Atherosclerosis Prevention in Youth

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Atherosclerosis-associated circulatory disturbance is one of the most important global issues. In patients with atherosclerosis, eccentric intimal thickening and lipid deposition progress over a long period (at least 20 to 30 years). On the other hand, in patients with atherosclerosis-associated circulatory disturbance represented by myocardial infarction, the direct cause of death is thrombus formation rather than marked stenosis; wall destruction may lead to a fatal outcome. In the future, atherosclerosis susceptibility, that is, intrinsic genes, should be investigated.

Keywords: atherosclerosis, thrombosis, PDAY, lifestyle, prevention

INTRODUCTION

Along with the results of many studies, the acute myocardial infarction-related mortality rate in patients in the United States has decreased by 30% over the past 20 years. However, in the United States, the ischemic heart disease (IHD)-related mortality rate is still significantly higher than in Japan. Briefly, the number of patients who die remains very large despite a marked decrease.

In Japan, a Western lifestyle has recently been introduced. The IHD-related mortality rate shows a tendency similar to that in the United States. It remains controversial whether the IHD-related mortality rate will similarly increase in the future, or will not increase due to differences in factors such as IHD susceptibility in which recently clarified genes are involved. In Japan, the most common cause of death is malignant tumors. In addition, the malignant tumor-related mortality rate has been increasing.

Under the circumstances like this, it is easy to understand that today they have so much concern about and are looking for unknown more available risk factors of malignant tumors. However, at the same time, we should pay much attention to prevent atherosclerosis typically represented by IHD, because we should be able to prevent atherosclerosis remarkably by eliminating established major risk factors such as smoking, salt consumption, animal lipid rich diet, and so forth. It is generally accepted that atherosclerosis is a definite leading cause of death especially among elders over eighties even in Japan. The process of atherosclerosis is usually required for decades. Continuous lifestyle interventions would be recommended for many people. Risk factors of atherosclerosis have been studied systematically. For example PDAY, a study of Pathobiological Determinants of Atherosclerosis in Youth, points out the importance of clinical pictures, epidemiology, biochemistry, molecular biology, and histopathology. Today, atherosclerosis both in youth and elderly is gradually getting serious, it is worthy of review it systematically.

SERIAL CHANGES IN ATHEROSCLEROSIS

The primary etiology of IHD, represented by acute myocardial infarction, is atherosclerosis. Currently, it is known that atherosclerosis causes a serious complication through at least 20- to 30-year course. Based on autopsy findings in persons who died during the Korea War in the 1950’s, the onset of atherosclerosis in young persons was accepted for the first time. Subsequently, the entity...
of a risk factor was proposed, and epidemiological studies have clarified concrete risk factors\(^6,7\): hyperlipidemia, smoking, hypertension, and diabetes. Atherosclerosis prevention is not always a warning against obesity. Epidemiologically, obesity was not selected as a risk factor, contrary to many investigators’ prospects, over a long period. However, smoking was verified as a major risk factor. Among young Japanese females, the rate of smoking, which contributes to the onset of atherosclerosis, has not decreased, although they pay attention to obesity prevention from the perspective of esthetics.

On the other hand, not only epidemiological studies but also the results of animal and cell culture experiments have shown the association between atherosclerosis and diet. Previously, as a global consensus, the histological classification of atherosclerosis established by the American Heart Association (AHA)\(^8\)–\(^10\) was commonly accepted. In this classification, atherosclerosis was classified into 6 grades: initial lesion, fatty streak, preatheroma, atheroma, fibroatheroma, and complicated lesion, with respect to the progression of eccentric intimal thickening and lipid deposition over a long period (at least 20 to 30 years). It was taken for granted that, as a rule, the condition must progress in this order. This classification is advantageous with respect to the following points: the contents are based on evidence obtained from a large number of autopsy cases, epidemiological data, and animal experiments, reflecting a consensus among leading investigators at that time. As for the number of autopsy cases, more than thousand, it is too large to reproduce it once again today. Concerning the natural history of atherosclerosis, that is, serial changes and those corresponding to the greatest common measure, the AHA classification is still a gold standard. However, further supplements were required from other perspectives.

