Hematological Risk Factors for Coronary Heart Disease

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Key Words

Coronary heart disease · Antithrombin III deficiency · Protein C · Protein S · Factor V Leiden · Prothrombin · Homocysteine · Fibrinogen

Abstract

Coronary heart disease (CHD) is a leading cause of morbidity and mortality in the developed and developing countries. Several underlying genetic and environmental factors have been implicated in its etiology. Some of the hematological risk factors implicated in the development of coronary heart disease include antithrombin III deficiency, protein C and protein S deficiency, factor V Leiden mutation, prothrombin gene (20210A) mutation, hyperhomocystinaemia, elevated factor VIII levels, plasminogen activator inhibitor type 1 and dysfibrinogenemia. In general, these factors result in thrombosis, thus having a negative effect on the heart and blood vessels. This paper presents an overview of some of the hematological risk factors involved in the development of CHD.

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Introduction

Coronary heart disease is a frequently encountered multifactorial disorder and is recognized as a major cause of morbidity and mortality both in developed and devel-

oping countries [1]. Table 1 presents cardiovascular disease death rate in some countries of the world. Interactions between genetic and environmental factors contribute to the development of coronary heart disease.

One of the largest prospective studies, the Framingham Study initiated in 1948 has provided insight into the prevalence, incidence, full clinical spectrum and predisposing factors for coronary heart disease [2]. It coined the term 'risk factors' and listed the 'traditional risk factors' for development of coronary heart disease [2]. Thus, the risk factors for CHD can now be classified as (i) traditional (established) risk factors, and (ii) non-traditional (novel) risk factors. Both traditional and non-traditional risk factors are listed in figure 1 [2, 3] and a negative risk factor is high-density lipoprotein-cholesterol (HDL-cholesterol) when its level is equal to or greater than 60 mg/dl (≥ 1.6 mmol/l).

Interest in the non-traditional risk factors became important when it was realized that the well-known traditional factors failed to explain the high incidence of coronary heart disease in different populations [3]. Over the last decade the search for novel risk factors has been actively pursued and interesting facts have emerged.

Arteriosclerosis and Coronary Heart Disease

A common mechanism underlying the development of CHD seems to be arteriosclerosis which is associated with thickening of the intima due to a combination of fibrosis,

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Fig. 1. Cardiovascular risk factors.

Table 1. Cardiovascular disease death rates in some countries¹

	Total CVD ²	IHD (%) ³	CD (%) ³	Others (%) ³
Scotland	435.1	59.3	25.9	14.8
Austria	382.4	39.5	26.5	35.2
Sweden	368.1	56.8	16.7	24.5
USA	375.4	52.6	15.0	32.3
Italy	324.5	30.0	31.5	38.5
Switzerland	288.8	37.9	19.8	42.3
Japan	226.5	16.7	39.8	43.5
France	215.2	29.8	27.5	42.7

¹ WHO Report.

² Age standardized death rate per 100,000.

³ % of total CVD. IHD = Ischemic heart disease; CVD = cardiovascular disease; Others = other acute MI.

blocking of the arteries occurs either by large atherosclerotic plaques or thrombosis. The thrombus formation is frequently due to secondary formation of blood clots by platelets blocking the flow of blood. The formation and accumulation of what are known as foam cells in the intima is the hallmark of the early atherosclerotic lesion. These 'foam cells' are believed to be derived from macrophages and smooth muscle cells and the atherosclerotic lesion is promoted by two blood cells, i.e. macrophages and platelets. Figure 2 lists the prothrombotic risk factors and figure 3 schematically presents the pathophysiological mechanism by which coronary risk factors lead to atherosclerosis.

