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Cardiometabolic risk factors and venous thrombosis

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Chapter 7

Summary and General discussion

The aim of this thesis was to investigate the associations of traditional cardiometabolic risk factors with risk of a first and recurrent venous thrombosis. Additionally, associations between lipids and levels of several hemostatic factors were assessed. This chapter provides an overview of the main findings, and addresses some methodological considerations. Furthermore, the clinical implications of the thesis' findings and directions for future research will be discussed.

OVERVIEW OF MAIN FINDINGS

Lipid levels and risk of a first venous thrombosis

In **chapter 2**, the association between lipid levels and risk of a first venous thrombosis was assessed in the MEGA study. In contrast to arterial cardiovascular disease (CVD), levels of major lipids, i.e. total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and triglycerides, were not associated with risk of venous thrombosis. However, decreasing levels of apolipoprotein (apo) B and apo A1 were associated with an increased risk of venous thrombosis in a dose-response fashion, also after adjustment for potential confounders. Although apo B and to a lesser extent apo A1 levels were related to levels of several hemostatic factors and C-reactive protein, none of these factors explained the association of apolipoproteins B and A1 with risk of venous thrombosis.

While there is strong evidence that elevated apo B and LDL-C levels are associated with an increased risk for arterial CVD [1,2], we observed an inverse relationship between apo B levels and risk of venous thrombosis. Since venous and arterial CVD have different pathophysiology (see Fig.1 chapter 1), we hypothesized that apo B may play different roles in the mechanisms that are at the basis of venous thrombosis versus arterial CVD. Indeed, our findings on the protective role of apo B and apo A1 against venous thrombosis are in line with experimental data, in which both apolipoproteins have been suggested to have anticoagulant properties [3-6].

On the basis of our results, dyslipidemia does not explain the relationship between venous thrombosis and increased risk of subsequent arterial CVD, as none of the major lipids was associated with risk of venous thrombosis. In addition, risk estimates for venous thrombosis associated with apo B levels pointed in the opposite direction to that reported in arterial disease. One might argue that our findings on apo B and venous thrombosis are not consistent with the putative protection conferred by statins against venous thrombosis, since these drugs decrease apo B levels [7,8]. It is noteworthy that statins may have antithrombotic effects that are unrelated to their lipid-lowering activity, such as downregulation of tissue factor [9]. It is currently unknown, however, to what extent the antithrombotic potential of statins would influence the thrombosis risk or the anticoagulant properties of apo B demonstrated *in vitro*.

Since the study design used to answer our research question was a case-control study, we cannot exclude the possibility of reverse causation, i.e. that the venous thrombotic event has led to changes in lipid levels. Indeed, as discussed in **chapter 2**, patients may have modified certain lifestyle factors after the event of venous thrombosis, which could have affected their lipid profile. Randomized clinical trials published during the nineties showed that changes in diet affected lipid levels in individuals with dyslipidemia. However, the reduction in TC, LDL-C and apo B levels produced by a low-fat diet taken from 9 weeks to 1 year in these trials was small or virtually absent without concomitant statin use or aerobic-exercise program. It is quite unlikely that venous thrombosis patients would systematically adhere to a low-fat diet in addition to statin use and/or exercise after the thrombotic event, especially considering that such recommendation is not routinely given, in contrast to arterial disease. Another mechanism for reverse causation would be the effect of acute phase reactions brought about by the thrombotic event on lipid levels. During acute phase reactions in humans, triglyceride levels typically increase and HDL-C and apo A1 levels decrease, whereas TC, LDL-C and apo B levels can either decrease or do not change. Nevertheless, this is an unlikely mechanism for reverse causation, since blood was collected with a median of 10 months after the thrombotic event, by which time the effects of the acute-phase reaction will have worn off. Finally, changes in lipid levels in our study population owing to reverse causation would be expected to affect not only the direction of the point estimates related to the apolipoproteins but also to the other lipids, such as TC, which also makes it unlikely that our findings can be due to this explanation.

Clinical implications and directions for future research

It is not possible to suggest directly new approaches for preventing or treating venous thrombosis based on our findings, apart from exclusion of most lipids from risk factor profiles. Still, our results on the inverse association between apolipoprotein B and A1 levels and risk of venous thrombosis may form the basis for further studies to confirm our findings, as well as to assess the physiological relevance of the anticoagulant properties of apo B and apo A1, and to determine the mechanism, whether or not causal, underlying the link between these apolipoproteins and venous thrombosis. A deep understanding on the possible mechanisms by which apolipoproteins B and A1 could affect venous thrombosis risk might provide insight to the development of novel strategies to prevent venous thrombosis at a minimum cost of bleeding risk.

