaviors of complex systems are themselves inherently complex. Genetic diversity as SNPs alters metabolic predisposition (ie, the efficiency and specificity of particular reactions or functions) in some cases, which results in the development of overt symptoms. For example, a polymorphism in the gene encoding for apolipoprotein A-V leads to a more atherogenic lipoprotein profile—elevated fasting triacylglycerols, elevated remnant lipoproteins, and decreased LDL size—in response to diets high in n-6 polyunsaturated fatty acids (3). To add to the complexity, evidence exists that SNPs interact with one another in different ways to produce an overall effect, or more accurately, a discrete phenotype, that could not necessarily have been predicted from the effects of any one SNP in isolation (4). Furthermore, transcription factors, which modify the expression of genes directly, hormone concentrations, which may be secreted in various patterns or in response to changing conditions, and many other factors further affect the state of a system at any one point in time.

Assessment of metabolic function

Given that metabolic function is influenced by a variety of factors—from variations at the genetic level to the interplay of genes and environment—it follows that a comprehensive analysis of multiple metabolic endpoints is necessary to ascertain health status in an individual. For example, if only total cholesterol and LDL-cholesterol concentrations were measured, the metabolic syndrome, by any of the diagnostic criteria available, may be undetectable. Each additional risk factor, if measured accurately and interpreted within the context of metabolic regulation, adds another piece to the puzzle of understanding both the risk of outcome and, even more importantly, the causal metabolic basis of the dysregulations and hence the appropriate pathway to successful intervention. If diagnosis stops at a predetermined set of risk factors, the complete metabolic picture cannot be revealed.

Let us suppose that an individual has all of the risk factors commonly associated with the metabolic syndrome, including abdominal obesity, high BMI, high fasting triacylglycerol concentrations, low HDL concentrations, small dense LDLs, decreased insulin sensitivity, and high blood pressure. Now, let us suppose that on further examination this individual also has elevated liver enzymes but does not drink alcohol. Fatty liver is suspected and progression to nonalcoholic steatohepatitis is a possibility. A recommendation to follow a low-fat, high-carbohydrate diet for weight loss and to reduce heart disease risk might exacerbate the overproduction of fatty acids via de novo lipogenesis and thus worsen the hypertriglyceridemia in this individual.

The metabolic environment is highly dynamic, and it is necessary to document and annotate all particulars that might affect any given measurement. For instance, the follicular phase of the menstrual cycle is different from the luteal phase in terms of blood lipid profiles in women, and the time of day influences the concentrations of certain

compounds that are secreted according to a diurnal rhythm. Approaches that measure and analyze many endpoints simultaneously provide a more complete picture of system functioning and the possible underlying disorders involved in a particular disease state. In effect, the measurement of multiple endpoints adds resolution to the metabolic profile.

Measure more, more often

In light of the points discussed above, we propose that individual variability among people should be a prominent component of the diagnosis of metabolic syndrome and other metabolic disorders. A move away from a one-size-fits-all approach in diagnosis and toward a more individualized approach that recognizes the variability among people is necessary. As Grundy points out, the clustering of metabolic factors that defines the metabolic syndrome is a step toward recognition that the metabolic diseases of today are complex and require different solutions than do diseases that have one clear cause.

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