Associations between cardiovascular risk factors, hyper- and hypocoagulability
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General introduction and outline of thesis

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GENERAL INTRODUCTION

Inappropriate coagulation activation can lead to an imbalance between the production and inhibition of enzymes in the coagulation cascade, resulting in obstructive clot formation. Arterial thrombosis develops in blood vessels that carry blood from the heart to organs (e.g. heart and brain) and in the majority of the cases results from atherosclerosis, a chronic systemic inflammatory process. Atherosclerosis is associated with well-established cardiovascular risk factors. If a thrombotic occlusion occurs in vessels that carry blood back to the heart (e.g. legs and lungs), it is referred to as a venous thrombo-embolism (VTE). Over 150 years ago, Rudolf Virchow described that apart from a hypercoagulable state, venous stasis and injury of the vessel wall, known as ‘a triad of changes’, contribute to the development of VTE. This theory is still widely accepted and the number of risk factors associated with these changes is however expanding. Risk factors for VTE are generally classified as inherited (e.g. protein S and C deficiency, factor V Leiden mutation) and acquired (e.g. malignancy, immobility, surgery). Novel risk factors include classical risk factors for atherosclerotic disease such as older age, obesity and smoking but drugs such as non-steroidal anti-inflammatory drugs and thyreomimetic agents have also been associated with VTE. Atherosclerosis and VTE not only share risk factors, but a link between arterial and venous thrombosis has most clearly been illustrated by numerous clinical trials. In patients with VTE both preclinical signs of atherosclerotic disease as well as a higher incidence of future arterial events have been described. If arterial and venous thromboses are no longer seen as separate disease entities, this may also imply common therapeutic approaches may be effective. Indeed, statin therapy which has proven highly beneficial in the prevention of cardiovascular disease, has shown benefit in the prevention of venous thrombotic disease too. Although the exact mechanism underlying the association remains unclear, common pathologic processes such as endothelial dysfunction and inflammation could facilitate both disease processes.

Elevated levels of coagulation markers such as factor VIII, fibrinogen, plasminogen in patients suffering from atherothrombotic events, further illustrate an association between arterial and venous thrombosis. In fact, there is increasing evidence which supports that some coagulation factors may also be involved in the process of atherogenesis. Whereas thrombotic complications can result from a hypercoagulable state, hypocoagulability has been associated with protection against thrombosis. Hemophilia A is an X-linked genetic disorder, in which individuals have an inherited deficiency of factor VIII. The factor VIII deficiency induces a life long hypocoaguable state, which is clinically associated with a bleeding tendency. In hemophilia patients a considerable protection against cardiovascular disease has been reported. It is not known whether factor VIII solely plays a role in the formation of the occluding thrombus, or also contributes to the process of atherosclerosis. In this respect, the study of hemophilia patients is an ideal model to study the role of factor VIII in atherogenesis. Furthermore, since cardiovascular risk factors like obesity, hypertension and dyslipidemia are equally prevalent in the hemophilia population and the life expectancy of hemophilia patients
has normalized, hemophilia physicians recognise the risk of cardiovascular disease in these patients. Considering the fact that cardiovascular prevention in hemophilia patients is challenging due to high risk of bleeding complications when treated with oral anticoagulant therapy, whether or not factor VIII deficiency protects against CVD is especially intriguing.

OUTLINE OF THE THESIS

Part I of the thesis focuses on the associations between cardiovascular risk factors and hypercoagulability. In the first chapter, the risk of cardiovascular disease in patients with venous thrombo-embolism is assessed by studying the occurrence of aortic calcifications on chest X-ray. In chapter 2 the effect of statin therapy on the occurrence of recurrent VTE is assessed in a Dutch population-based registry. In chapter 3 the effect of statin therapy on VTE is further assessed in a meta-analysis of previous large randomized controlled trials. Chapter 4 describes a multicentre study which is conducted to assess the proportion of VTE patients who already require statin therapy given their risk of cardiovascular disease. In chapter 5 the risk of venous thrombosis in individuals who use non-steroidal anti-inflammatory drugs is studied. In chapter 6 the association between thyroid hormone (and treatment for thyroid disease) and pulmonary is assessed in a large population-based registry. Chapter 7 describes a small case-control study in which the utility of urine prothrombin fragment 1+2 in diagnosing venous thrombosis and myocardial infarction is assessed.

In part II of this thesis, associations between cardiovascular risk and a hypocoagulable state, i.e. hemophilia are described. Chapter 8 provides a systematic review of current literature on the effect of hemophilia and von Willebrand disease on arterial thrombosis and in chapter 9 the prevalence of cardiovascular risk factors and associated cardiovascular risk is determined in 100 hemophilia patients using a validated risk assessment tool. In chapter 10 the incidence of preclinical atherosclerosis in hemophilia A patients with obesity is studied with use of ultrasonography. In chapter 11, obesity related hemostatic changes in hemophilia patients are studied and in chapter 12 the impairment in daily life of obese hemophilia patients is assessed using a validated questionnaire, the hemophilia activities list (HAL).
REFERENCES


