Diabetes mellitus and rhegmatogenous retinal detachment

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General introduction

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The life expectancy of the world population at birth increased from 65.3 years in 1990 to 71.5 years in 2013.[1] The number of years in good health, however, does not keep up with this increasing lifespan. Therefore, ageing of the world population is leading to a substantial increase in the number of patients with sequelae of diseases and injuries.[2] To be able to keep health care available and affordable in the long run, it is important to focus research on healthy ageing and the prevention of diseases and its complications.

Along with population growth and ageing, the decrease of physical activity and the increase of overweight have led to a significant increase in the number of adults with diabetes: from 108 million in 1980 to 422 million in 2014.[3] In Europe, it has been estimated that approximately 40% of people with diabetes are unaware of their disease.[4] In these persons with mainly type 2 diabetes mellitus (T2DM), silent development of micro- and macrovascular complications frequently occurs which may be prevented or delayed by early screening of high risk individuals.[5] Among these complications, diabetic retinopathy has become one of the leading causes of blindness.[6] The observation that diabetic retinopathy is already present in large patient groups at the moment of diabetes diagnosis[7] also emphasizes the need for early diabetes detection in order to prevent or delay visual disability in diabetes.

Another important, but less prevalent, sight-threatening disease of which the incidence is increasing with the world's ageing population is rhegmatogenous retinal detachment.[8–10] Although developments in surgical treatment have improved the prognosis of retinal detachment, functional results remain poor in many patients, especially in those with redetachments due to proliferative vitreoretinopathy (PVR).[11]

Advanced glycation endproducts (AGEs) are proposed to accelerate the decline of anatomical integrity and function across multiple organ systems that occur with ageing.[12] Evidence is emerging that AGEs play an important role in the pathogenesis of many chronic diseases that disproportionally affect older individuals, such as diabetes mellitus,[13] atherosclerosis,[14] cataract,[15] and Alzheimer's disease.[16]

In this thesis, the role of AGEs as a potential biomarker for occurrence of disease and its complications was investigated in diabetes and retinal detachment patients. We focused on skin autofluorescence as a non-invasive technique that reflects AGE accumulation. This general introduction provides background information on AGE accumulation in diabetes mellitus and ocular pathology. Furthermore, knowledge gaps in this research field are indicated and the aims of the different following chapters are formulated.

Advanced glycation endproducts

AGEs are formed in a multistep process by glycation and oxidation of free amino groups of proteins, lipids and nucleic acids. In addition to the classical Maillard reaction,[17] AGEs are formed through the reaction of amino groups with α-dicarbonyls, such as 3-deoxyglucosone, methylglyoxal, and

glyoxal.[13] Furthermore, AGEs can be formed during lipid peroxidation of fatty acids in the presence of peptides or proteins.[18] These distinct metabolic processes are complex and heterogeneous, yielding numerous different AGE adducts, such as pentosidine, Nε-(carboxymethyl)lysine, and 5-hydro-5- methylimidazolone.

Several mechanisms are involved in the accumulation rate of AGEs in the human body. Firstly, endogenous AGE formation is part of the natural metabolic processes in the human body. The natural AGE accumulation, however, will be increased when oxidative stress, for example due to infection or inflammatory disease, and hyperglycaemia are present. On the other hand, an inhibiting effect on AGE accumulation is seen as a result of the detoxification of α-dicarbonyls by the glyoxalase system.[19] Secondly, the absorption of consumed AGEs play an important role.[20] In the past decades, the increased consumption of highly processed food is associated with an increased exposure to dietary AGEs. This was shown to be primarily the result of the dry-heat treatment of protein- and lipid-rich foods.[21] Accumulation of AGEs also strongly depends on tissue turnover because AGEs are mainly irreversibly linked to tissue proteins. Therefore, in tissues with slow turnover (such as the skin,[22] cartilage,[23] lens,[24] and vitreous[25]), AGEs accumulate gradually over decades. In tissues with fast turnover (such as epidermis and mucosa), AGEs accumulate to a lesser extent[26] since they are rapidly broken down to AGE peptides or free AGEs. Finally, excretion of AGEs by the kidney[27] influences AGE accumulation. This becomes evident in patients with decreased renal function. To illustrate, numerous studies have shown 2- to 10- fold increased serum AGE levels in patients with end-stage renal disease.[28]

