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REAL-WORLD TREATMENT OUTCOMES OF PROLIFERATIVE DIABETIC RETINOPATHY AND DIABETIC MACULAR EDEMA

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Abstract

Diabetic retinopathy is a vision-threatening complication of diabetes and a leading cause of blindness globally. Complications are a major burden to the healthcare system. This study was carried out to evaluate the real-world treatment outcomes of proliferative diabetic retinopathy (PDR) and diabetic macular edema (DME).

The first study (I) included 103 patients with type 1 (T1D) or type 2 diabetes and PDR with vitreous hemorrhage (VH). Intravitreal anti-vascular endothelial growth factor (anti-VEGF) agent bevacizumab showed superiority to panretinal photocoagulation, pars plana vitrectomy and observation alone in shortening the time for clearance of VH ($p<0.0001$). An average of 1.7±1.1 injections were needed to clear the VH, and the reinjection interval was 7.2±3.9 weeks. In addition, during the 5-year period, patients had 2.2±2.7 VH recurrences and the number of vitrectomies decreased 72% ($p<0.0001$).

To evaluate functional vision and health-related quality of life (HRQoL) after 35-year duration of T1D, 29 patients with PDR from the population-based cohort with T1D since childhood were re-evaluated in 2019 (II). The visual acuity was 73–77 ETDRS letters and only two patients were visually impaired. Visual field sensitivity and reaction time were impaired in patients with PDR compared to healthy controls, (23.2±3.9 dB vs. 26.9±1.0 dB, and 14.9±5.6 dB vs. 21.0±2.0 dB, respectively, $p<0.001$). However, contrast sensitivity was not significantly affected (490.5 ms vs. 462.8 ms, $p=0.004$). HRQoL remained good despite declined functional vision.

The third study (III) consisted of a population-based cohort of 206 patients diagnosed with T1D and DME. Anti-VEGF or a combination of anti-VEGF and laser seemed to be beneficial in terms of visual gain after the initial episode of DME (+4.9 and +5.5 ETDRS letters, $p<0.001$ and $p<0.001$, respectively) and long-term treatment stability (+4.1 and +5.1 ETDRS letters, $p<0.001$ and $p<0.001$, respectively). The visual impairment due to DME decreased from 2.4% to 1.0% during the 15-year period.

In conclusion, these results underline the importance of timely and effective treatment of PDR and DME in preventing visual impairment in patients with diabetes. Furthermore, modern treatment of DR with intravitreal anti-VEGF agents has revealed promising results in real-life setting and greatly improved the visual prognosis in patients with diabetes.

Keywords: diabetes, diabetic macular edema, diabetic retinopathy, proliferative diabetic retinopathy, vitreous hemorrhage

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Tiivistelmä

Diabeettinen retinopatia on diabeteksen yleisin komplikaatio ja yleinen sokeuden aiheuttaja maailmanlaajuisesti. Näön heikentymisen ja näkövammautumisen ehkäisemiseksi diabeettisen retinopatian tehokas hoito on tarpeen. Tämän tutkimuksen tavoitteena on lisätä tietoa proliferatiivisen diabeettisen retinopatian (PDR) ja diabeettisen makulaturvotuksen hoitotuloksista tosielämässä.

Ensimmäisessä osatyössä (I) oli mukana 103 tyypin 1 (T1D) tai 2 diabetesta sairastavaa potilasta, joilla oli PDR ja lasiaisverenvuoto. Työssä selvitettiin lasiaisvuotojen esiintyvyyttä ja hoitotuloksia. Lasiaisvuotoja esiintyi yleisemmin T1D:sta kuin T2D:sta sairastavilla (16 % vs. 9 %). Lasiaiseen annosteltava verisuonikasvutekijäestäjä bevasitsumabi osoittautui laserhoitoa, lasiaisenpoistoleikkausta eli vitrektomiaa ja seurantaa tehokkaammaksi hoitomuodoksi lasiaisvuodon kirkastamiseksi ($p<0.0001$).

