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Mechanism of Thrombus Formation in Regard to Diet

Shinya Goto

Abstract

The majority of diseases causing sudden death or sudden onset of serious restriction of quality of life are thrombotic disease. Myocardial infarction is often caused by thrombotic occlusion of coronary arterial branches. Ischemic stroke is also caused by occlusion of cerebral arteries with thrombi. In patients admitted to the hospital and immobility, venous thromboembolism causing pulmonary embolism is a major cause of death. The risk of cardiovascular events is influenced by food intake. Yet, the mechanism between specific food intake and the risk of thrombotic disease is still to be elucidated. Recent progress of computer and information technology allows us to describe complex biological phenomena such as thrombosis from basic principles of physics and chemistry. Coupling blood flow, platelet, coagulation, and fibrinolysis allows us to understand the contributing role of each factor for thrombus formation. Yet, the precise role of food intake to influence the risk of thrombosis is still to be elucidated. Coupling basic research and large-scale clinical research will further clarify the role of various types of food intake in the risk of thrombosis.

Keywords: myocardial infarction, stroke, arterial thrombosis, platelet, coagulation

1. Introduction

Thrombosis is the leading cause of death in the world. Indeed, atherothrombosis including coronary artery diseases and cerebrovascular diseases is the top cause of death in various regions of the world [1]. Venous thrombosis including deep venous thrombosis and pulmonary embolism is the third cause of death in hospitalized patients [2]. Thrombosis is a disease caused by thrombi formed at various vessels. The major symptom differs substantially depending upon the site where the thrombi developed. Typically, arterial thrombosis such as myocardial infarction and ischemic stroke is symptomatic even when the thrombi are small (e.g., less than 1 mm in diameter) [3]. On the other hand, venous thrombosis is asymptomatic until thrombi become substantially large such as the ones that occlude several pulmonary arteries to cause pulmonary embolism [4]. In both arterial and venous thromboses, platelets are cells that contribute to initial thrombus formation. Coagulation and fibrinolysis are systems necessary to regulate the size of fibrin thrombi.

It is noteworthy that there is homogeneity in risk factors for various arterial/venous thromboses despite wide variation of clinical manifestation [5]. Framingham study demonstrated that cigarette smoking, diabetes mellitus (DM), dyslipidemia, and hypertension are strong predictors for the future onset of arterial thrombosis represented by acute myocardial infarction [6]. Recent international

registries also confirm that these risk factors are contributing factors for the recurrence of cardiovascular events [7]. Moreover, international registries also suggested these parameters as risk factors of venous thrombosis [8]. These clinical observations suggested the presence of common pathways for the onset of arterial and venous thrombosis [9].

The Framingham registry suggested the contributory role of obesity and less exercise as the predictors for future prevalence of risk factors. These abnormalities represented as visceral obesity-related syndrome is named as "metabolic syndrome." In metabolic syndrome patients, insulin resistance is one of the major contributors [10]. Increased body weight, high blood pressure, and dyslipidemia are common manifestations of metabolic syndrome. Long-term exposure to a high-calorie diet and lack of good exercise are supposed as underlining mechanisms for the onset of metabolic syndromes. The risk of thrombotic disease including arterial and venous thrombosis is speculated to be high in patients with metabolic syndrome.

