Metabolic Syndrome: Future prospects


Nobuhiro YAMADA*1

Abstract
In modern times, disease structures have changed greatly along with changes in the social environment. The incidence of atherosclerotic diseases, such as myocardial infarction and stroke, and diabetes mellitus has been increasing rapidly, and these diseases account for major impairments to health. Since the Framingham study, attention has been focused on overlapping risk factors that are likely to contribute to cardiovascular events. The initially proposed multiple risk factor syndrome has now become metabolic syndrome. In multiple risk factor syndrome, emphasis was placed on the significance of a wide range of overlapping risk factors including smoking, aging, and gender. In contrast, metabolic syndrome is regarded as a condition in which related risk factors that have a common pathologic basis overlap, and therefore a clear distinction should be made from conditions that include the overlapping of incidental and independent risk factors.

Key words Metabolic syndrome, Obesity, Diabetes mellitus, Insulin resistance, Atherosclerosis

Introduction: Circulation of “seeds” and “needs”
Scientific development steadily progresses when seeds and needs are well balanced. For example, if people determine that they want cars that obtain good gas mileage, this represents needs. To meet these needs, automakers develop automobiles that provide better gas mileage, leading to new growth in science and technology, representing seeds. As seeds and needs circulate, society benefits from increased convenience.

In the field of medicine, the circulation of seeds (elucidation of pathologic conditions and establishment of concepts) and needs (formulation of diagnostic criteria) is rather difficult and complicated, because the subject is human beings. It takes time to apply the seeds to human subjects, as it requires the accumulation of evidence and verification of safety and efficacy.

In the area of metabolic syndrome, we are now seeing the growth of seeds. Taking advantage of the increasing knowledge of pathology, concept, and mechanism of occurrence as the basis, explicit criteria for the diagnosis of metabolic syndrome have been developed to meet the needs of the population. However, since the concept of metabolic syndrome has only a brief history, it is necessary to improve the criteria through further discussion to promote the circulation of seeds and needs. It is also necessary to fully understand that needs alone do not lead to knowledge in all aspects of the pathology and characterization of this syndrome.

“Needs” in the Field of Metabolic Syndrome

The needs in regard to metabolic syndrome require reversing the increase in myocardial infarction, stroke, and diabetes mellitus resulting from poor lifestyle choices (particularly, overeating, excessive fat consumption, physical inactivity) and to somehow prevent these conditions. The Ministry of Health, Labor and Welfare is now formulating strategies against cardiovascular disease (myocardial infarction), stroke,
diabetes mellitus, and cancer. The great deals are expected from the prevention of metabolic syndrome because it can suppress three of the four major diseases (excluding cancer). Although it appears that the circulation of seeds and needs in this field began just recently, E. Joslin, known as the true founder of diabetology, said the following as long ago as 80 years, i.e., only several years after the discovery of insulin (1921): “I believe that the major factor for the early progression of atherosclerosis in diabetes mellitus, except for aging, is ‘excessive fat ingestion,’ i.e., excessive fat in the body (obesity), excessive dietary intake of fat, and excessive fat in the blood (hyperlipidemia). Beginning with high fat intake, it has been common recently that people die from atherosclerosis resulting from excessive fat accumulation in the vascular wall.”

The above description corresponds exactly to metabolic syndrome. We should identify individuals at high risk of developing atherosclerotic diseases, with the above statement borne in mind. In identifying high-risk individuals, we can assess risk accurately by examining relevant risk factors including low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, smoking, age, gender, diabetes mellitus, and hypertension, according to relevant guidelines. As a result of our efforts, we now have target values of lipid control for each risk level as prescribed in the 2007 Japan Atherosclerosis Society (JAS) Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases.

Guidelines, however, have limitations. Guidelines become effective only after a diagnosis of hypertension, lipid abnormality, or diabetes mellitus is made, and, unfortunately, cannot currently capture high-risk individuals in borderline areas. Conventional guidelines based on tabulating risk assessment cannot fully respond to the need for prevention. This leaves room for the role of metabolic syndrome (Fig. 1). Improvement in the accuracy of screening of high-risk individuals has been attempted by introducing the concept of metabolic syndrome, arousing the “anti-metabo campaign” that assumes the idea of effectively preventing atherosclerotic diseases and diabetes mellitus.

