Intervention strategies in the glycation pathway with methylglyoxal as the primary target

Impact statement

Future perspectives and scientific impact

The treatment of multifactorial chronic diseases like diabetes is a continuing struggle. In recent years large advances have been made. In diabetes, treatments with metformin, GLP-1 receptor agonists, and SGLT-2 inhibitors, have greatly progressed disease management[65,66]. However, the increasing prevalence of diabetes, accompanied by many micro- and macrovascular complications, requires a continuous improvement of treatments and more focus on prevention and personalized healthcare, in combination with improved self-management[67].

As mentioned in the introduction, the WHO states, "*Diabetes can be treated and its consequences avoided or delayed with diet, physical activity, medication and regular screening and treatment for complications*". In our research we search for new perspectives and new interventions strategies in the glycation pathway.

A reduction in glycation could relieve part of the burden of obesity and diabetes. However, there are currently no clinical implementations of treatments focusing on the excessive endogenous production of dicarbonyls and consequent accumulation of advanced glycation endproducts (AGEs). In our research we studied the effect of a weight loss, exercise, flavonoid, and pyridoxamine intervention trial for their potential as strategies to inhibit the glycation pathway.

The treatment of complex metabolic diseases without a single molecular target and many interrelated pathways is a difficult feat. When focusing on the reduction of dicarbonyl species and AGEs, we found many reassuring effects in our intervention studies. These clinical studies, as described in this thesis, show that it is possible to reduce dicarbonyl stress and glycation in humans, without apparent side effects. Pyridoxamine and quercetin both show a 10% reduction in plasma MGO, accompanied by positive effects on markers of inflammation and endothelial dysfunction. Pyridoxamine also shows promise with regard to the inhibition of AGEs, but we did not find effects on insulin sensitivity or vascular function. In comparison, the effect size of MGO reduction by quercetin and pyridoxamine of 10% is similar to that what we found in our weight loss intervention. Our weight loss intervention study shows significant effects on fasting MGO and postprandial MGO levels. In contrast, high intensity exercise did not reduce glycation markers.

Many cohort and experimental studies have established the relation between glycation markers and vascular complications. It is reassuring that we were able to reduce dicarbonyl stress and glycation markers in our clinical studies. These data serve as a basis for future interventions; the focus could thereby shift towards treatment effects on

metabolic and vascular function as a consequence of lower dicarbonyl stress. Furthermore, higher dosages and longer duration of treatment should be considered in order to improve efficacy. Individuals with increased MGO stress, such as in diabetes, could benefit the most.

With regard to the prevention and treatment of diabetic complications, I believe the most important question is that of effect size. The evidence showing associations between dicarbonyl stress, AGEs, and disease progression is abundant and irrefutable[57,60,68]. Based on the studies described in the thesis, we now know it is possible to effectively target MGO in apparently healthy individuals. The question remains what the treatment effect of a nutraceutical or lifestyle intervention on plasma MGO should be, to achieve an improved disease outcome in the long term.