Traditional Risk Factors for CHD Development

smooth muscle cell proliferation and the development of an intercellular lipid core [4]. Most of the traditional risk factors are shown to contribute to the initial events and towards the progression of coronary heart disease [5]. Formation of arteriosclerosis results from accumulation of deposits on the inside of arterial walls leading to narrowing or clogging of the arterial lumen. Intimal layer injury attracts cholesterol deposits, macrophages and calcium salts, which leads to formation of scar-like fibrous tissue forming an atherosclerotic plaque [5]. The occlusion or

Extensive studies have confirmed the role of the traditional risk factors in the development of CHD. Each of these factors contributes significantly and the additive effect is obvious when two or more of these factors are co-existent [6]. A major factor is the hypercholesterolaemia associated with elevated LDL-cholesterol and a low level of HDL-cholesterol. Increased circulating cholesterol is believed to increase the risk of oxidative disease process due to its susceptibility to oxidation while in circulation. The low density lipoproteins are cholesterol-rich particles with a life span of about 2.5 days. They carry

Fig. 2. Genetic prothrombotic risk factors for CHD.

Fig. 3. Pathophysiological mechanism by which coronary risk factors lead to atherosclerosis.

almost 45% cholesterol, 20% triglycerides, 23% phospholipids and 20% proteins, which are mainly Apo-B (95%). LDL-cholesterol is the major vehicle carrying cholesterol to the tissues, it binds to the LDL-receptor and hence facilitates uptake of cholesterol by cells by the process of pinocytosis. Elevation in LDL-cholesterol level and decrease in HDL-cholesterol/LDL-cholesterol ratio increases the risk of coronary heart disease [4, 7–9].

High-density lipoprotein (HDL) is referred to as the ‘scavenger form’ of cholesterol as it is believed to protect against oxidative processes. Its half-life in plasma is 3–5 days and it is composed of 18% cholesterol, 2% triglycerides, 30% phospholipids and 50% proteins, which are mainly Apo A-I (65%) and Apo A-II (25%). HDL plays an important role in regulation of triglyceride catabolism and conversion of cholesterol to cholesterol esters by providing Apo C-II for activation and Apo C-III for inhibition of lipoprotein lipase activity. Since HDL transports cholesterol from tissues to the liver, it provides a protection against coronary heart disease development. The ratio of HDL cholesterol to LDL-cholesterol is a useful indicator of the risk of coronary heart disease.

In addition to cholesterol, smoking, age greater than 45 years in males and 55 years in females, diabetes mellitus, hypertension and a family history of coronary vessel diseases are other well-documented traditional risk factors for the development of CHD [4, 7–9, 10].

Non-Traditional (Novel) Risk Factors for CHD Development

A number of novel risk factors (fig. 2) have been proposed for CHD development. Among these is a whole group of haematological risk factors since they are prothrombotic and play a significant role in development of thrombus hence predisposing to CHD [11–19].

It has been shown that any defect in haemostasis may lead to thrombus formation. Different factors contribute to venous thromboembolism, while others play a role in arterial thromboembolism. The defect may be in the fibrinolytic system, blood vessel walls, circulating platelets or the circulating coagulation factors. Figure 2 presents some of the major aetiological factors in familial thrombophilia which have been investigated in detail and the findings have led to the identification of several novel risk factors for CHD. Some of the factors contributing to the pathogenesis of venous thromboembolism are discussed below.

Prothrombin 20210A Mutation

Prothrombin (factor II) is the zymogen precursor of thrombin and is directly related to thrombus formation. Any elevation in the level of prothrombin is considered significant for the health of the cardiovascular system. An allele of prothrombin in which a 20210 G→A transition occurs in the 3-untranslated region (UTR) of the prothrombin gene results in an increased prothrombin level in plasma and also an increase in prothrombin clotting activity [20, 21]. Studies have confirmed that in individuals with this allele there is a 2.7-fold increased risk of venous thrombosis in adults of both sexes and a 4.0-fold increased risk of myocardial infarction in the young age group [22–25]. Though several studies point to a role of prothrombin gene 20210 G→A transition in development of CHD [23–25], some studies fail to show any association [20, 24–26].