Toisessa osatyössä (II) tutkittiin diabeteksen 35 vuoden sairastamisajan ja PDR:n vaikutusta potilaiden toiminnalliseen näkökykyyn ja elämänlaatuun. Tutkimusaineisto koostui lapsena T1D:seen sairastuneiden kohortin PDR:aa sairastavista potilaista. Näöntarkkuus säilyi hyvänä ja vain kahdelle potilaalle kehittyi näkövamma. Näkökyvyn herkkyys ja reaktioaika olivat alentuneita verrattuna terveisiin verrokkeihin. Kontrastinäkö ei merkittävästi muuttunut. Elämänlaatu pysyi hyvänä, vaikka potilaiden toiminnallinen näkökyky oli diabeteksen pitkän keston myötä heikentynyt.

Kolmannessa osatyössä (III) selvitettiin diabeettisen makulaturvotuksen hoitotuloksia T1D:sta sairastavilla potilailla väestöpohjaisessa aineistossa. Bevasitsumabi-kasvutekijäestäjähoitoa tai bevasitsumabin ja laserin yhdistelmähoitoa saaneiden potilaiden näkö parani merkittävästi ensimmäisen turvotusjakson jälkeen ja hoidon teho säilyi myös pitkäaikaisseurannassa. Diabeettisen makulaturvotuksen aiheuttama näkövammautuminen väheni 15 vuoden seurannan aikana.

Tämän väitöstutkimuksen osatöiden tulokset painottavat PDR:n ja diabeettisen makulaturvotuksen oikea-aikaisen ja tehokkaan hoidon merkitystä diabeteksen aiheuttaman näkövammautumisen ehkäisemisessä. Erityisesti diabetesta sairastavien näköennuste on kasvutekijäestäjälääkkeiden yleistyttyä huomattavasti parantunut.

Asiasanat: diabeettinen makulaturvotus, diabeettinen retinopatia, diabetes, lasiaisverenvuoto

When the reflection is seen under the influence of a dim light, as that from a candle, or a few solar rays, a red lurid glare, like that from a dull coal fire, is observed.

- William Cumming, On a luminous appearance of the human eye, 1846

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5.5.2023 Joonas Wirkkala

Abbreviations

ACE	angiotensin-converting enzyme
AGE	advanced glycation end-product
ATP	adenosine triphosphate
ATR	angiotensin-II-receptor
BCVA	best corrected visual acuity
BMI	body mass index
BRB	blood-retinal barrier
CI	confidence interval
CI-DME	center-involved diabetic macular edema
DKD	diabetic kidney disease
CLARITY	clinical efficacy and mechanistic evaluation of aflibercept for proliferative diabetic retinopathy
cpd	cycles per degree
CVD	cardiovascular disease
CRT	central retinal thickness
CWS	cotton-wool spots
dB	decibel
DCCT	diabetes control and complication trial
DM	diabetes mellitus
DME	diabetic macular edema
DRCR.net	diabetic retinopathy clinical research network
ESKD	end-stage kidney disease
ETDRS	early treatment diabetic retinopathy study
FAG	fluorescein angiography
GAD	glutamic acid decarboxylase
GCK	glucokinase
GFAT	glutamine: fructose-6-phosphate aminotransferase
GDM	gestational diabetes mellitus
G6P	glucose-6-phosphate
HbA1c	glycated hemoglobin
HDL	high-density lipoprotein
HRQoL	Health-Related Quality of Life
HNF1/4A	hepatocyte nuclear factor 1/4 A
ICD-10	tenth revision of the International Classification of Diseases

IL	interleukin
IOP	intraocular pressure
IVB	intravitreal bevacizumab
LDL	low-density lipoprotein
logMAR	logarithm of the minimum angle of resolution
mmol/L	millimole per liter
mmol/mol	millimole per mole
MODY	maturity-onset diabetes of the young
NAPDH	nicotinamide adenine dinucleotide phosphate
NFkB	nuclear factor kappa-light-chain-enhancer of activated B cells
OCT	optical coherence tomography
O-GlcNAc	O-linked β-N-acetylglucosamine
OGTT	oral glucose tolerance test
PDR	proliferative diabetic retinopathy
PKC	protein kinase C
PRP	panretinal photocoagulation
PPV	pars plana vitrectomy
PSC	posterior subcapsular cataract
ROS	reactive oxygen species
SD	standard deviation
SGLT2	sodium-glucose co-transporter 2
TA	triamcinolone
THL	Finnish institute for health and welfare
T1D	type 1 diabetes
T2D	type 2 diabetes
TNF-α	tumor necrosis factor alpha
TRD	tractional retinal detachment
UKDPS	United Kingdom diabetes prevention study
VEGF	vascular endothelial growth factor
VH	vitreous hemorrhage
VTDR	vision-threatening diabetic retinopathy
WESDR	Wisconsin epidemiologic study of diabetic retinopathy
WHO	World Health Organization