2. Platelet adhesion at the site of endothelial injuries

Blood is flowing to maintain homeostasis inside the human body. Blood cells have specific functions: erythrocytes bring oxygen to tissues, leukocytes protect from infection, and platelets stop bleeding promptly. As shown in **Figure 1**, large and heavy erythrocytes tend to be located in the center of blood flow. Small cells of platelets circulate interacting with endothelial cells [11]. In the case where endothelial cells have a physiological function, platelets do not interact with them [12]. Platelets collide with the vessel wall and promptly go back to the blood flow without platelet activation. On the other hand, when endothelial cell function was disturbed by physical or chemical stimuli, endothelial cells lose their ability to keep antithrombotic function. Then, platelets immediately start the interaction with endothelial cells [12]. At the time, von Willebrand factor (VWF) is expressed on the cell surface of stimulated endothelial cells. Platelets capture VWF through glycoprotein (GP)Ibα. GPIbα is expressed on the surface
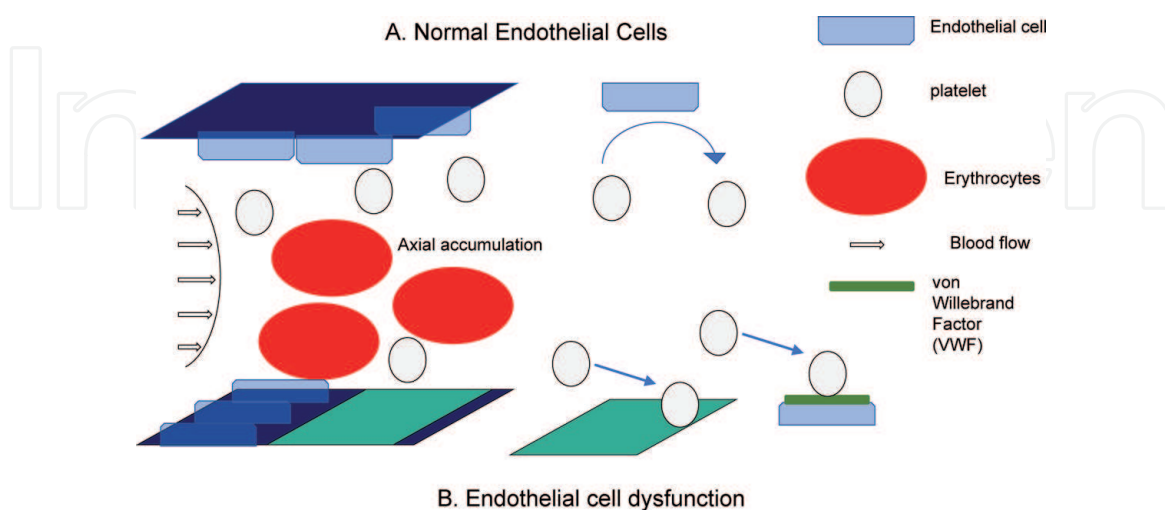

Figure 1.
Role of erythrocytes and blood flow in platelet adhesion at the site of endothelial injury. This figure demonstrates the three-dimensional distribution of erythrocytes, platelets, and endothelial cells. Erythrocytes accumulate in the center of blood flow by biorheological effects. Accordingly, platelets circulate close to endothelial cells. In the presence of normally functioning endothelial cells, platelets do not adhere nor are activated, but just return to blood flow (panel A). If the endothelial cell function was disturbed by various stimulations, platelets are adhered and activated through their interaction with von Willebrand factor (VWF).

of platelet regardless if they are activated or not [13]. Thus, initial adhesion of platelets at the site of endothelial cell damage occurs predominantly as a physical phenomenon, which occurs immediately without time-consuming biological process. Historically, the vast majority of vessel damage is caused by trauma. Rapid accumulation of platelets at the site of endothelial injury plays an important role to keep our blood in our vessel system for surviving.

The potential impact of erythrocytes for the onset and growth of thrombosis has first caught the interest of researchers in the 1960s [14]. Biorheological axial accumulation of flowing platelets was also recognized at the same time [15]. Clinical studies also support the notion that higher hematocrit values are related to higher risk of thrombotic diseases such as myocardial infarction [16]. These results strongly suggest the biophysical role of erythrocytes for thrombus formation. These rheological effects could hardly be controlled by food intake. In another aspect, erythrocytes also influence the function of platelet with biochemical modulation [17–19]. Indeed, erythrocytes are a huge source of ADP [20], which is one of the most potent platelet-stimulating agents [21, 22]. There is potential effects of food intake for influencing erythrocytes components which can influence thrombogenicity of platelet [23, 24].