Factor V Leiden in CHD

Factor V Leiden plays a role in stabilization of the growing thrombus and is known to be a common risk factor for venous thrombus formation. An allele of factor V Leiden with an A→G substitution at nucleotide 1691 in the exon 10 of factor V gene, results in a substitution Arg→Gln at position 506. This factor V Leiden polymorphism occurs in approximately 3% of the general population and in about 20–50% of patients with a history of unexplained recurrent venous thrombosis. The presence of the glutamine instead of an arginine residue removes a site in factor V that is normally cleaved by activated protein C and is associated with in vitro resistance to activated protein C. This results in defective termination of coagulation by activated protein C. Several well-designed studies confirm an association between factor V mutation and venous thrombosis and coronary heart disease [24, 27–29]. However, other studies fail to report any association [20, 21].

Homocysteine

Homocysteine, a sulphhydryl-containing amino acid, is an intermediate derived from methionine and its normal plasma levels varies from 5 to 15 mmol/l [30]. Homocysteine is metabolized either by a remethylation pathway which is catalysed by methionine synthase that produces methionine or transsulfuration pathway which produces cystathionine and finally cysteine. For the remethylation

pathway, both vitamin B₁₂ and folate are required, since vitamin B₁₂ is an essential cofactor for methionine synthase and N⁵-methyl tetrahydrofolate is the methyl donor in this reaction, catalysed by N⁵,N¹⁰ methylene tetrahydrofolate reductase [31]. The transsulfuration pathway is activated when an excess of methionine is present or when cysteine synthesis is required [31]. Since the first report of an association between elevated plasma homocysteine and vascular disease in 1969 [32], extensive studies have been carried out and have confirmed this association [33, 34]. Hyperhomocysteinemia has been shown as a risk factor for both venous and arterial thrombosis [35].

A thermolabile variant of N⁵,N¹⁰ methyltetrahydrofolate reductase, produced as a result of a single point mutation at position 677 (C→T) in the coding region of N⁵,N¹⁰ methyltetrahydrofolate binding site, is associated with hyperhomocysteinemia in homozygotes and an increased risk for vascular disease [36]. It is shown to play an important role in thrombotic vascular disease and in the development of atherosclerosis [37–39]. Studies have shown that hyperhomocysteinemia is associated with coronary artery disease, myocardial infarction, peripheral vascular disease, cerebrovascular disease, stroke and an early death from coronary artery disease. It is shown that elevation in the fasting level of homocysteine by 5 mmol/l increases the incidence of coronary disease by 1.6- to 1.8-fold [40]. In a rare, autosomal recessive disorder, homocystinuria, which results from deficiency of cystathionine β-synthase associated with elevated levels of homocysteine in blood and urine, the patients develop vascular disease. However, a few prospective studies have failed to show the relationship between homocysteine level and coronary artery disease [14]. The controversial results may be a consequence of genetic variability in different populations.

Fibrinogen in CHD

Fibrinogen is a major protein in blood plasma occurring at a level of 200–400 mg/dl. It is synthesized in the liver and during the clotting process it is converted to a polymer, fibrin, under the action of thrombin. It also affects blood rheology and platelet aggregation in addition to the blood coagulation process. Several extensive studies have shown that elevated fibrinogen increases the risk of CHD, stroke, myocardial infarction, and peripheral arterial disease [41–43]. In a study on 333 patients it was shown that elevation of 1 mg/dl of fibrinogen correlated with a twofold increase in probability of death within 6 years. Hence, it is considered an independent and excel-

lent risk marker for cardiovascular diseases [42]. Several factors play a role in elevating fibrinogen level and these include cigarette smoking, age, race, sedentary lifestyle, gender, oral contraceptive use, obesity, stress, inflammation and diabetes mellitus. In addition, a few rare mutations in the fibrinogen gene are associated with thrombophilia. On the other hand, factors that reduce fibrinogen include diets rich in omega–3 and omega–6 fatty acids, exercise, weight reduction, smoking cessation and stress management [7, 10, 13, 14, 17].

von Willebrand Factor

von Willebrand factor has a pro-coagulant activity. It binds to factor VIII and stabilizes coagulation. It is also considered a marker of endothelial cell dysfunction. Elevation in the level of von Willebrand factor has been shown to increase the relative risk of CHD to 1.71 [44–46].