Publications

This thesis is based on the following publications, which are referred throughout the text by their Roman numerals:

I Wirkkala, J., Bloigu, R., & Hautala, N. M. (2019). Intravitreal bevacizumab improves the clearance of vitreous hemorrhage and visual outcomes in patients with proliferative diabetic retinopathy. BMJ open ophthalmology, 4(1), e000390. https://doi.org/10.1136/bmjophth-2019-000390

II Wirkkala, J., Kubin, A. M., Ohtonen, P., Falck, A., & Hautala, N. (2023). Outcomes of 35-year duration of type 1 diabetes and proliferative diabetic retinopathy on functional vision and quality of life: Benefits of good glycemic control. Journal of diabetes and its complications, 37(2), 108408. Advance online publication. https://doi.org/10.1016/j.jdiacomp.2023.108408

III Wirkkala, J., Kubin, A. M., Ohtonen, P., Yliselä, J., Siik, T., & Hautala, N. (2022). Visual outcomes of observation, macular laser and anti-VEGF in diabetic macular edema in type 1 diabetes: a real-world study. BMC ophthalmology, 22(1), 258. https://doi.org/10.1186/s12886-022-02482-z

Table of contents

1 Introduction

Diabetic retinopathy (DR) is a vision-threatening complication of diabetes and a potential source of vision loss in patients with poor glycemic control (Teo et al., 2021; Yapanis et al., 2022). The incidence of diabetes is increasing and despite modern treatments for hyperglycemia the incidence of DR is also rising (Teo et al., 2021). With screening and effective treatment, severe visual loss is prevented and less patients will be visually impaired than without treatment (ETDRS Research Group, 1991a; Hautala et al., 2014; Klein et al., 2008).

In this study, the effects of DR regarding vision and treatment in the real-world setting was studied. The aim was to evaluate how vitreous hemorrhage (VH) as a complication of progressed proliferative diabetic retinopathy (PDR) is managed in the real-world setting, and how treatment with intravitreal bevacizumab promotes the clearance of VH (I). In the second study (II) our aim was to evaluate the outcomes of functional vision including visual acuity, visual field sensitivity, contrast sensitivity and reaction time, in addition to health-related quality of life (HRQoL) in patients with type 1 diabetes (T1D) after 35 years and PDR. The final aim was to evaluate how diabetic macular edema (DME) is treated in a population-based, real-world setting in patients T1D, and how visual outcomes changed after the first DME episode in relation to the long-term follow-up (III).

Diabetes is a systemic disease, which means that its effects cover the whole human body. Due to insulin resistance or insulin deficiency, the blood glucose level rises, which in turn, is followed by the disruption of normal biochemical processes. When the diabetic milieu sustains, complications in different organs will appear (Romero-Aroca et al., 2009; The Diabetes Control and Complications Trial Research Group [DCCT], 1993). One of the first complications can include retinal microaneurysms that can be spotted in the biomicroscope examination by an ophthalmologist. Eventually, even more severe ocular complications, or other micro- and macrovascular complications develop (ETDRS Research Group, 1985; Klein et al., 2008; Porta et al., 2001). The severity of these complications varies from mild microaneurysms all way to chronic hyperglycemia, severe kidney failure or even death.

The duration of diabetes and glycemic control are strongly associated with the onset of DR and its severity (Klein et al., 1984a, 2008; UKPDS Group, 1998b). Vision-threatening diabetic retinopathy (VTDR) consists of severe non-proliferative diabetic retinopathy, PDR, and DME. These stages of retinopathy DR usually have the need for ophthalmic treatment in order to prevent vision loss.

Retinal laser treatment in combination with photocoagulation can be used to decrease the retinal oxygen demand by permanently destroying mid or peripheral retinal tissues or to photocoagulate individual microaneurysms to treat vascular leakage causing macular edema (DRS Research Group, 1978; ETDRS Research Group, 1991a).

