

# 1 Introduction

The metabolic syndrome is a multiplex risk factor for cardiovascular disease (CVD) and atherosclerosis. From a historical point of view, Jean Vague, a physician from France, is one of the investigators who first linked abdominal obesity with metabolic abnormalities in the mid-1940s. However, Gerald B. Phillips, in 1978, was the first who stated clearly the hypothesis that aging, obesity, and other clinical manifestations, which are now referred to as metabolic syndrome, are associated with heart disease (1).

In 1988, Reaven noted that dyslipidemia, hypertension, and hyperglycemia commonly cluster together and called this clustering *Syndrome X*, which was recognized as a multiplex risk factor for CVD (2). Subsequently, it was observed that insulin resistance underlies Syndrome X and hence, the term *insulin resistance syndrome* is also used for this constellation of manifestations. The term *metabolic syndrome* or *metabolic syndrome X* is also used for this clustering of metabolic risk factors. It is now common to use the term metabolic syndrome X or simply metabolic syndrome because it avoids the implication that insulin resistance is the primary or only cause of associated risk factors. Most subjects with the metabolic syndrome have insulin resistance that confers increased risk for type 2 diabetes mellitus. When diabetes becomes clinically apparent, CVD risk rises sharply. Other conditions that are common in those with metabolic syndrome include polycystic ovary syndrome, fatty liver, cholesterol gallstones, asthma, sleep disturbances, and some forms of cancer (2).

The National Cholesterol Education Program's Adult Treatment Panel III report (ATP III) identified six components of the metabolic syndrome that relate to CVD. They are: (a) abdominal obesity, (b) atherogenic dyslipidemia, (c) raised blood pressure, (d) insulin resistance with or without glucose intolerance, (e) pro-inflammatory state, and (f) prothrombin state. Thus, in essence, those who have one or more features of abdominal obesity, atherosclerosis, insulin resistance and hyperinsulinemia, hyperlipidemias, endothelial dysfunction, essential hypertension, type 2 diabetes mellitus, and coronary heart disease (CHD) are considered to have the metabolic syndrome. Other features of the metabolic syndrome include hyperfibrinogenemia, increased plasminogen activator inhibitor-1 (PAI-1), low tissue plasminogen activator, nephropathy, microalbuminuria, and hyperuricemia.

Thus, in summary, the metabolic syndrome is characterized by abdominal obesity, atherosclerosis, insulin resistance and hyperinsulinemia, hyperlipidemias, essential hypertension, type 2 diabetes mellitus, coronary heart disease (CHD), hyperfibrinogenemia, increased plasminogen activator inhibitor-1 (PAI-1), low tissue plasminogen activator, nephropathy, microalbuminuria, and hyperuricemia.

However, it should be noted that all subjects with the metabolic syndrome need not necessarily have all the features just described. It is apparent that most of the subjects initially show some features, and as the disease progresses or over a period of time they develop other features of the metabolic syndrome. It is important to note that there is a high degree of variation from individual to individual as to what specific features of the metabolic syndrome are seen in each. For instance, one subject

may present only with abdominal obesity at a particular point, and as time passes he or she may develop other features of the metabolic syndrome such as hypertension, dyslipidemia, or atherosclerosis. On the other hand, another individual may present with more than one or more features of the metabolic syndrome such as abdominal obesity, hypertension, and dyslipidemia, and yet other features may manifest after a while. This individual variation in the presentation of some specific features in a given individual but not in others and the development of other features over a period of time suggests that, perhaps, all individuals who show various features of the metabolic syndrome are different from each other. It is perfectly possible that at the molecular level the pathophysiologies of various individual features that form the constellation of the metabolic syndrome are different. Understanding the specific molecular events that are responsible for each specific feature of the metabolic syndrome is a challenge. Nevertheless, there are some common features that underlie the various components of the metabolic syndrome.

In order to clarify the issue and to develop a uniform definition of the metabolic syndrome, the World Health Organization (WHO) defined the metabolic syndrome as a constellation of features that included impaired glucose regulation (includes diabetes mellitus) and/or insulin resistance: the 25% of subjects with the lowest insulin sensitivity (measured directly) in the “background” population were defined as insulin-resistant (3, 4). This definition has been criticized by the European Group for the Study of Insulin Resistance (5). The National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP-III) has recently defined metabolic syndrome based on clinical and biological measures that are routinely available (6–8), a definition in which neither insulin resistance nor insulin concentrations were considered. The prevalence of the metabolic syndrome using this definition was evaluated in US adults from the third Nutritional Health and Nutrition Examination survey (NHANES III) (3). However, the researchers also included those subjects treated for hypertension and/or diabetes as having the corresponding abnormalities. Results of this study suggested that more than 20% of the adult population was found to have metabolic syndrome.

Both WHO and NCEP ATP-III presented metabolic syndrome as an enhancer of cardiovascular risk beyond elevated low-density lipoprotein (LDL) cholesterol.

Although WHO and NCEP used the same term, that is, metabolic syndrome, the two groups have different goals for creating this diagnosis and different criteria to identify individuals that relate to their different institutional goals. For example, the NCEP definition, unlike that of WHO, does not include measurement of insulin and therefore fail to detect insulin resistance. In addition, when the NCEP and WHO definitions are compared, it seems that the NCEP definition better predicts risk than the WHO definition, suggesting that failure to detect insulin resistance may not be a disadvantage. In view of these discrepancies in 2005, the International Diabetes Federation (IDF) Epidemiology Task Force group suggested a new definition for metabolic syndrome that focused on central obesity (9).

## References

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