Recent advances in computer technology allowed us to predict the structure and function of VWF bound with GPIbα from the physical movement of atoms and water molecules [25, 26]. By the method, physical force generated by VWF binding with GPIbα could be predicted. Platelet adhesion at injured vessel wall is summarized in **Figure 2**. Platelets are cells with a diameter of approximately 5 μm. But, when platelet adhered at the site of vessel damage, only part of platelet bound with VWF. Molecular dynamic prediction revealed that single bond of VWF and GPIbα could generate binding force approximately 70 pN [25]. Fluid dynamic force applied to platelets reaches to a couple hundred pN when the cell receives detaching force from arterial blood flow. Theoretically, several bonds between VWF and GPIbα are enough to stop platelets from adhering to the vessel wall. The mechanism of thrombus formation is a complicated process, but platelet adhesion under blood flow condition could now be constructed from physical movement of atoms and water molecules.
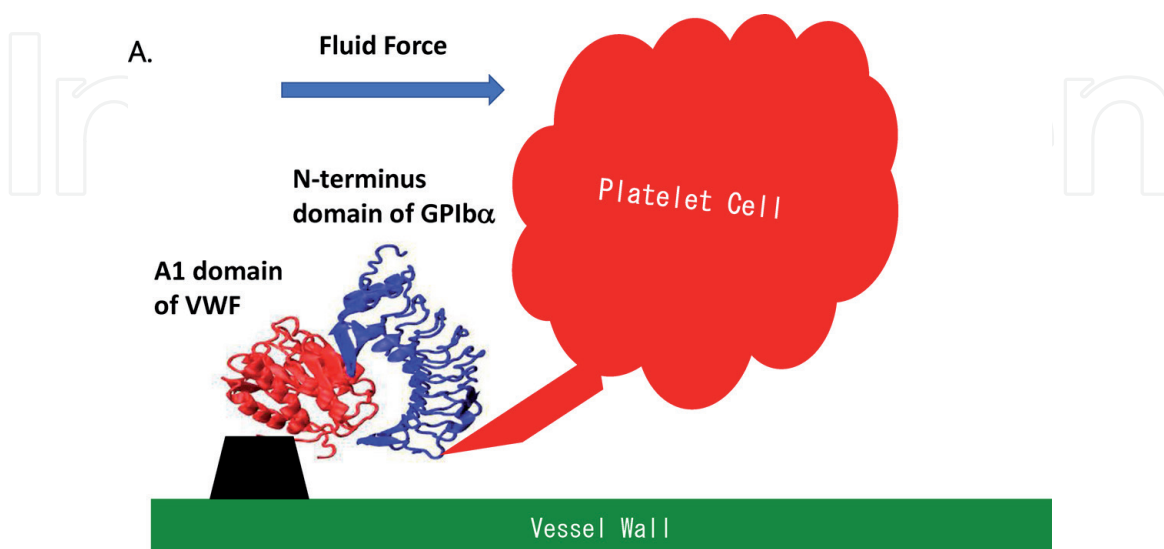

Figure 2.
Platelet adhesion at the site of endothelial damage under blood flow conditions. Platelet adhesion is mediated exclusively by its glycoprotein (GP)Ibα binding with von Willebrand factor (VWF). Adhered platelets receive fluid dynamic force, but platelets continue to adhere until the detaching force becomes larger than the binding force generated between VWF and GPIbα.

It is of particular importance that endothelial damage is not caused only by acute physical or chemical stimulation. In the recent era, human beings enjoy longer life than those who lived hundreds of years ago. Just like carrying human being, vessel system become old when people become old. Longer time exposure of vessel wall to atherogenic lipids such as LDL cholesterol and its related local biological reaction causes atherosclerosis [27, 28]. Antithrombotic potential of endothelial cell in patients with atherosclerosis is reduced when compared to younger normal ones. Moreover, plaque rupture exposes subendothelial thrombotic materials to vessel lumen. Thus, atherothrombotic events occur frequently [29] in the era of aging society. The initial event resulting in symptomatic atherothrombosis is always platelet adhesion at the site of endothelial injury.

By understanding the mechanism of atherosclerosis and atherothrombosis, it is rather easy to understand that various types of food intake influence the risk of thrombosis. As regards nutritional factor, there is a hot discussion concerning cholesterol. Some suggested potential benefit of cholesterol restriction for prevention of atherothrombosis. The other suggest there are no relationship between daily cholesterol intake and the risk of atherothrombotic event risk.