The increased oxygen demand promotes the vascular endothelial growth factor (VEGF) mediated hypoxia and thus exacerbates DR (Aiello et al., 1994). In patients with changes caused by DME and in cases of advanced PDR, such as VH or persistent neovascularization, anti-VEGF treatment with intravitreal injections of bevacizumab, ranibizumab and aflibercept are often used (Avery et al., 2006; Ip et al., 2015; Sameen et al., 2017). Treatment with anti-VEGF may also improve visual outcomes and reduce the need for surgical intervention with pars plana vitrectomy (PPV) (Fallico et al., 2021; Yates et al., 2021). Center-involved DME (CI-DME) cannot be treated with focal photocoagulation if microaneurysms are within 500 μm of the fovea (ETDRS Research Group, 1985). If center of the macula is involved, anti-VEGF injections may be used to decrease the leakage from pathological vessels (Aiello et al., 2011; Brown et al., 2015; DRCR.net, 2015).

Multiple international and national guidelines have been established to help assist in choosing evidence-based treatments (Finnish Medical Society Duodecim, 2014; Flaxel et al., 2020; Schmidt-Erfurth et al., 2017; Wong et al., 2018). Guidelines are usually easily accessible, are based on clinical trials and selected patient populations. However, the effect of these treatments in the general population is not well known because of specific patient selection criteria in clinical trials and frequent follow-ups. Our aim was to report real-world outcomes on how intravitreal bevacizumab (IVB) improves the clearance of VH in patients with PDR and how observation, macular laser and anti-VEGF in treatment of DME positively effect visual outcomes in patients with T1D. This study provides information on how effective treatment of PDR and DME in patients with T1D preserves vision and prevents severe vision loss and visual impairment in a real-life setting.

2 Review of the literature

2.1 Diabetes as a disease

The word ‘diabetes’ comes from the Greek word diabainein (go through, dia; prefix, through and bainein; verb, go on) providing us with the classical description of the disease in question. In order to accomplish a more figurative impression of the term diabetes, the word mellitus from Latin (mel, honey) was added to form the official name, diabetes mellitus. However, diabetes mellitus is commonly referred to and used by its shortened version, diabetes, worldwide.

The World Health Organization (WHO) classifies diabetes as a state of absolute or relative insulin deficiency, characterized by hyperglycemia and the risk of microvascular and macrovascular complications (World Health Organization [WHO], 2019). In order to attain a clinical diagnosis of diabetes, a fasting plasma glucose value, oral glucose tolerance test (OGTT) or glycated hemoglobin (HbA1c) can be used. The diagnosis may be set if one of the following conditions is observed:

- Plasma fasting glucose is ≥7.0 mmol/L
- Plasma glucose is ≥11.1 after 2 hours of starting OGTT
- HbA1c ≥48 mmol/mol
- Blood glucose at any time is ≥11.1 mmol/L.

A single test is adequate if a patient has characteristic symptoms, otherwise another test is needed to confirm the diagnosis. Classical symptoms include an increased sensation of thirst, polyuria, and unexplained loss of weight (WHO, 2011).

2.1.1 Epidemiology

In 2021 it was estimated that 537 million people suffered from diabetes, resulting in a global prevalence of 11% (Sun et al., 2022). Furthermore, the statistical prevalence is even more interesting: where type 2 diabetes (T2D) accounts for an estimated 90–95% of all diabetes cases, type 1 diabetes only accounts for the remaining 5–10% (Deshpande et al., 2008). It is also worthwhile to acknowledge the rising number of new diabetes cases and the global trend which can be seen. It has been estimated that as many as 780 million people will have diabetes in 2045 (Sun et al., 2022). Another concerning factor, in addition to rising amount of new diabetes cases, is the fact that half of the people with diabetes are unaware of the underlying disease (Saeedi et al., 2019; Whicher et al., 2020).

In a study conducted by Lammi et al., a ten-year period between 1992 and 2001 was observed. It was shown that in Finland, the incidence of diabetes in young adults is 18 per 100 000 for T1D and 13 per 100 000 for T2D during the 10-year period between 1992 and 2001 (Lammi et al., 2008). A 4% yearly increase in the incidence of diabetes was noted in both groups, thus being in line with the increasing global trend (Lammi et al., 2008). In contrast to this, childhood incidence of T1D is globally highest in Finland compared to other countries, being 52 per 100 000 in children under 15 years of age between 2003 and 2018, after reaching the peak value in 2006 (Parviainen et al., 2020). Currently, the Finnish Institute for Health and Welfare (THL) reports that almost 500 000 people have diabetes in Finland, and T2D covers almost 90% of all cases (Arffman et al., 2020) (Figure 1).