AGEs can induce damaging effects to cells and tissues in several ways, including (1) crosslinking of extracellular matrix proteins, (2) activation of the receptor for AGEs (RAGE), and (3) direct glycation of intracellular proteins and lipids. AGE-crosslinking of structural proteins in the extracellular matrix leads to reduced elasticity, increased stiffness of vessels,[29] and resistance to proteolytic digestion.[30] Moreover, extracellular AGE accumulation may disturb the interaction of matrix and cells through modulation of biological attachment sites.[31] Interaction of AGEs with RAGE activates multiple cell signalling pathways leading to increased production of reactive oxygen species, adhesion molecules, and pro-inflammatory cytokines.[32] Activated RAGE upregulates its own receptors providing an increased number of binding sites for RAGE-ligands. Therefore, sustained RAGE expression in proximity to their ligands will lead to chronic activation of inflammation and subsequent tissue damage.[12] The deleterious potential of intracellular AGEs results from structural changes that modify the function of intracellular proteins, including enzymes and regulatory proteins. Furthermore, intracellular AGEs can directly bind to electron transport chain mitochondrial proteins leading to inhibition of oxidative adenosine triphosphate (ATP) synthesis and increased superoxide formation by mitochondria.[33] This may have deleterious effects by inducing increased oxidative stress.

Measurement of advanced glycation endproducts

AGEs can be measured using enzyme linked immunosorbent assay (ELISA), fluorescence spectroscopy, and fluid chromatography and gas chromatography with mass spectrometry.[34]

Originally, AGEs were measured according to their fluorescent and browning properties. Later, instrumental analyses provided methods to differentiate between distinct and non-fluorescent AGEs and immunochemical methods made it possible to perform AGE measurements in multiple clinical samples and to clarify the localization of AGEs in tissues. Currently, ultra performance liquid chromatography tandem mass spectrometry is considered the most accurate technique.[35] However, the different detection methods have their own advantages and disadvantages and should, therefore, be used depending on the purpose of the AGE measurements.[36]

While the measurement of circulating AGEs shows high physiological fluctuations (e.g. postprandial) and is strongly dependent on kidney function, the measurement of tissue-bound AGEs is more stable. In particular, tissues with slow turnover display a high degree of AGE accumulation over time. Since a close relation exists between the level of AGEs and their effect on tissues, tissues with slow turnover are more exposed to the damaging effects of AGEs. Thus, to investigate general damage due to AGE accumulation, tissues with slow turnover are most suitable for AGE assessment.[37] The skin represents the most accessible tissue, with the biochemical analysis of skin biopsies constituting the gold standard.[38] However, this method is invasive, expensive, requires analysis in specialised centres, and results are available within days to weeks.

In 2004, a first report appeared that skin autofluorescence (SAF), non-invasively assessed in the skin of the forearm, was related to AGE levels in dermal biopsies in diabetes patients and in healthy controls.[39] These dermal biopsies were obtained from the same measurement site as on which SAF was performed and several AGEs were determined using chromatographic and mass spectrometric methods. The study pointed out that SAF reflects dermal AGE levels and may be used as a biomarker in AGE-related diseases. The device used to measure SAF was developed in Groningen, the Netherlands, and was later called the AGE reader. The exact molecular structures and the diversity of species contributing to SAF have not been established, but the used wavelength band of the AGE Reader was selected such that the major contribution in fluorescence comes from fluorescent AGEs.

Because of its non-invasive character, the small size of the AGE reader, and its ease to perform measurements, SAF would be more suitable to evaluate the deleterious effects of AGEs in large scale studies and clinical practice than the still laborious biochemical assessment of AGEs in tissue biopsies and plasma samples.

Diabetes mellitus

Diabetes mellitus is a group of metabolic diseases that is primarily characterized by elevated blood glucose levels (hyperglycemia) as a result from defects in insulin secretion, insulin action, or both. The majority of diabetes patients fall into two broad etiopathogenetic categories: type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM).[40] T1DM is caused by an absolute deficiency of insulin secretion and is often characterised by serological evidence of an autoimmune pathologic process in the pancreatic islets and by genetic markers. T2DM is caused by a combination of

resistance to insulin action and an inadequate compensatory insulin secretion response. The latter category may be unnoticed for a long time, since mild hyperglycemia can be present without clear clinical symptoms. However, during the asymptomatic period hyperglycemia will already cause pathologic and functional changes in various tissues. Therefore, an early diagnosis is very important in preventing diabetic complications.

One of the most important effects of hyperglycaemia is damage to the vascular system. Depending on large or small blood vessels that are affected, most long term damage can be accordingly grouped into macrovascular (such as myocardial infarction or stroke) and microvascular complications (such as retinopathy, nephropathy, and neuropathy). Several mechanisms leading from hyperglycemia to diabetic complications have been described, among them the accumulation of AGEs due to the damaging mechanisms described in a previous section. Furthermore, AGEs have been proposed to play a role in the phenomenon of 'metabolic memory' that was seen in the long-term follow-up of the diabetes control and complications trial (DCCT)[41] and the United Kingdom prospective diabetes study (UKPDS)[42]: the prolonged beneficial effects of intensive therapy and the deleterious effects of conventional, less stringent, therapy long after cessation of the relatively brief intervention period.

