Extracellular matrix remodeling and vascular complications in type 1 diabetes

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Valorization
Valorization

As the burden of diabetes mellitus and its complications is increasing worldwide, research regarding the partly unresolved pathophysiological mechanism leading to vascular complications is needed. To date, vascular remodeling is often referred to in case of vascular complications. However, thorough investigations studying extracellular matrix (ECM) remodeling by matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs) in humans with type 1 diabetes have been scarcely published and are lacking extensive adjustments for potential confounders and/or have a small sample size. This thesis focussed on individuals with type 1 diabetes and we showed various associations between circulating MMPs and TIMP-1, as markers of ECM remodeling, and a variety of vascular complications (prior or incident cardiovascular disease (CVD), all-cause mortality, albuminuria, retinopathy, carotid-femoral pulse wave velocity and pulse pressure). In addition, we showed several associations between advanced glycation endproducts (AGEs) and MMPs and/or TIMP-1. However, these findings are primarily epidemiologically and mechanistically, but did not evaluate, for example, social and economical aspects. In this valorization we want to highlight our thoughts on social, economical and clinical issues as this chapter is intended to transfer scientific knowledge into practice.

Social and economical implications

As the number of individuals with type 1 diabetes is increasing,\(^1\) decreased quality of life for more individuals worldwide is observed, because type 1 diabetes is chronic disease. Quality of life can even further decrease as patients can become invalidated by its complications.\(^2\) In addition, complications lead to a rise in costs. Many interventions to prevent and/or control diabetes (type 1 and type 2) have shown to be cost saving or cost-effective.\(^3\) Therefore, increased knowledge on this subject can lead to several advantages for society. Firstly, with current treatment options we are insufficiently able to prevent or reduce vascular complications in type 1 diabetes. Therefore, this thesis potentially provides additional therapeutical targets and may eventually contribute to the development of new drugs by the pharmaceutical industry. In addition, the use of certain current treatment options can perhaps be started in an earlier stage of the disease to intervene in the MMP-TIMP system,\(^4\) for example: more intensive insulin treatment and use of ACE-inhibitors and/or statins. Secondly, prevention of these complications may result in increased quality of life and may lead to prolonged lives, as these complications are associated with increased mortality.

Thirdly, prevention of complications can lead to a reduction of, for example, workplace absenteeism, hospital admissions and medicine use. In total, this could lead to an increase in quality of life of patients and a significant decrease in costs for society.
Clinical implications

Our research focussed only on individuals with type 1 diabetes (5-10% of the total diabetic population) and in-hospital diabetic specialists treat these patients. As mentioned previously, perhaps we can intervene earlier with current treatment regimens to prevent early ECM remodeling. However, this option needs to be further investigated.

We do not know if and to what extent the MMP-TIMP system acts similarly in type 2 diabetes. If so, more diabetic individuals worldwide could benefit from our findings. In the Netherlands, type 1 diabetic individuals are treated in hospital, whereas general practitioners mainly treat individuals with type 2 diabetes. In case of (largely) similar actions of the MMP-TIMP system in the two types of diabetes also the general practitioners could benefit from our research.

Future perspectives

To date, most observed associations, including ours, were cross-sectional and additional (longitudinal) research should be performed to reveal the exact pathophysiological mechanism underlying vascular complications and therefore our research could provide a starting point. Several new questions have also arisen following this thesis:

- Can one of these markers of the MMP-TIMP truly become a therapeutical target to prevent or reduce vascular complications?
- Are our current treatment options (e.g. statins and/or ACE-inhibitors) suitable for prevention or do new pharmaceuticals have to be developed?
- Does the MMP-TIMP system act similarly with regard to the mechanism leading to vascular complications in individuals with type 2 diabetes?

We hope that this thesis and future research will help us to prevent or reduce vascular complications in individuals with type 1 diabetes as well as to prevent additional costs for society.
References