To improve the accuracy of the screening of high-risk individuals, it is necessary to detect overlapping risks (blood sugar, blood pressure, lipid levels) related to common pathologic conditions including obesity and insulin resistance. Since these risks are interrelated, the elimination of obesity and improvements in insulin resistance may eventually result in a comprehensive improvement of health. The concept of metabolic syndrome is important in this respect. More specifically, it is expected that, with the idea of metabolic syndrome, the overall modification of risk, rather than the specific modification of individual risk factors, may achieve enhanced control of atherosclerosis and diabetes mellitus.

“Seeds” in the Field of Metabolic Syndrome

By understanding the process through which risks accumulate with poor lifestyle, thereby leading to the worsening of common pathologic conditions with aging, and if this process can be better understood, it may make it possible to obtain an optimal medication with minimal necessary doses. We believe that watering the seeds of development will lead to more accurate diagnostic criteria.

Major factors underlying the development of metabolic syndrome in the Japanese population include aging and hereditary predisposition in addition to the westernization of eating habits, overeating, excessive fat intake, and physical inactivity.\textsuperscript{1,2} If a person with these predisposing factors has a poor lifestyle, an imbalance in energy metabolism that nutrient storage can occur within the body arises. To correct this, gene expression may be changed, and there may be adjustments among organs including the liver, muscle, heart, and brain structures involving
However, when such adjustments fail to occur, abnormalities in blood sugar, blood pressure and lipid levels in the body take place, resulting in obesity, and eventually causing metabolic syndrome.

Therefore, to prevent metabolic syndrome, lifestyle needs to be improved to prevent an imbalance in energy metabolism. Thus, preventive medicine plays an important role. When patients fail to improve their lifestyle, blood sugar, blood pressure, and lipid levels need to be treated in an individualized manner.

To deal with metabolic syndrome, there are a number of pathologic conditions such as insulin resistance, obesity, inflammation, oxidant stress, and appetite regulation that occur in the process from energy imbalance to atherosclerosis and diabetes mellitus through an accumulation of risk factors, namely, blood sugar, blood pressure, and lipid levels (Fig. 2). Currently, treatment targeting each risk factor (multidrug regimen) is employed. However, if elucidation of the various pathologic conditions progresses, monotherapy specific to each pathologic condition will likely be developed in the future.

**Fig. 2 Pathologic condition of metabolic syndrome: search for comprehensive treatment**

**Treatment of Lifestyle-related Diseases**

**Control of risk factors:** Data obtained from the Steno-2 Study indicate the difficulty of controlling risk factors for cardiovascular diseases in patients with type 2 diabetes mellitus. Blood sugar control has achieved its target level only in 15% of patients, even with aggressive drug treatment. The corresponding rates for lipid levels and blood pressure have been better, but have remained at about 70%.

In the Japan Diabetes Complication Study (JDCS) covering patients with type 2 diabetes mellitus treated in 60 facilities nationwide, more than half the subjects developed lipid abnormality, and 40% developed hypertension, despite rigid control. This reflects the difficulty of sufficiently controlling risk factors.

**Current status of treatment of lifestyle-related diseases:** There has been substantial progress in the treatment of lipid abnormality and hypertension. However, utmost effort is still needed to enhance treatment. The treatment of hyperglycemia and control of obesity and smoking strongly depends on self-control by the patient, and thus represents the most intractable clinical area. Physicians are now facing the question of how to solve these problems.

As a result of these circumstances, the issue of metabolic syndrome has been highlighted. The treatment of metabolic syndrome is aimed at resolving the issue of obesity and subsequent hyperglycemia. Cessation or reduction of smoking is a major target for prolonging the life expectancy of the Japanese population. To achieve these targets, a new system has been initiated, by which people between the ages of 40 and 75 years are checked for metabolic syndrome (visceral fat-type obesity) and those with distinct or borderline metabolic syndrome receive specific health counseling. The item “metabolic syndrome” has been added to “Healthy Japan 21,” an ongoing large-scale project aimed at decreasing diabetes and other lifestyle-related diseases. Despite these measures, lifestyle-related diseases are increasing. On the other hand, cases of successes such as the following have occurred.