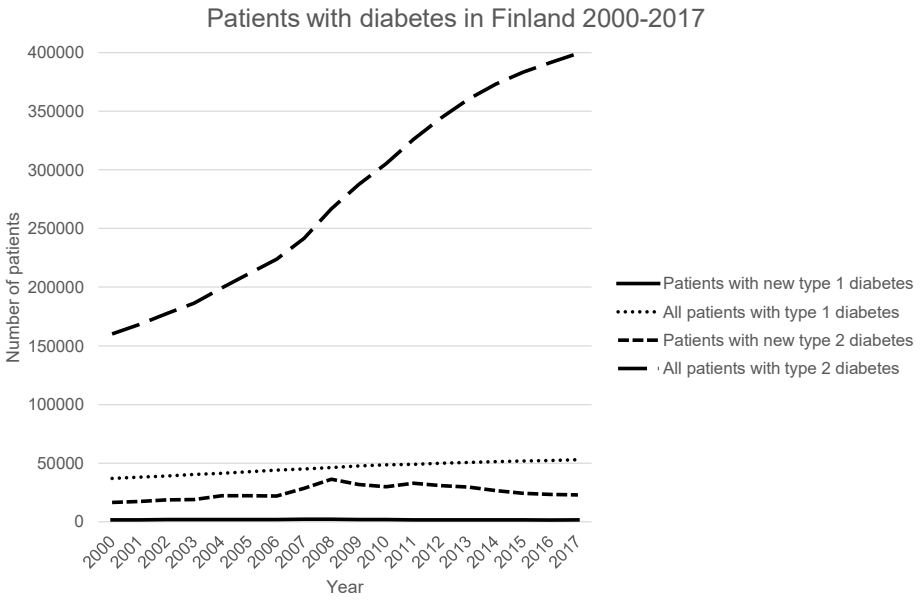


Fig. 1. Patients with either type 1 or 2 diabetes in Finland in 2000–2017 according to the Finnish Institute for Health and Welfare (Arffman et al., 2020).

The International Diabetes Foundation estimated that in 2021 45%, cases of diabetes were undiagnosed (Ogurtsova et al., 2022). Diabetes screening is therefore needed to avoid long-term morbidity and reduce the economic burden to the healthcare system (Gillies et al., 2008). In Finland, the Diabetes Risk Score tool is

used in diabetes screening to identify possible diabetes in high-risk patients (Lindström & Tuomilehto, 2003).

2.1.2 Type 1 diabetes

T1D usually starts at a young age during childhood but it can also be diagnosed later during early adulthood. Impaired and insufficient insulin production characterizes the pathophysiology of T1D which is caused by an autoinflammatory destruction of β-cells in the pancreatic islets of Langerhans (Powers & Eisenbarth, 1985).

In the pancreas, β-cells produce proinsulin and before excretion to the blood circulation, proteolytic cleavage breaks proinsulin to insulin and C-peptide. For diagnostic purposes, to measure the insulin secretion and islet β-cell function, C-peptide levels can be measured (Jones & Hattersley, 2013; Klein et al., 1995).

To aid the diagnosis, and sometimes in the screening process of T1D, markers connected to the autoinflammatory process can be looked for. Glutamic acid decarboxylase (GAD) antibodies are a sign of inflammation and linked to later insulin deficiency (Baekkeskov et al., 1990). The lack of GAD antibodies can assist in excluding the underlying autoinflammatory process behind diabetes (Pietropaolo & Eisenbarth, 2001).

Positive GAD antibodies are more commonly seen in younger patients. The use of GAD antibodies in diabetes diagnostics is recommended only to patients of age 40 or under according to the Finnish Current Care Guidelines (Finnish Medical Society Duodecim, 2018). However, if diabetes starts in adulthood and is not insulin-dependent at first, but GAD antibodies are positive, it is a sign of latent autoimmune diabetes in adults. These cases account only for 2–12% of all cases of diabetes (Nambam et al., 2010). After a while, insulin deficiency appears, leading to the disease being classified as a T1D subtype (Maruyama et al., 2011; Tuomi et al., 2014).