The first link between glycated proteins and diabetes was the discovery of an altered form of haemoglobin (now known as HbA1c) in red blood cells of patients with diabetes.[43] Since HbA1c, in fact an Amadori product (an intermediate in the Maillard reaction pathway), reflects glycaemia over a longer period (approximately 3 months), HbA1c is now commonly used as a measure of glycaemic control and as a predictor for complications in diabetes. Currently, there is increasing evidence from clinical studies that AGEs serve as potential biomarkers for diabetic complications,[13] although the causal relationship needs to be further clarified. To illustrate, AGE levels have been shown to correlate with diabetic retinopathy,[44] nephropathy,[45] and cardiovascular disease.[46] Furthermore, strong associations have been found between glycation markers in skin collagen and the risk of progression of microvascular disease.[22,47] In recent studies, the relation of SAF with diabetic complications has also been investigated.

*In **Chapter 2** the technique of skin autofluorescence, its validation as a marker of tissue AGE accumulation, and its use as a clinical tool for the prediction of long-term complications in type 1 and type 2 diabetes mellitus is reviewed.*

SAF in diabetes screening

Skin fluorescence has been proposed to be useful as a cost-effective, simple, and reproducible test for diabetes screening.[48] In subjects at risk for diabetes, skin fluorescence was comparable or superior to HbA1c and fasting plasma glucose for detection of impaired glucose tolerance and diabetes as detected by the oral glucose tolerance test (OGTT),[49,50] the current gold standard for diabetes diagnosis. To further improve sensitivity and specificity of diabetes detection, a SAF based decision tree has been developed. It was shown that this decision tree had an equal or superior performance in the detection of diabetes and impaired glucose tolerance in comparison

with conventional risk predictors in an intermediate risk group.[51] However, it was pointed out that validation and predictive value of this model in lower risk groups was still needed.

A variety of other tools have been proposed to identify individuals with an increased risk of developing T2DM. Of these tools, the Finnish Diabetes Risk Score (FINDRISC) is currently the most validated and widely used. It is a simple, safe, and inexpensive screening test that has been developed to predict drug-treated T2DM and to increase awareness of modifiable risk factors and the benefits of a healthy lifestyle.[52] The FINDRISC has also been validated in 3 Dutch cohort studies in which 3 risk categories have been proposed: low risk for score <7, slightly elevated risk for score 7, 8 or 9, and elevated risk for score ≥10. Because of the potential of SAF in diabetes detection, SAF may be able to further improve the FINDRISC in its performance to detect diabetes. A population based cohort study would be most suitable to address the additional value of SAF in an 'a priori' low risk group.

LifeLines is a population based cohort study that was established as a resource for research on complex interactions between environmental, phenotypic and genomic factors in the development of chronic diseases and healthy ageing in a three-generation structure.[53] At baseline, approximately 167,000 participants (aged 6 months to 93 years) completed extensive questionnaires, physical examination, and collection of biomaterials. Follow-up visits are scheduled every 5 years and participants receive follow-up questionnaires in between. Adjusted for differences in demographic composition, the LifeLines adult study population was found to be broadly representative for the adult population of the north of the Netherlands.[54] SAF measurements are available in approximately 80,000 adult participants of LifeLines.

*In **Chapter 3** the following research question was addressed: Does the addition of SAF to the FINDRISC improve the model in its performance to detect diabetes in the LifeLines cohort study?*

Advanced glycation endproducts and ocular pathology

Since many differentiated cells of the human eye have little or no regenerative capacity, cell structures of the eye are highly susceptible to ageing processes and systemic diseases that alter structural proteins and result in metabolic imbalance. Accordingly, accumulation of AGEs has been found in many different compartments of the human eye (including the lens, vitreous, retina, and optic nerve) during ageing and at a higher rate in metabolic diseases.[15,55] Therefore, an important role of AGEs has been postulated in the initiation and progression of several sight-threatening disorders of ageing such as cataract formation, glaucoma, age-related macular degeneration, and diabetic retinopathy.

Structural changes of the vitreous, such as liquefaction and (incomplete) posterior vitreous detachment, are also associated with ageing and are likely to occur earlier in diabetic patients than in non-diabetic individuals.[56,57] AGEs have been described in human vitreous where they correlate with age[58] and where AGEs may accumulate at an higher level in diabetic patients.[59] It has also been demonstrated that glycation can induce abnormal cross-links between vitreous

collagen fibrils which may cause destabilization of the gel structure.[60] Therefore, it seems likely that AGEs play a significant role in vitreous dysfunction during ageing.

