

Determinants of microvascular function in individuals with and without type 2 diabetes

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Valorization addendum

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Knowledge valorization can be defined as the “process of creating value from knowledge, by making knowledge suitable and/or available for societal purposes, and suitable for translation into competitive products, services, processes, and new commercial activities” (adapted definition based on the National Committee Valorization 2011:8). In this addendum we describe how society may benefit from the work conducted in this dissertation.

The results in this dissertation were based on data of the first 3451 participants of The Maastricht Study, an observational prospective population-based cohort study, which is unique for its extensive phenotyping of individuals including a comprehensive characterization of microvascular function¹. The Maastricht Study is currently one of the world’s largest studies on type 2 diabetes (T2D), its complications, and comorbidities and aims to include 8000 participants by the end of 2018. The deep phenotyping approach allowed the investigation of the associations of different (modifiable) cardiovascular risk factors with microvascular function (assessed as flicker light-induced retinal arteriolar dilation and heat-induced skin hyperemia). Through The Maastricht Study several collaborations with (inter)national universities have been established, which further improve the reputation of Maastricht and the university.

This dissertation focused on microvascular (endothelial) dysfunction, an important underlying mechanism in common diseases such as heart failure², (lacunar) stroke³, cognitive decline⁴, depression⁵, chronic kidney disease⁶, retinopathy⁷, and neuropathy⁷, which occur in the general population and more frequently in individuals with T2D⁸. These microvascular diseases put an enormous burden on patients, their families, and social health care systems. Therefore, it is important to explore determinants of microvascular dysfunction. Although the findings in this dissertation may not lead to societal benefits at first glance, they have increased insight into the pathophysiology of microvascular dysfunction, which adds new fuel to future research initiatives.

The first key finding of this dissertation is that generalized microvascular dysfunction is a feature of both prediabetes (which affects 21% of the individuals in our study population, with an even higher prevalence in American cohort studies⁹) and T2D¹⁰, and was mainly attributable to hyperglycemia¹¹. This indicates that microvascular risk already starts before the onset of T2D, which may consequently explain the increased risk of microvascular diseases in prediabetes and early T2D (ticking clock hypothesis¹²). These findings may open the discussion on the implementation of screening for prediabetes and/or early treatment of individuals with prediabetes with glucose-lowering medication¹³. Obviously, attempts to prevent prediabetes, for instance by stimulating a healthy lifestyle, should have the highest priority. According to the Dutch guidelines for

cardiovascular risk assessment, individuals with mild hypertension and/or dyslipidemia are advised to adopt a healthy lifestyle, and importantly, also qualify for antihypertensive and/or lipid-modifying medication when their cumulative cardiovascular risk is (highly) elevated¹⁴. Currently no such (low-threshold) guideline for prevention and treatment of early hyperglycemia (including prediabetes) exists, although this may lead to fewer transitions from prediabetes to T2D¹⁵. Early treatment with metformin may be an option, as it has been shown to improve microvascular function¹⁶ and is generally well-tolerated¹⁵. However, future research should first focus on how to implement and improve screening programs for chronic (mild) hyperglycemia. In addition, the benefits of screening and early treatment on outcomes such as reductions in micro- and macrovascular complications, reduction in transition from prediabetes to T2D, side-effects, cost-efficiency, and quality of life should be further investigated¹⁷.

Another key finding of this dissertation was the identification of cardiovascular risk factors, such as hyperglycemia (as in prediabetes and T2D), aging, male sex, smoking, and low levels of physical activity, as determinants of microvascular (endothelial) dysfunction in the general population. Hence, from a clinical point of view, efficacy of strategies which target these risk factors in order to prevent microvascular dysfunction, and thereby to reduce risk of microvascular diseases, should be examined. Physicians should be aware of individual clustering of these risk factors as well as combinations of them and the concordant increased microvascular risk. In addition, physicians should encourage individuals to adopt a healthy lifestyle by stimulating physical activity and healthy eating as they have been shown to be associated with ameliorated glycemic levels (i.e. consequently may lower the prevalence of T2D)¹⁸, which may coincide with improved microvascular function^{19, 20}. Importantly, our results demonstrated that physical activity may especially be beneficial for microvascular function in individuals with T2D. Based on our data, the results are promising, as only 10 extra minutes of higher-intensity physical activity per day are already associated with a 6.3% greater skin microvascular endothelial function, in individuals with T2D. However, the necessary beneficial amounts of physical activity and possible health effects of breaking up sedentary time on microvascular disease outcome deserve further investigation before physical activity healthcare guidelines can be revised. In addition, early treatment of elevated blood pressure and dyslipidemia and stimulation of smoking cessation are likely other valuable targets to prevent or reduce microvascular dysfunction. Besides a role for physicians in helping individuals to adopt a healthy lifestyle, for instance via motivational counselling, population-based strategies to promote healthy living should be expanded; for instance via targeted television campaigns, (school) education, and awareness of product warning labelling (i.e. dissuasive pictures on smoking packages)²¹.

Although the conclusions of this dissertation are relevant for clinic and society, it should be noted that associations presented here were based on cross-sectional data. Therefore future longitudinal data are eagerly awaited to elucidate the temporality of the associations reported. The Maastricht Study is a valuable cohort study for follow-up measurements. Ideally, both cardiovascular risk factors and microvascular function are measured during follow-up, taking into account an adequate follow-up time for the risk factors to exert an (deleterious) effect on microvascular function. Importantly, annual follow-up questionnaires on morbidity, mortality, and complications have already been introduced in The Maastricht Study and may soon add valuable new information on whether impairment of microvascular function may constitute a pathway through which an adverse cardiovascular risk factor pattern may increase risk of diseases of (partly) microvascular origin.

In conclusion, in this addendum, several research initiatives have been described which can be translated into new PhD projects. The results of this dissertation contribute to a better understanding of which cardiovascular risk factors are associated with microvascular (dys)function on a population-based level. Further longitudinal studies should elucidate temporality of the associations reported. In addition, physicians should be aware of individual risk factors or clustering of risk factors in their patients, motivate them to adopt a healthy lifestyle, and eventually treat prediabetes, in order to reduce the concordant microvascular risk. The ultimate goal is to prevent, and/or reduce the risk of diseases which are partly or wholly of microvascular origin.

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