3. Activation of coagulation cascade and fibrinolysis

Symptomatic atherothrombotic events such as acute myocardial infarction occur when organ perfusing arterial branch was occluded by thrombi. The diameter of organ perfusing vessels is substantially larger than a single cell of platelet. Indeed, the diameter of platelets is just 2–5 μm, while the diameter of myocardial perfusing coronary arterial branches is 2–3 mm. The size of vessel diameter is typically 1000 more than the size of platelet diameter. It is nonrealistic to imagine that coronary arterial branches were occluded by platelet thrombi. Indeed, when coronary arterial thrombi causing myocardial infarction are aspirated by thrombo-aspiration therapy, the main component of occlusive thrombi was fibrin (**Figure 3**). It is
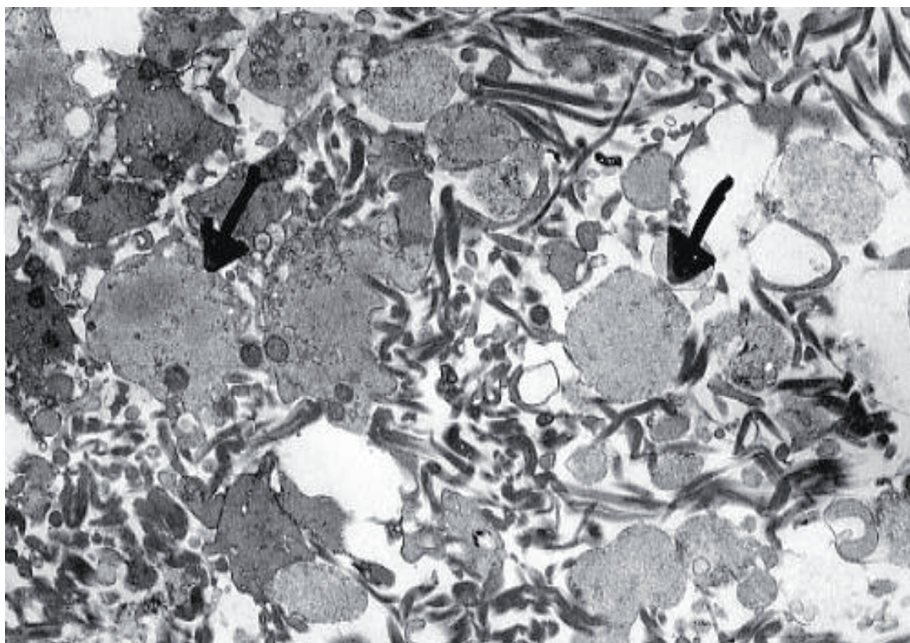

Figure 3.
Major components of thrombi causing acute myocardial infarction. Sample thrombi were aspirated from patients with acute myocardial infarction. The main results and study protocols were published elsewhere [53]. Here, electron microscopy results are shown. Fibrin fibrils could be seen around activated platelets (arrow).

noteworthy that fibrin fibrils are detected around activated platelets (**Figure 3** is the product in collaboration with Prof. Yujiro Asada at Miyazaki University).

The lipid components of activated platelet changed from the ones at the quiescent state. Negatively charged phospholipids appeared on the surface of activated platelets [22]. Then, various coagulation factors accumulated around the lipid to form pro-thrombin complex. On the activated platelet, thrombin generation occurs extremely efficiently. Indeed, thrombin generation rate in the absence of activated platelet and tissue factor is almost 0 as compared to that in its presence. At the site of atheroma rupture, large enough fibrin thrombi were formed as a result of the accumulation of activated platelet and exposure of tissue factor from the ruptured atheroma. Tissue factor accumulated in the atheroma is generated from inflammatory cells, which migrated into the atheroma. In the animal study, dietary lipid restriction reduces the amount of tissue factor accumulated in the atheroma [30]. The clinical factor of the reduction of the onset of myocardial infarction by the use of lipid-lowering therapy [31] may be related to reduction of lipid accumulation and subsequent reduction in tissue factor accumulated in the atheroma. Moreover, there are several publications indicating the impact of food intake for the lipid component of blood cells [23, 24]. The rate of fibrin formation at the site of endothelial damage and platelet accumulation should be modified by food from both activated platelet-derived procoagulant activity and the amount of tissue factors accumulated in the atheroma.

The process of thrombus formation at the site of endothelial injury is complex. We have attempted to develop the process model of thrombus formation as shown in **Figure 4** [32]. The model is still simple but includes various physically and chemically different events. First, the model implemented the effect of blood flow, which is a purely physical phenomenon. Second, the model includes platelet
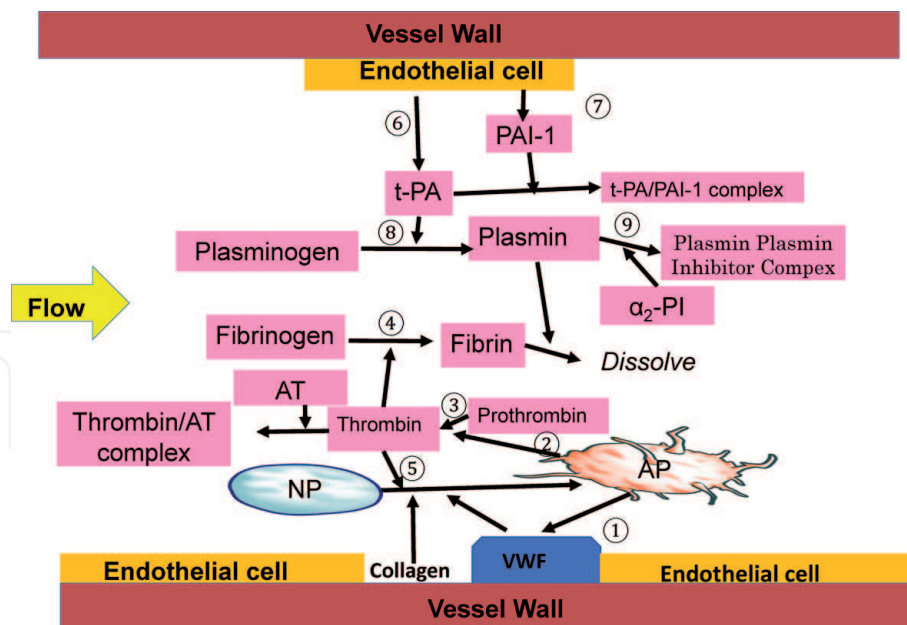

