Microvascular dysfunction and diabetes: a vicious cycle?

Valorisation addendum

VALORISATION ADDENDUM

Type 2 diabetes mellitus (T2DM) currently affects an estimated 285 million people worldwide, with a further seven million people developing T2DM each year.[1] In addition, the prevalence of obesity is increasing worldwide and has reached epidemic proportions in Western society.[2] As adults with obesity have an approximately 7-fold increased risk of T2DM,[3] it is important to unravel the pathophysiology of obesity-related T2DM. Experimental evidence suggests that microvascular dysfunction may be an intermediate step linking central obesity to T2DM.[4-6] In the research project reported on in this thesis, we investigated the associations of obesity, T2DM, and other cardiovascular risk factors with microvascular dysfunction in a population-based setting. The population-based studies discussed in this thesis are important because they provide further insight into the pathophysiology of obesity-related T2DM. We demonstrated that microvascular dysfunction is associated with diabetes and prediabetes, and thus contributes to the translation to the general population of this concept as investigated in experimental studies. Our findings do indeed suggest a role for the microcirculation in the pathogenesis of T2DM. Hence, from a clinical point of view, targeting the microcirculation may reduce the risk of developing T2DM. In addition, unravelling how microvascular dysfunction is determined and how it leads to T2DM may lead to new treatment targets as well as to a better understanding of the reason why certain existing treatments are associated with a decreased risk of developing T2DM. Importantly, unravelling this concept may reduce health care costs in the near future (through a lower prevalence of T2DM and its complications).

Although this thesis underlines the importance of microvascular dysfunction in the pathogenesis of T2DM, we cannot prove any causal relationship. More studies are therefore required to unravel the pathophysiology of obesity-related T2DM. Unfortunately, the assessment of microvascular function in specific vascular beds is technically demanding and time-consuming. Therefore, we developed a semi-automatic image analysis application (CapiAna) for the assessment of skin capillary density, which agrees well with the classic manual counting procedure, saves time, and has a better reproducibility than the classic procedure. Since CapiAna saves time, thus eventually reducing research costs, the use of skin capillaroscopy has become feasible in large-scale studies. Hence, this semi-automatic image analysis application considerably extends the possibilities of performing microcirculation research in humans. In addition, making this new software freely available on the Internet may consolidate Maastricht University's reputation as an innovative university. This may then help to attract new Dutch and international students, thus further improving the university's reputation.

It is important to note that this thesis is based on the first dataset of the Maastricht Study (an observational prospective population-based cohort study), and thus

opens avenues for potential new research in the context of the Maastricht Study. More precisely, the Maastricht Study is valuable for investigating the longitudinal associations between microvascular dysfunction and incident T2DM. The Maastricht Study is ongoing and annual follow-up on morbidity and mortality is in progress. The study is also valuable because of its extensive phenotyping approach, and in particular the extensive characterization of microvascular function.[7] This allows the role of microvascular dysfunction in the pathogenesis of obesity-related T2DM to be investigated with additional measures of microvascular function (i.e., heat-induced hyperaemia,[8] funduscopy,[9] dynamic vessel analysis,[10] markers of endothelial dysfunction,[11-13] and microalbuminuria[14]). As a consequence, the Maastricht Study will generate new jobs in the Southern part of Limburg. In addition, it creates new opportunities for collaboration with large-scale studies at other Dutch and international universities. This, in turn, may improve the international reputation of Maastricht University.

Besides targeting the microcirculation with drugs, physicians should encourage their patients to lose weight and adopt a healthy lifestyle in order to prevent obesity and obesity-related microvascular dysfunction. For instance, several studies have demonstrated improvements of microvascular function after weight loss in morbidly obese patient having bariatric surgery.[15,16] In addition, a recent study in healthy subjects demonstrated that a dietary pattern characterized by high intakes of high- and low-fat sweets was associated with microvascular dysfunction, while a pattern characterized by increased consumption of vegetable oils, poultry, and fish and seafood was associated with improved microvascular function.[17] Physical activity may also prevent obesity-related microvascular dysfunction and T2DM.[18] Indeed, physical activity has been associated with improved microvascular function[19,20] and, more importantly, regular exercise can enhance the vascular insulin mechanisms.[21] Taken together, these findings suggest that the prevention of obesity and the implementation of a healthy lifestyle may reduce obesity-related microvascular dysfunction and consequent obesity-related T2DM. Besides an important role for physicians, population-based strategies should be introduced to effectively promote lifestyle change, such as media and educational campaigns; product labelling and consumer information; taxation, subsidies, and other economic incentives.[22]

More studies are thus needed to investigate the pathophysiology of obesity-related T2DM. Their findings may contribute to a more precise assessment of risk of this disorder. In addition, unravelling how microvascular dysfunction is determined and how it leads to T2DM may lead to new treatment targets as well as to a better understanding of the reason why certain existing treatments are associated with a decreased risk of developing T2DM. Importantly, the implementation of a healthy lifestyle may reduce obesity-related microvascular dysfunction and consequent obesity-related T2DM.

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