The alternative pathway of the complement system in vascular comorbidities of obesity and type 2 diabetes

Chapter 7

Impact and concluding remarks

Social and economic relevance

Obesity, a global epidemic, nowadays affects over 650 million adults, and over 1.9 billion adults at the previous stage, overweight, tend to be affected all over the world [1, 2]. Obese persons are at higher risk to suffer from obesity-related diseases such as cardiovascular disease (CVD) and type 2 diabetes (T2D). [3, 4]. People with obesity, CVD and/or T2D suffer from more physical issues and have a shorter life-span. CVD is the major challenge for global health, and the leading cause of death worldwide [5]. According to the World Health Organization, CVD took an estimated number of 18 million lives in 2019, an estimated 32% of deaths, globally. T2D, a chronic metabolic disease, is another one of the top four major causes of mortality all over the world. According to World Health Organization, over 400 million adults aged 18 years and older have T2D, and an estimated 2 million deaths were caused by diabetes in 2019. These metabolic diseases also increase economic burden for individuals and society as a result of higher medical expenses and productivity losses.

In this thesis, we add more knowledge to the academic research field. We obtained a clearer understanding of the aetiological role of complement factors in cardiometabolic disease and its explaining role on how obesity contributes to cardiometabolic disease. In addition, one of our studies also showed that weight loss-induced changes in complement components may contribute to better vascular function. Based on our findings, further longitudinal studies, experimental studies in animals and/or intervention studies may be designed. These further studies may concentrate on the value of individual complement components as markers to predict these metabolic diseases. In order to study their value in prediction, the associations of (the change in) concentration of complement factors with incident cardiometabolic disease should be evaluated. Alternatively, these studies may focus on the value of individual complement factors as a target to treat these related metabolic diseases. If further evaluations show that these complement factors have added values in prediction and/or treatment of these metabolic disease, the use of complement

factors as risk predictor or target may reduce mortality and the medical burden that results from these metabolic diseases.

Target group

Participants in The Maastricht Study are Caucasian and aged between 40 and 75 years old, and those in weight loss study are abdominally obese male Caucasian aged 18-65 years old. In general, our findings show the possible aetiological role of complement factors in cardiovascular disease, how much of the association between obesity and type 2 diabetes could be explained by complement factors, as well as the reduction effect of weight loss on complement factor, which improve endothelial dysfunction marker. Our results hence support the concept that complement may be the part of the path via which obesity contributes to cardiometabolic disease.

The potential of C3, C3a and factor D in risk-prediction for risk obesity-associated cardiometabolic diseases: In the future, the use of complement factors in risk-prediction for risk obesity-associated cardiometabolic diseases is likely. Complement factors are associated with metabolic disease, and these associations were confirmed in longitudinal study. Although longitudinal analyses make the case for a role of complement stronger, these analyses still cannot prove causality. Nevertheless, complement factors could be regarded as a predictor.

C3, C3a and factor D as potential targets in treatment of obesity-associated cardiometabolic diseases: In the future, intervention trials aiming to reduce complement factors, e.g. by changes in lifestyle, may improve cardiometabolic disease. In addition, novel therapeutic drugs may be developed promisingly to improve cardiovascular disease by targeting complement. However, because, complement is part of immune system, inhibiting complement factors and/or its activation may lower the ability of the immune system to defense against pathogen infection. Therefore, a potential intervention with therapeutic drugs that affect complement activation may make patients more vulnerable to infectious disease. One possibility to prevent this is combination of such a potential intervention with therapeutic drug boosting the

immune system to compensate the loss of protection from immune system that is weakened by the complement inhibitor. Moreover, an intervention that inhibits factor D may also worsen fasting glucose levels and T2D status, since factor D suppressed the association between obesity and disturbed glucose metabolism. Therefore, the interventions are supposed to be applied cautiously, and attention should be paid how to compensate for the loss of the ability of complement factors to defense against pathogen.

Summary of the main findings reported in this thesis and concluding remarks

Our current findings confirmed and expanded results reported in previous publications and fill part of the knowledge gap in this field. Many previous studies on the role of complement in CVD focused on clinically diagnosed disease. The deep-phenotyping information of The Maastricht Study [6] allowed evaluation of several aspects of the underlying (subclinical) processes that may lead to CVD (**chapter 2**). In the large observational population-based cohort, we showed factor D was associated with low-grade inflammation, endothelial dysfunction which is in line with previous publication conducted in a middle-sized cohort [7]. We also showed factor D has a positive association with CVD, which has a comparable odds ratio with the results from the middle-sized cohort [7] that had a non-significant P-value. We showed a non-significant association between factor D and carotid IMT, which was in line with previous publication. The observed association with ABI added new knowledge to this field. The large number of participants and enrichment for T2D in this cohort allowed us to investigate whether T2D status influenced the associations of factor D with adverse vascular disease. We found in people without T2D has a stronger positive association of factor D with ED, and a stronger reverse association with carotid IMT, which adds relevant knowledge to the field.

In chapter 3, we improved the study design compared to previous studies by analyzing the associations of C3 and factor D with arterial stiffness within the same

study: The Maastricht Study. Previous studies about complement factors were relatively small. The Maastricht Study is a large population-based cohort study, which give our analysis more power. We were able to study whether T2D status influenced the associations of complement factors with arterial stiffness, based on the large number of participants and enrichment for T2D in this cohort. We found that factor D was positively associated with cf-PWV in individuals with T2D instead of C3 or non-diabetic individuals. These findings show us relative comprehensive knowledge of associations of C3 and factor D with arterial stiffness.

In **Chapter 4**, This study consisted of various phenotyping, for instance, main exposures (BMI, waist, VAT, SAT), outcome (T2D, fasting glucose level, insulin resistance), and plasma concentration of complement factors, and this allowed us to investigate the explaining effect of complement C3, C3a and factor D on the association of various obesity measures with disturbed glucose metabolism in the same one study. Novel findings in this chapter were that C3 explained 12.7%-41.4% of the association between obesity measures and fasting glucose, C3a explained 0.31%-1.92% of the association of obesity measures with fasting glucose and T2D, however factor D suppressed the association of obesity with fasting glucose and T2D. These findings suggest that complement C3 and factor D may work on these metabolic diseases via different mechanisms.

In **chapter 5**, we are the first to show, in abdominally obese men, that weight-loss induced a decrease in plasma C3 concentration which was explained by reduction of VAT. This intervention also improved endothelial function, which was partly explained by the achieved reduction in C3. Our results suggest that a reduction in complement C3 with subsequent improvement in endothelial dysfunction may be part of the mechanism by which diet-induced weight loss improve cardiovascular disease risk. These findings show us the potential of reduction of C3 on improving vascular disease, which may provide a new target for further study focusing on predicting and/or improving cardiometabolic diseases.

In summary, the investigations that are presented in this thesis show a potential effect of key components of the alternative complement pathway in cardiovascular disease and how much of the association between obesity and these cardiometabolic disease could be explained by these complement factors. This thesis may provide a clue for prediction, prevention, perhaps even treatment of cardiometabolic disease. However, rationale and validation of further investigation in potential clinical practice must be critically evaluated.

References

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