Plasminogen Activator Inhibitor Type I

The plasminogen activator inhibitor type-1 (PAI-1) inhibits the conversion of plasminogen to plasmin and hence inhibits fibrinolysis as it disrupts dissolution of thrombus. As PAI-1 frequently occurs in patients with thrombotic disease, it has been considered an important aetiological factor in the development of CHD.

Other Coagulation Factors

Several studies have been carried out on other coagulation factors and their roles in the development of CHD [23, 48, 49]. These include factors II, V, VII and X. In a study measuring the levels of factors II, V, VII, and X, it was shown that in patients with myocardial infarction the levels of these factors are significantly elevated ($p < 0.05$). The relative risk of myocardial infarction was calculated as only 1.0 for factor II, and 3.3, 5.2, 2.2, for factors V, VII and X, respectively. High clotting activity of factor VII is shown to be significantly associated with an increased risk of CHD.

Since thrombophilia is shown to be closely related to the risk of developing CHD, any factor which increases the tendency to form thrombus, such as an ongoing stimulus to thrombogenesis, or a defect in natural anticoagulant activity or a defect in fibrinolytic mechanism plays a role in predisposing to CHD.

Some inherited defects that have been shown to play a role in the development of thrombophilia include deficiency in antithrombin III, protein C, protein S and activated protein C resistance [50]. Antithrombin III deficiency is a rare disorder, inherited as an autosomal dominant trait. In patients with combined deficiency of protein C and antithrombin III, both arterial and venous thrombosis have been reported. However, some studies fail to show an association between these factors and risk of coronary events [44]. In the heterozygotes the AT III level is 50% of normal, while homozygous state is incompatible with life. Increase in the frequency of both arterial and venous thromboembolic state in adults and children have been reported [51]. In patients with a novel nonsense mutation in the antithrombin III gene (Cys 4→stop) recurrent venous thrombosis has been reported [52].

Protein C deficiency is more common and is reported in 1:1,350 blood donors. It also exists as an autosomal-dominant disorder and increases the risk of both arterial and venous thromboembolism by severalfolds. The homozygous state is associated with neonatal purpura. In addition, plasminogen deficiency and reduced plasminogen activator activity also play a role in thrombophilia. Almost 20–60% of patients with thrombophilia are shown to have activated protein C resistance. This is strongly related to the generation of thrombus.

Several infectious agents have been implicated in the development of atherosclerotic lesions. These include *Chlamydia pneumoniae*, *Helicobacter pylori* and *Cytomegalovirus* (CMV). *C. pneumoniae* is a common bacterium that infects a large percentage of the population at some time in their lives. It causes almost 10% of all pneumonias and has a role in the pathology of acute asthma and chronic bronchitis. Studies have shown the presence of *C. pneumoniae* in the atherosclerotic lesions of coronary arteries, carotid arteries, the aorta, smaller cerebral vessels and larger peripheral arteries [53, 54]. In addition, studies have documented rising or elevated levels of antibodies to this bacterium in some patients during the months just preceding a heart attack [55]. Treatment with antibiotics after a first heart attack has been shown to reduce the risk of a second attack [56].

H. pylori, as organism most frequently associated with gastrointestinal infections [57], and *Cytomegalovirus* (CMV), a common viral infection that is usually silent and self-limited, have also been implicated in the development of CHD.

Conclusion

Hematological risk factors constitute an important group of the novel (nontraditional) risk factors for CM development and require careful monitoring in high-risk groups and in patients on therapy such as those on cancer therapy, or hormonal treatment for infertility since these predispose to thrombophilia and hence may precipitate CHD.

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