In the retina, AGEs can have detrimental effects in the blood-retinal barrier and on microvascular function. Accumulation of AGEs has been found in retinal pigment epithelium (RPE) and Bruch's membrane which are important structures in maintaining the blood-retinal barrier function. The RPE function can be influenced by AGEs and α-dicarbonyls through depressing lysosomal enzymatic activity[61] and by inducing cell apoptosis.[62] Furthermore, AGEs have been found to alter transcriptional regulation of VEGF in different retinal cells.[63] In addition to its importance in the pathologic angiogenic process of neovascularization, VEGF can cause increased endothelial permeability in the retinal microvasculature.[64] Moreover, detrimental effects of AGEs on retinal pericytes[65] may also play a role in microvascular retinal dysfunction.

Rhegmatogenous retinal detachment

Rhegmatogenous retinal detachment (RRD) is a sight-threatening disease with an annual incidence of 18.2 per 100,000 in the Netherlands.[10] RRD is caused by a retinal tear, most often initiated by a posterior vitreous detachment. In early childhood, the vitreous is a solid gel attached to the lens and the retina. With ageing, liquid-filled spaces and optically dense condensations are formed within the matrix.[66] Simultaneously, the attachment to the posterior retina weakens, while the anteriorly located vitreous base, which is strongly connected to the retina, broadens towards posterior.[67,68] These structural age-related changes in the vitreous body will often lead to a posterior vitreous detachment which can induce retinal damage such as intravitreal hemorrhage, retinal tear, and retinal detachment.[69]

Before surgical treatment became available, an RRD would lead to blindness in almost all cases.[70] Nowadays, pneumatic retinopexy, scleral buckling, and trans pars plana vitrectomy can make surgical reattachment of the detached retina successful in 95% of cases after one or more of these surgical procedures.[71] However, functional results remain poor in many patients, especially in those with redetachments due to proliferative vitreoretinopathy (PVR).[11] Because of the complexity of risk factors associated with the development of PVR, it is currently difficult to select patients at high risk of PVR and ensuing retinal redetachments.

Both AGEs and AGE-receptors (RAGE) have been found to be increased in the vitreous of patients with PVR and were present in their epiretinal membranes.[72] Furthermore, AGEs can induce the expression of several cytokines that have been shown to be elevated in PVR.[63,73,74] Since these studies support a potential role of AGEs in the development of PVR, AGEs may represent a biomarker for PVR and retinal redetachment. Although local measurement of AGEs in the vitreous would be the most accurate reflection of AGEs that may be involved in the disease process, its invasive and time-consuming character makes it unsuitable to be used as a biomarker. However, the rate of pentosidine accumulation with ageing has been found to be similar in the vitreous and the skin.[25] Therefore, SAF might reflect AGE accumulation in the vitreous and might be useful as a biomarker for PVR and retinal redetachment.

*In **Chapter 4** the following research question was addressed: Are skin autofluorescence and vitreous pentosidine elevated in patients with a (severe) RRD?*

*In **Chapter 5** the following research questions were addressed: Is SAF able to identify patients at high risk of a retinal redetachment? Does local AGE accumulation support a role of AGEs in the development of a redetachment?*

Diabetic retinopathy

Diabetic retinopathy is the collective name for the characteristic retinovascular damage seen in patients with diabetes. It is the most common microvascular complication of diabetes which, after two decades of disease, affects almost all T1DM patients, more than 80% of insulin-treated T2DM, and 50% of T2DM patients not requiring insulin.[75] Diabetic retinopathy may be broadly classified into two stages based on the level of microvascular degeneration and related ischemic damage: non-proliferative diabetic retinopathy and advanced, proliferative diabetic retinopathy (PDR).[76]

Several studies have shown elevated serum and vitreous AGE levels in diabetic retinopathy and have suggested that AGEs influence the transition of retinopathy from the non-proliferative to the proliferative state.[77] However, vitreous AGE levels have mainly been measured in patients with PDR or diabetic macular edema and have always been compared to non-diabetic controls undergoing vitrectomy for several eye conditions. Currently, it has not been shown whether vitreous AGE levels are already elevated in diabetes before the development of PDR. This information would be relevant, because it is unclear whether AGEs have a causative role in the development of diabetic retinopathy or, alternatively, AGEs are just by-products of the disease process. If the former would be true, this would lead to opportunities for AGE focused therapy in (the prevention of) diabetic retinopathy.

*In **Chapter 6** the following research question was addressed: Are AGEs already elevated in the vitreous of patients without proliferative diabetic retinopathy?*

*The final chapter, **Chapter 7**, summarizes the overall findings of this thesis, provides a general discussion of clinical implications, and presents subsequent ideas about future research directions.*

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Part I.
Skin autofluorescence in diabetes mellitus