Figure 4.
Coupling model of blood flow, platelet, coagulation, and fibrinolysis. Thrombus formation at the site of endothelial injury is modeled. Nonactivated platelets (NP) adhered at the site of endothelial injury through von Willebrand factor (VWF) and collagen are exposed there. NP become activated platelets (AP) by their interaction with VWF/collagen (①). AP has a potential to convert prothrombin to thrombin on their membrane surface (②). After production of thrombin from prothrombin (③), thrombin converts soluble fibrinogen to fibrin thrombi. (④) thrombin also has a function to further activate platelets through thrombin receptor stimulation. (⑤) Fibrinolytic system is also incorporated in this model. Functional endothelial cells constitutively release both tissue-type plasminogen activator (t-PA: ⑥) and plasminogen activator inhibitor (PAI)-1 (⑦). T-PA converts plasminogen to plasmin, which has fibrinolytic activity (⑧) unless inactivated by binding with PAI-1. Plasmin is a strong enzyme able to degrade fibrin. Its function is immediately neutralized by its binding with a2-plasmin inhibitor to form plasmin a2-plasmin inhibitor complex (PIC: ⑨).

adhesion and activation. Platelet adhesion is implemented to be medicated by its GPIbα binding with von Willebrand factor (VWF) (① in **Figure 4**). GPIbα binding with VWF is a chemical phenomenon, but the binding force is a physical one. We have implemented both in the same model. Platelets were implemented to be activated to change their biological roles (② in **Figure 4**). This process is a biological process. The detailed process model of platelet activation was published elsewhere [33]. Briefly, platelets were settled to be captured by VWF under blood flow condition. Collagen exposed at the site of endothelial injury also interacts with platelet and contributed to platelet activation through its receptor, namely, GPVI [34]. Then, activated platelet was settled to have stronger capacity to bind with injured vessel wall, cohesion each other, and possess the capacity to express coagulogenic phospholipids. Then, prothrombin conversion to thrombin was settled to occur only on the surface of activated platelets (③ in **Figure 4**). Thrombin function is neutralized promptly by its interaction with antithrombin III. Thrombin implemented to have function to convert fibrinogen to fibrin (④ in **Figure 4**) and further activated platelet through thrombin receptor stimulations [35].

There are several coagulation factors, the function of which is regulated strongly by food intake. Gla-domain of coagulation factors plays crucial roles in the accumulation of coagulation factors around exposed negatively charged phospholipids on activated platelets [36]. Gla-domain also plays crucial roles for enzymatic function of coagulation factors. Carboxylation of Gla-domain is mediated by vitamin K. Thus, coagulation cascade does not work well in the absence of vitamin K or in patients taking vitamin K inhibitor. It is noteworthy that there are many foods including fermented food that are known to contain abundant vitamin K. Strict food restriction is necessary to keep the anticoagulant effects of vitamin K inhibitors. Recently, a larger load of vitamin K on health is cautioned [37].

The amount of fibrin formed at the site of endothelial injury was reduced by the effect of intrinsic fibrinolysis. Fibrinolysis is a complex pathway, but the details of which is simplified to be incorporated as shown in **Figure 4**. Vascular endothelial cells have balanced roles for fibrinolysis by releasing both fibrinolytic tissue-type plasminogen activator (t-PA: ⑥) and the one has antifibrinolytic effects of plasminogen activator inhibitor (PAI)-1 (⑦). Both of them are constitutively released from endothelial cells. But the rates of their releases were individually controlled in individual endothelial cells. When the rate of t-PA release increases, the amount of fibrin formed around the endothelial cells becomes smaller. It becomes larger in the case when the rate of PAI-1 release increases. Free t-PA has a potential to convert plasminogen to plasmin. (⑧) Plasmin is a strong protease, which can dissolve many functional proteins including fibrinogen. To avoid too much protein degradation, activity of plasmin is promptly neutralized by the function of α_2-plasmin inhibitor (α_2-PI: ⑨).