**Successful treatment of lifestyle-related diseases:** In regard to hypertension, efforts have been focused on the improvement of lifestyle habits and reduced salt intake, since death from stroke is common among Japanese people. As a result, the incidence of stroke has decreased markedly. The increasing life expectancy of the Japanese population is partly attributable to progress in the treatment of hypertension. Properly addressing this issue should produce good results. It is said that lifestyle-related diseases, particularly diabetes mellitus, can shorten average life expectancy by 10 years. If the environment is adjusted to combat these diseases, in the same way as in the fight against cancer, it will certainly contribute to increased longevity.

Another success story can be found in the US.
Behind the recent decline in cardiovascular diseases in the US is the national Healthy People initiative that has been in effect since the 1960s. Prior to this effort, cholesterol levels were high, and deaths from myocardial infarction were common among the American public. The Healthy People initiative, a campaign that focused on smoking cessation, diet, and exercise was expanded and succeeded in lowering people’s cholesterol levels. Since the lipid-lowering agent statins became commercially available shortly before 1990, the US succeeded in lowering cholesterol levels, and thus decreasing cardiovascular diseases, by improving lifestyle habits even before the advent of statins.

On the other hand, as the population of obese people continues to increase, diabetes and diabetes-related death has been on the upswing in the US. Therefore, programs to counter diabetes mellitus have been implemented, and the United Nations has been carrying out a worldwide campaign, “Unite for Diabetes,” to hold back the increase of diabetes mellitus.

**Future problems:** Most patients with lifestyle-related disease (known as the silent killer) do not have subjective symptoms, but are at high risk of future development of myocardial infarction or stroke. Therefore, improved quality of medical care is extremely important. However, although the need is high, the seeds development is insufficiency, because the concept of lifestyle-related diseases is relatively new. Therefore, it is necessary to accumulate more scientific evidence to respond to the need. A steady effort is needed in guiding patients to efficiently manage their lifestyle diseases for a long time. Lifestyle habits vary substantially among patients. Some patients cannot abstain from alcohol, and others have to work until the late hours of the night. Customized medicine for the adverse lifestyle habits of each patient will be necessary to modify whatever aspects can be modified.

If pathologies are elucidated in the future, drug therapies will also be developed. For example, agents that improve insulin resistance include thiazolidine derivatives for diabetes mellitus, PPAR-γ (peroxisome proliferator-activated receptor γ) agonists for disorders of lipid metabolism, ACE (angiotensin-converting enzyme) inhibitors and ARB (angiotensin II receptor blockers) for hypertension. In the future it may be possible to optimize drug treatment by accumulating evidence about combinations of these drugs to achieve best-fit improvement in insulin resistance without causing obesity or diabetes mellitus.

Elucidation of the pathologic condition of metabolic syndrome will lead to breakthroughs in the prevention and comprehensive treatment of diabetes mellitus, a hard-to-control disease, as well as atherosclerotic diseases such as myocardial infarction and stroke that continue to increase in developed countries. For instance, the transcription factor TFE3, as identified previously, regulates the expression of a nutrient metabolism-related gene. This transcription factor activates insulin signals to decrease blood sugar levels not only in animal models of obesity but also in animal models of type 1 diabetes mellitus. Thus, research into metabolic syndrome suggests the possibility of another seed, i.e., a new treatment for type 1 diabetes mellitus (or insulin-dependent diabetes mellitus) for which insulin injection is currently unavoidable.

### Conclusion

Metabolic syndrome is a disease that results from caloric accumulation based on current lifestyle habits. The basic treatment of this disease consists of improvement of lifestyle habits, and the priority in prophylaxis should be given to increase the accuracy of screening for individuals at borderline high risk. Efforts to search for the optimal comprehensive treatment should allow us to obtain drug treatments that involve lower and safer dosing than the multidrug treatments currently in use.

To this end, progress in research based on a good balance of the elucidation of the pathologic conditions (seeds) and establishment of the disease concept (seeds) and the formulation
of diagnostic criteria (needs) is indispensable (Fig. 3). At present, visceral obesity is assessed by waist circumference and insulin resistance by the HOMA index. It should not be long before the advent of new solutions leads to better diagnostic accuracy, better quality of medical care, and effective, comprehensive treatment.

References