The accumulation of advanced glycation endproducts in diabetes and its relation to vascular disease

CHAPTER 9

VALORISATION ADDENDUM

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In today's health care system, evidence-based medicine is considered to be of great importance. The interpretation of study results and their relevance and possible impact and contribution to the current health care system may be difficult to implement for the individual reader. For that purpose, the valorisation of our research results will be discussed in this addendum.

Social and economical relevance

The global prevalence of diabetes was estimated to be 8.8% in adults aged 20-79 years in 2015[1], and is believed to increase even further to 10.4%, or one in every 10 adults, in 2040[1]. Due to this high prevalence, diabetes is the leading cause of renal failure in many populations[2]. Furthermore, more than half of all non-traumatic lower limb amputations are due to diabetes[2, 3] and diabetes is one of the leading causes of visual impairment and blindness in developed countries[2, 4]. Besides the impact on their health and general life, the costs of health-care resources of an individual with diabetes are two to three times higher compared with individuals without diabetes[2, 5]. Taken together, this illustrates the great impact of diabetes on modern-time society and healthcare. Therefore, studies investigating the link between diabetes and its complications, such as ours, may help to reveal opportunities to prevent or delay the development and progression of these complications. Furthermore, relevant markers of disease progression or severity may more effectively identify individuals at risk of vascular complications of diabetes.

Target group

Our main target group is the academic community. As discussed before, our research reveals potential new pathways in the development of cardiovascular disease in the general population and cardiovascular complication in diabetes. As with all studies, more new studies are needed to further investigate and validate our results. Overall, our results confirm the hypothesis that advanced glycation endproducts (AGEs) are involved in the development of multiple (cardio)vascular diseases and diabetes complications.

Implementation in daily practice

In the current health care system, diabetes is monitored by fasting glucose measurements and HbA1c, a precursor of AGEs. HbA1c provides an indication of the average glucose level over the past weeks, corresponding to the half-life of haemoglobin. This makes the HbA1c suitable to monitor the glucose burden and dietary and medicine compliance over a short term period. AGEs are accumulating on long-lived proteins in tissues, e.g. vascular tissue, the skin and vital organs. Therefore, AGE measurements are thought to represent the glucose burden over a longer period compared with HbA1c, especially when measured in tissues. Naturally, tissue biopsy specimens for the determination of AGE-levels are not suitable for daily practice. The measurement of skin autofluorescence (SAF) provides an alternative for tissue biopsies. As discussed in the introduction of this thesis, SAF has been associated with neuropathy, nephropathy and retinopathy in individuals with T1DM[6-10] and T2DM [7, 9, 11-14] and macrovascular complications in both T1DM [7, 15, 16] and T2DM[7, 12, 14, 15, 17, 18]. Additionally, SAF has shown to provide additional information to the UK Prospective Diabetes Study (UKPDS) risk score for the estimation of cardiovascular prognosis in T2DM [17]. In this thesis, we have shown that SAF in associated with arterial stiffness (Chapter

4), endothelial dysfunction (Chapter 5), peripheral arterial disease (Chapter 6) and cognitive impairment (Chapter 7). Since SAF is a relatively new measurement, researchers are currently studying its potential for implementation in daily practice. For now, it seems a promising new tool in the prediction of the cardiovascular risk of individuals with diabetes.

Contribution to the current field

AGE accumulation and its relation to the development of complications of diabetes is an area which is studied by numerous researchers, as shown by the multiple references throughout the former chapters. Multiple experimental studies have been and are currently being performed to look into the possible causal nature of this relation. Others have used observational studies to investigate this association in humans, such as we did in this thesis. With research presented in this thesis we believe we made some unique contributions to the current field. First, we developed and studied a new antibody against MGO-derived AGEs, which showed to be specific for THP. Second, we used state-of-the-art ultra-performance liquid chromatography (UPLC) in combination with tandem mass spectrometry or, in case of pentosidine, with high-performance liquid chromatography (HPLC) and fluorescence detection to determine different AGEs-levels in plasma. These techniques are considered to be the most accurate techniques for the measurement of AGEs at this moment. Moreover, we were able to investigate skin autofluorescence (SAF), a relatively new and promising marker of AGE accumulation, in relation to plasma AGEs and markers of vascular disease. Third, we used large cohort studies with extensively phenotyped individuals with and without diabetes, making it possible to adjust for numerous possible confounding factors. Fourth, as outcome measures in our analyses, e.g. for vascular stiffness, microvascular complications and markers endothelial dysfunction or low-grade inflammation, we did not use only one maker, but several well-known validated markers of the same processes, which makes our results more likely to reflect true associations and which strengthens our conclusions.

Future research

As described in the former chapters, we found consistent results for the associations between higher SAF and markers of vascular disease. This may implicate that AGEs are indeed implemented in the development of vascular diseases and vascular complications of diabetes. We found less homogenous results for the association between plasma AGEs and vascular diseases. Associations for plasma pentosidine were similar to SAF, but plasma CML and CEL showed nonexistent or even inverse associations. Future studies are needed to evaluate these negative associations. For now, SAF seems to provide a more consistent measurement in relation to vascular disease and vascular complications of diabetes. Prospective studies are required to investigate whether or not SAF is indeed a more valid marker of AGE accumulation than plasma AGEs.

Lutgers et al. show that SAF provides additional information to the UK Prospective Diabetes Study (UKPDS) risk score for the estimation of cardiovascular prognosis in T2DM[17]. However, the possible influence of the implementation of SAF measurements in daily practice for patients with diabetes on cardiovascular morbidity and mortality remains uncertain. In our health care system, individuals with diabetes are already intensively monitored and treated with regard to glycemic control, micro- and macrovascular complications and other risk factors of cardiovascular disease. Therefore, without new treatment options, the potential impact of adding SAF-measurement to the current protocol for diabetes management requires further investigation.

As AGE accumulation is proposed be involved in the development of vascular disease, AGE-lowering therapies may be able to diminish the increased risk of CVD in individuals with increased AGE accumulation, e.g. in diabetes. Several therapeutic interventions aiming to limit AGE-related vascular damage have been investigated. Aminoguanidine is one of the most extensively studied AGE inhibitors. Aminoguanidine was shown to increase elasticity of large arteries in diabetes animal models[19]. However, because of disappointing results from clinical studies in individuals with diabetic nephropathy[20, 21] and its detrimental side effects, such as deteriorated liver function and gastrointestinal toxicity[21], it is unlikely that aminoguanidine will be implemented in anti-AGE therapy in humans. Another well-studied potential anti-AGE therapy is the cross-link breaker alagebrium (ALT-711). It has been shown that alagebrium is able to reduce large artery stiffness in different animal models, including diabetes animal models[22]. One double-blind RCT correspondingly showed a decrease in pulse pressure and cfPWV in individuals with hypertension who received alagebrium[23]. However, another double-blind RCT showed no treatment effects in individuals with chronic heart failure [24]. Therefore, more large, specific and well-designed studies are needed to elucidate their potential effect in humans.

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