**Supplements for the AHA Classification**

It was proposed that the histological classification should be revised to clarify the etiology of sudden coronary death, away from investigating serial changes in atherosclerosis.\(^11\) Briefly, even when the grade of atherosclerosis is evaluated as severe according to the AHA classification, the condition is asymptomatic in some patients. In contrast, even when mild atherosclerosis is suggested according to the AHA classification, coronary atherosclerosis-related sudden death may occur in others. A study indicated that 10% of patients with grade VI plaque rupture evaluated according to the AHA classification died of other factors.\(^12\) Plaque rupture may be asymptomatic in some cases. In contrast, sudden coronary death associated with coronary obstruction-related thrombus with erosion in the absence of plaque rupture was observed in 20 to 30% of patients; when reperfusion occurs, stenosis alone may not lead to a fatal phenomenon.\(^13\)–\(^15\) These studies suggest that it is not stenosis but thrombus formation that directly contributes to mortality. It is sometimes difficult to verify whether or not stenosis alone leads to a fatal outcome, because this depends on the lesion site. On autopsy, we have sometimes encountered patients who may have died of another factor, as there were no clinical symptoms of ischemic heart disease despite marked stenosis.

We cannot rule out the possibility that thrombus formation may be involved in stenosis. In particular, chronic disorders in elders, hypertension and diabetes, may be important, latent risk factors. However, as a rule, there may be no correlation between stenosis and thrombus formation in the initial lesions; thrombi may not be involved in the formation of initial lesions in young persons, differing from advanced lesions. In other words, prevention in young persons is not always consistent with that in high-risk elderly patients. The results of the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study support this. More than 1000 young persons who suddenly died without an underlying disease were reviewed and found it out that the detection rate of thrombus formation in the common sites of atherosclerosis was very low. Therefore, thrombus formation may not be a significant factor for initial stenosis formation. On the contrary, in advanced atherosclerosis lesions, thrombus formation may cause fatal events; its significance is the direct cause of death in many cases (Fig. 1). That is to say, thrombus formation closely contributes to most fatal phenomena. It is unclear whether thrombus formation is correlated with the progression of atherosclerosis or independently occurs. Therefore, it is necessary to supplement the AHA classification.

For this point of view, the following histological features directly involved in the cause of death, which may lead to lethal thrombus formation, are important: thinning of the fibrous capsule (65 microns or less), neovascularization, plaque formation (50% or more of the vascular cross sectional area), and necrotic core/plaque &gt;25%.\(^16\)

Such lesions are not always distributed at sites of the most advanced stenosis, as described above. Stenosis frequently occurs in areas where the wall shear stress is low. However, in patients with atherosclerosis, thrombus
formation frequently occurs in areas where the wall shear stress is high, that is, at stenotic lesions. Previously, the distribution of lesions was reported as follows: as the wall shear stress is high in advanced stenotic lesions, thrombus formation predominantly occurs. There is a strong correlation between the grade of stenosis and thrombus formation. In most advanced stenotic lesions, thrombus formation occurs, inducing heart attacks. However, thrombus formation is a complex phenomenon depending on the vascular wall, blood flow, and blood components. The above hypothesis previously reported was mainly based on blood flow. Recently, vascular wall features have been reviewed from a new standpoint. Thrombi formed in intact blood vessels are small, and do not induce a heart attack. As a rule, fatal events may be associated with atheroma rupture- or erosion-related thrombus-associated complete obstruction.\textsuperscript{17,18} In particular, atheroma rupture-related complete obstruction may comprise the greater portion of patients with myocardial infarction. That is why the details on mechanism of atheroma rupture has been actively investigated.