Cardiometabolic risk factors and risk of recurrent venous thrombosis

The role of cardiometabolic risk factors in assessing risk of recurrent venous thrombosis has not been extensively studied.

In **chapter 3**, we evaluated the associations between levels of several lipids (i.e. TC, triglycerides, LDL-C, HDL-C, apo A1 and apo B) and risk of recurrent venous thrombosis. None of the lipids studied identified patients at an increased risk of recurrence, including those with unprovoked first events. In **chapter 4**, we further assessed the association of estimated glomerular filtration rate (eGFR), glucose levels and hematologic variables (i.e. blood cell count) with recurrence. We found that testing for glucose levels and hematologic variables did not identify patients at increased risk of recurrent venous thrombosis, including those with unprovoked first events, and an association between renal dysfunction, as measured by a decreased eGFR, and recurrence appeared to be slight at most.

It is important to address that in the MEGA study, levels of apolipoproteins B and A1 (**chapter 2** of this thesis), eGFR [10], red cell distribution width [11], and monocyte count [11] were all associated with a first venous thrombosis. However, in the MEGA follow-up study, a decreased eGFR was only marginally associated with recurrence, and no associations with recurrent events were observed for the other aforementioned factors. These results are consistent with the fact that risk factors for a first event do not necessarily predict recurrence [12,13]. For instance, inherited thrombophilia, a classic risk factor for a first event, only poorly predicts recurrence in unselected patients [12].

Clinical implications and directions for future research

Testing for lipid levels, glucose levels, and hematologic variables did not identify patients at increased risk of recurrent venous thrombosis, and these should not influence decisions on duration of anticoagulant treatment. Renal dysfunction appeared to predict recurrence to some extent. Still, given the well-established increased risk of major bleeding in patients with renal dysfunction during anticoagulant treatment [14,15], studies with larger samples sizes, using a uniform measurement of kidney function, are needed to allow a detailed assessment of the ability of a decreased eGFR to identify patients at increased risk of recurrent venous thrombosis, in particular, those with unprovoked first events.

Association between lipid and hemostatic factor levels

The interrelation between hemostatic factor and lipid levels is not known in detail, as studies on this topic are few, involve small sample sizes, and study a limited number of lipids and hemostatic factors. In **chapter 5**, we investigated how levels of several hemostatic factors (procoagulant, anticoagulant, and fibrinolytic factors) were interrelated, forming clusters, and how these clusters related to lipid levels in 2874 population controls. Among our main findings is that vitamin K-dependent factors (VKDFs), including procoagulant (factor II, factor VII, factor IX, and factor X)

and anticoagulant (protein C and protein S) factors, clustered together. Upon addition of lipids to the analysis, all VKDFs consistently clustered with triglyceride levels.

In **chapter 6**, we studied the relationship between liver fat content, measured as hepatic triglyceride content (HTGC), and levels of coagulation factors associated with an increased risk of venous thrombosis. We found that fibrinogen, factor VIII, factor IX, and factor XI levels increased dose-dependently across HTGC quartiles, even after adjustment for several demographic and lifestyle potential confounding factors. However, with further adjustment for total body and visceral fat, the associations between HTGC and levels of fibrinogen, factor VIII and factor XI disappeared, whereas the associations between HTGC and factor IX levels, albeit attenuated, persisted, as did the dose-response relation. This observation could be relevant, as high levels of factor IX related to HTGC have the potential to be a critical pathway by which obesity increases the risk of venous thrombosis.

Clinical implications and directions for future research

Taken together, results from both studies support the existence of a close association between VKDFs, including factor IX, and triglycerides. One may speculate that common mechanisms lying outside the genes coding for VKDFs and triglycerides could explain, at least in part, this association. Clarification of this issue is worth pursuing, as therapeutic strategies targeting possible common regulatory mechanisms of VKDFs and lipids, in particular, triglycerides, might have the potential to decrease the risk of both venous thrombosis and arterial CVD.

CONCLUSIONS

This thesis provided epidemiological evidence that some traditional cardiometabolic risk factors are related to first and recurrent venous thrombosis. Most lipids were not associated with risk of a first or recurrent venous thrombosis. In contrast, decreasing levels of apolipoproteins B and apo A1 were associated with an increased risk of first venous thrombosis, which we could not explain through several proposed mechanisms, such as confounding or other non-causal explanations, or through mediation via inflammation or changes in the hemostatic factors. Overall, testing for cardiometabolic risk factors does not seem useful to identify patients at an increased risk of recurrence. In addition, vitamin K-dependent factor levels are associated with both serum and hepatic triglycerides. Future research should focus on clarifying the possible mechanisms underlying this association.

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Chapter 8

Nederlandse samenvatting

Acknowledgements

Curriculum Vitae

List of publications