If not treated, insulin deficiency causes secretion of counter-regulatory hormones, and free fatty acids are released from the fat tissue. These fatty acids are transformed to ketones in the liver, causing blood to become acidic, which in turn, leads to a disturbance of the normal metabolic state. Eventually, ketoacidosis leads to severe unconsciousness and death. Ketoacidosis is therefore a severe and acute complication of insulin-dependent diabetes (Nyenwe & Kitabchi, 2016; Umpierrez & Korytkowski, 2016). However, for some patients that are unaware of the

underlying disease, ketoacidosis can be the first mark of diabetes and the diagnosis can be made after the first episode of ketoacidosis (Mallare et al., 2003).

Genetics plays a role in both T1D and T2D pathogenesis, also family history is a known risk factor (Hemminki et al., 2010a; B. Klein et al., 1996). Twin studies further back up the underlying genetic background of T1D. It had been shown that up to 43–65% of monozygotic twins are estimated to develop T1D if the other twin has been diagnosed with T1D (Hyttinen et al., 2003; Redondo et al., 2008). Familial diabetes accounts for 10% of all T1D (Hemminki et al., 2009) and history of first-degree family member having T1D is associated with markedly an increased risk for T1D (Weires et al., 2007). Also, T2D has a genetic contribution and patients with first-degree family members diagnosed with T2D have a two-fold risk for developing the disease themselves (Hemminki et al., 2010b; Weires et al., 2007).

Mutations in the human leukocyte antigen region (Ilonen et al., 2016) and some single-nucleotide polymorphisms (Klinker et al., 2010) are associated with an increased risk and onset of T1D. In Finland, one out of five patients with T1D are known to have the high-risk human leukocyte genotype (Ilonen et al., 2016). However, diabetes is a multifactorial and polygenic disease and environmental factors mainly affect the onset of diabetes (Deshpande et al., 2008; Hivert et al., 2011).

Although dietary habits are mainly involved in the onset of T2D due to insulin resistance, it is important to consider the effect of environmental factors related to the onset of T1D. Not all is known about the environmental factors and only a few have been identified. For example, pollution, psychological factors, and viral infections can play a role in the onset of diabetes (Eze et al., 2015; Hivert et al., 2011; Prigge et al., 2022; Pyykkönen et al., 2011; Quinn et al., 2021). Furthermore, the so-called hygiene hypothesis is a factor to be considered. Due to a more sanitized living environment, different immune-mediated disorders have risen in number, which in turn, can explain the increase of incidence of T1D (Bach & Chatenoud, 2012; D'Angeli et al., 2010).

2.1.3 Type 2 diabetes

Unlike T1D, which is usually diagnosed during childhood or early adulthood, and characterized by impaired insulin secretion, T2D is often diagnosed in the aged population. Moreover, in most cases, insulin secretion is normal at the beginning of the disease (Beck-Nielsen & Groop, 1994; Kahn, 1997). Whereas insulin

secretion might be normal or increased, the tissue sensitivity for insulin is decreased leading to elevated blood glucose levels and hyperglycemia (WHO, 2011).

After long-term exposure to dietary sugars and constantly needed insulin secretion, tissues become resistant to insulin. Lifestyle and dietary habits of patients, have a role in the pathogenesis and overweight is the most important risk factor for T2D, in addition to a sedentary lifestyle and inactivity (Sullivan et al., 2005). Therefore, dietary changes are important in the prevention and treatment of type 2 disease (Tuomilehto et al., 2001). Obese patients with T2D experiencing weight loss are known to have more beneficial glycemic control (Elsayed et al., 2023; Lindström et al., 2013). Even remission of diabetes is possible, further emphasizing the importance of proper weight control in patients with T2D (Elsayed et al., 2023).

When tissues become resistant to insulin, hyperglycemia continues, and the pancreatic secretion of insulin is increased. Over a time, pancreatic islets will gradually fail to produce more insulin resulting in insulin deficiency (Beck-Nielsen & Groop, 1994; Kahn, 1997). Usually, after the diagnosis of T2D, patients receive medication for insulin resistance in order to lower blood glucose levels (Kahn et al., 2006a). However, in the later stage also insulin replacement therapy may be needed to treat the underlying insulin deficiency (American Diabetes Association Professional Practice Committee et al., 2021).

