

Type 2 diabetes beyond glycaemic control

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Chapter 5

Impact

Diabetes is a rapidly growing global health concern with 537 million people living with this condition currently, a number expected to rise to 643 million and 783 million in 2030 and 2045, respectively. This disease was responsible for 1 death every 5 seconds in 2021 and causes a great economic burden ¹. People living with diabetes report a lower quality of life (QoL) compared to people without, and the disease is associated with a wide range of complications. Particularly complications of the lower legs, such as diabetic foot ulcers (DFUs), have a **profound impact on a patient's life. People with diabetic foot problems have reported to fear lower limb amputation (LLA) even more than death** ². Diabetes is roughly divided into type 1, type 2 and other less prevalent types, with type 2 diabetes accounting for 90% of all patients. The focus of the current dissertation was type 2 diabetes.

A large issue with type 2 diabetes is that it is a highly heterogeneous disease. With over half a million people with this disease presenting a wide range of characteristics and problems, it can be difficult to provide adequate treatment to every individual. Therefore the first part of this dissertation (**Chapter 2**) focussed on evaluating ways to individualise treatment. Previously defined subgroups based on disease severity have labelled the subgroups as having **"moderate" or "severe" diabetes. The work in this dissertation showed that people labelled as having moderate obesity-related diabetes, report a QoL similar to those in the severe subgroups. Therefore the terms "moderate" and "severe" do not seem to hold up from a patient's perspective. This finding provides a starting point for further research towards subgroups of type 2 diabetes taking into account the patients' perception of their disease. The prediction models in this dissertation can aid in further target therapy to patients who need it most and in the future, prediction models could be combined with the subgroups of type 2 diabetes to improve performance and targeted treatment even further, while taking into account the patient's perspective.**

The second part of this dissertation (**Chapter 3**) focussed on exploring effects of glucose-lowering drugs with real-world data. The use of large databases with electronic health records allowed us to evaluate effects in every-day life. A couple of years ago, the results of a trial with the glucose-lowering drug from the sodium-glucose co-transporter-2 inhibitor (SGLT2-I) class canagliflozin caused a lot of concern among patients and health care providers when a two-fold increase in the risk of LLA was reported. Since LLAs are highly feared ² and associated with high costs ³ and death ⁴, many studies followed, but produced conflicting results. The studies in this dissertation may help ease concern around this issue, as we repeatedly found no association between the use of SGLT2-Is and the risk of LLA. Furthermore, we found that some studies that reported a higher risk of LLA with SGLT2-Is could have been affected by comparing this drug class to the class of glucagon-like peptide-1 receptor agonists (GLP1-RAs). We found that this drug class was associated with a lower risk of LLA. As GLP1-RAs were associated with various positive effects on complications of the lower legs, these results put forward GLP1-RAs as a potential treatment strategy in people with risk factors for these issues. Other results from this study indicated that SGLT2-Is were not associated with an increased risk of fracture, and

that another drug class, dipeptidyl peptidase-4 inhibitors (DPP4-Is) may also have beneficial effects on the risk of complications of the lower legs.

The work on this dissertation has been presented at several conferences. A poster of **Chapter 3.2** had a spotlight position on an international epidemiology conference and a poster of **Chapter 3.3** was presented on a national clinical pharmacology symposium. **Chapter 3.3** was selected for an oral presentation on two international conferences: one on the diabetic foot, and one epidemiology conference. The presentation of this chapter was awarded second prize in best oral presentation at the conference on the diabetic foot. This emphasizes the interest in this study from both a methodological- (epidemiology conference) and a clinical (diabetic foot conference) perspective in the scientific world. **Chapter 3.4** was shared in an oral presentation at an international conference on bone health. All presentations were well-received and provided the opportunity to have fruitful discussions with other scientist and clinicians.

This dissertation encourages health care professionals to reconsider what is perceived as severe type 2 diabetes and provides insights in the potential benefits of glucose-lowering drugs beyond glycaemic control. Both aspects aid in adopting an individualized approach in the treatment of type 2 diabetes.

Furthermore, this dissertation provides starting points for further research. The approaches in **Chapters 2.1** and **2.2** could be combined in a cluster-wise prediction model for more accurate prediction. Additionally, it would be useful to evaluate the effectiveness of different drugs per subgroup, or specifically in those who are likely not to reach glycaemic control. **Chapter 2.3** underlines the need for validation of DFU measures, and for improved DFU diagnosing and recording in daily practice. Although the findings in **Chapter 3** put forward GLP1-RAs as a treatment strategy in people at risk of lower limb complications, further study is required to confirm the findings and to justify the investment in these expensive drugs. Economic analysis could provide insights in the costs and benefits of the use of GLP1-RAs to prevent DFUs and LLAs.

In conclusion, the contents of this dissertation help taking steps toward individualised treatment of the heterogeneous disease we know as type 2 diabetes. This individualised treatment should go beyond glycaemic control and treat the whole patient, including **complications and take the patient's perspective** and QoL into consideration. The results add to the growing body of evidence that glucose-lowering drug classes have various beneficial effects. Finally, this dissertation provides starting points for further research toward a better future for diabetes.

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