**LIMITATIONS**

It is speculated that atheroma rupture, which is directly involved in the cause of death, is closely related to inflammation. Inflammatory cell infiltration directly contributes to rupture of an atherosclerotic focus and thrombus formation. In particular, monocyte-derived macrophages play an important role.\textsuperscript{6–10,19,20}

It is known that macrophage-related phagocytosis/foam cell formation/rupture are closely involved in the etiology of atherosclerosis. Whereas the involvement of macrophages in necrotic core formation remains to be controversial. In Europe and the United States, the hypothesis that a necrotic core is formed through

![Fig. 1](image_url) Right coronary artery with inferior-/posterior-wall infarction. Upper: Macroscopic examination, Lower: Histology (There was a partial crack related to an artificial product.)
macrophage rupture alone in humans is not accepted, because esters that accumulate in the necrotic core of atheroma consist of linoleic acid, as detected in serum, differing from macrophage-derived oleic acid. The pathway of macrophage-derived oleic acid, which does not accumulate in the necrotic core, remains still unclear. In humans, extracellular changes are more marked than in animals (Fig. 2). Considering this, all animal (rodent) experiment-based opinions are not adapted to humans. Not only differences between animals and humans but also laboratory animal type-related differences suggest many hypothetic things might be concealed in some cases. In the United States, various animals had been used as experimental materials, and experimental merits/demerits were compared. Therefore, the characteristics of each animal type are clear. In Japan, rabbits and rats may be frequently employed. When atherosclerosis is experimentally prepared with a high-fat diet, both rabbits and rats primarily show intracellular lipid accumulation, and extracellular deposit is extremely restricted. This should be considered. It must be carefully examined whether laboratory animals accurately reflect extracellular changes in humans closely associated with final/fatal events related to lesions.

In several studies including the PDAY study, the intramural infiltration of monocyte-derived macrophages was not always in proportion to the progression of an initial lesion. In the initial phase, lipid deposition in the coronary artery was delayed (about 10 years) compared to that in the abdominal/thoracic aorta. However, in middle-aged or older patients, coronary lipid deposition rapidly progressed. Libby described the discontinuity
as an issue to be resolved in Harrison’s Principles of Internal Medicine. Namely, fatty streaks are continuous, but fibrous plaques are discontinuous. A hemodynamic theory may be called for. Hemodynamic conditions must be sufficiently discussed. For example, pressure fixation of the heart was employed as a sampling method in the PDAY study. According to the hemodynamic theory described by Glagov, et al., as a rule, the cross-section of the vascular lumen is round in vivo, but not crescent. They indicated that its crescent-shaped appearance was a postmortem change related to blood outflow, a modified feature. For this reason, the heart was fixed under pressure in the PDAY study. Under this condition, we, The University of Chicago Group, extirpated more than 500 hearts to recognize that the cross-section of the anterior descending coronary artery lumen was round (not crescent-shaped in my memory). Without pressure fixation wall shear stress involved in atherosclerotic foci may be evaluated under conditions different from those in vivo. It is necessary to compare our results with those of experiments conducted under in vivo conditions, if possible.

Several studies have shown that proteases produced by macrophages, especially matrix metalloproteinase (MMP), play an important role in the rupture of atheroma. In the future, this issue should be further investigated. Most of histological studies on atherosclerosis especially domestic ones investigated from the viewpoint of lipid deposits and intimal thickening. It goes without saying that to clarify the relationship between lipid and intimal thickening is important. Further questions are coming up today, that is to say, it is necessary to show the relationship between cell populations and hemodynamics, atherogenic development, immunity, and extracellular matrix.

**Future Guidelines**

Epidemiological, biochemical, and molecular biological studies have clarified the etiology of atherosclerosis, as well as risk factors, as described above. Recently, studies to clarify differences in ischemic heart disease susceptibility at the genetic level have been emphasized. They made it possible to scientifically clarify issues that had been regarded as body constitutions without theoretical explanation.

As previously indicated, experiments in the field of atherosclerosis research had some limitations. The human lifespan is so much longer than that in laboratory animals. Therefore, it is difficult to objectively match experimental changes to the phase of atherosclerotic foci in humans. In addition, sites of predilection markedly differ among animals, and there are also marked differences in the mechanism: which of two factors, intra- or extracellular changes, is primarily involved. Molecular biological procedures involving genes have contributed to the prevention/treatment of atherosclerosis. Molecular biological studies have investigated the etiology from the perspective of extrinsic factors. In the future, susceptibility to ischemic heart disease, that is, an intrinsic factor, should be examined.

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