Previous publication suggested increased PAI-1 release after acute myocardial infarction and its role for the increased recurrence of myocardial infarction [38]. Animal experiments revealed that the food coloring agent of crocin reduces activity of PAI-1 and prevents thrombosis [39]. In human, increased PAI-1 activity is reported at the time of too much intake of fat [40]. Total fibrinolytic activity in humans is also reported to be low in obese patients [41]. Decreased fibrinolytic activity in patients taking too much lipid is one potential reason of increased risk of thrombosis in these patients.

4. Role of various types of food intake for the risk of thrombosis

There are many reports suggesting the increase/decrease in the risk of thrombosis by various food and beverage intake. Framingham study suggested that coffee

consumption is related to lower risk of myocardial infarction [42]. However, the influence of coffee intake for the onset and recurrence of myocardial infarction is still under discussion because other reports suggested higher rate of sudden cardiac death in coffee intake in patients after myocardial infarction [43]. People have consensus that food intake should influence the risk of arterial and venous thrombosis. The problem is that it is still hard to state which food reduces/increases the risk of thrombosis.

Old epidemiological studies suggested that the risk of myocardial infarction increased in Japanese people who immigrated to Hawaii or California than that of the ones staying in Japan. They have the same genetic background. Environmental factors including food should contribute to the change in the risk of population when moved to the US than staying in Japan. Lower cardiovascular death rate in Japan is still noted in the international registry of patients with atherothrombosis or non-valvular atrial fibrillation. Despite epidemiological data, it is still hard to identify what food specifically modulated the rate of thrombosis.

There are many specific diets that potentially influence thrombotic risk. Among them, sodium intake should be one of the most established factors to avoid cardiovascular diseases. Low sodium intake clearly decreases the risk of heart failure [44], but its direct effects for thrombosis is still to be elucidated. Mediterranean diet is also related to lower risk of cardiovascular diseases [45]. But it is still difficult to identify the specific content of Mediterranean diet related to the reduction in the risk of CV disease. A plant-based diet seems beneficial in reducing the risk of cardiovascular disease, but it has both good qualities and bad qualities [46]. The relationship between food and the risk of cardiovascular diseases (mostly arterial thrombosis) is complex.

A recent publication suggested the positive correlation between red and processed meat intake and risk of cardiovascular diseases. This study also suggested the negative relationship between the intake of yogurt, cheese, and eggs and CV disease risk [47]. The observation study is useful to find potential contributing factors but still includes many potential biases. Just like drug or medical intervention, randomized trials comparing a variety of food intake with hard endpoint of cardiovascular death, myocardial infarction, and ischemic stroke will give us more insight. However, in reality, it is hard to design such trials because people have the right to eat whatever they like. It is hard to make a restriction in food intake for a long period of time. The combination of observational study and the study to clarify the mechanism will give us the best available evidence now.

5. Metabolic syndrome and thrombosis: view from the mechanism

Metabolic syndrome is characterized as the presence of three apparent characteristics including visceral obesity manifested as increasing waist circumference, dyslipidemia, hypertension, and high blood glucose. Underlining pathophysiology is insulin resistance and lipid accumulation. It is noteworthy that various cytokines (adipocytokines) were identified from adipose tissue. Adiponectin is the one identified as factor reducing the risk of thrombosis by preventing endothelial dysfunction [48]. Indeed, decreased plasma concentration of adiponectin observed in obese patients may suggest the potential regulatory role of adiponectin for the onset of thrombotic diseases [49]. Despite difficulty in understanding the precise relationship among various cytokines and adiponectin [50], an apparent link between metabolic syndrome and decreased adiponectin is noteworthy. Various parameters for coagulation and fibrinolysis are also influenced in metabolic syndrome patients [51]. It is reasonable to recommend regular exercise to prevent metabolic syndrome and future onset of thrombosis [52].

6. Conclusion

Obviously, food intake influences deeply the risk of thrombotic disease such as arterial and venous thrombotic diseases. Deeply reliable population-based clinical trials or nicely designed registry studies are awaited. Precise understand the mechanism of thrombotic disease from hard science such as re-construction of biological phenomena from the physical movement of atoms.

Acknowledgements

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