Monogenic manifestations of diabetes are also known and currently 14 different genes covering 1–6% of all cases of diabetes have been identified (Delvecchio et al., 2020). These monogenic diabetic cases fall under the subtype maturity-onset diabetes of the young (MODY) when the diagnosis is confirmed with genetic testing. These patients are typically young (< 25 years) at the time of diagnosis and have a lack of autoantibodies and have a family history of diabetes which dates back several generations (Fajans & Bell, 2011). However, when MODY is caused by the de novo -mutation, it can be diagnosed without any prior family history (Fajans & Bell, 2011; Stanik et al., 2014).

These gene errors cause impaired insulin sensing and secretion, leading to insulin deficiency which is treated accordingly (Delvecchio et al., 2020). A great majority of all MODY cases are due to mutation in three genes, hepatocyte nuclear factor-1-alpha (HNF1A), glucokinase (GCK) and hepatocyte nuclear factor-4-alpha (HNF4A).

When compared to T1D, MODY can be treated with sulphonylureas to increase insulin secretion (Fajans & Bell, 2011). In Finland, a mutation in the glucokinase gene is the most common type of MODY; moreover, the prognosis is excellent, and

no treatment is needed due to slightly increased, mainly unchanged fasting glucose levels (Laakso, 2011).

A physiological increase in insulin resistance is observed during pregnancy. It is caused by placental hormones and rising blood glucose levels are classified as gestational diabetes mellitus (GDM) (Choudhury & Devi Rajeswari, 2021). The global prevalence of GDM estimated up to 13% and a global rise in the prevalence is estimated to stabilize as high as 16% at least in 2045 (Yuen et al., 2019). GDM is diagnosed with the OGT test and diagnostic levels for blood glucose at 0, 1 and 2 hours are ≥5.3, ≥10.0 and ≥8.6 mmol/l respectively according to Finnish Current Care Guidelines (Finnish Medical Society Duodecim, 2022).

2.2 Long-term effects of diabetes

2.2.1 Comorbidities and complications

At the onset of diabetes, hyperglycemia is present and at the very beginning of diabetes, it can even be asymptomatic. However, without effective treatment, hyperglycemia persists, and long-term complications will occur (DCCT 1993; UKPDS Group, 1998a). These complications and comorbidities are the main reason for diabetes caused burden for healthcare system and public expenditure (Gillies et al., 2008).

Complications that follow diabetes are well known and cause increased morbidity in patients diagnosed with diabetes. Microvascular complications affect small blood vessels, which in turn, can cause retinopathy, nephropathy, and neuropathy (DCCT, 1993). If this is not the case, macrovascular complications are mainly due to cardiovascular disease (CVD) (Khaw et al., 2004; Kuusisto et al., 1994). Major risk factors for diabetic complications include poor glycemic control with chronic hyperglycemia and long duration of diabetes (Fiorentino et al., 2017; Klein et al., 1988).

To prevent comorbidities, arterial hypertension and dyslipidemia should be effectively treated (Baigent et al., 2010; Perk et al., 2012). Conjointly, changes in lifestyle and dietary habits of the patient are necessary for adequate treatment of T2D. In some cases, a healthier diet and increased mobility can work as a sole treatment for hyperglycemia (Lean et al., 2018; Look AHEAD Research Group et al., 2013). Weight loss in patients with T2D is associated with improved glycemic control and may promote remission of diabetes (Elsayed et al., 2023; Lindström et

al., 2013). Other risk factors should also be considered; smoking cessation is part of the treatment of diabetes, not to mention the use of alcohol being addressed with patients (Emanuele et al., 1998; Willi et al., 2007).

2.2.2 Diabetes and the kidney

Diabetic kidney disease (DKD) is a common complication to the extent that approximately 20% of patients diagnosed with diabetes have nephropathy. Chronic hyperglycemia results in tissue hypoxia and oxidative stress, causing fibrosis and renal damage. Part of the pathophysiology is explained by the accumulation of advanced glycation end-products (AGEs) (Fiorentino et al., 2017; Vallon & Komers, 2011).

In a normoglycemic condition, no glucose or protein is secreted into the patient's urine. Due to nephropathy, microalbuminuria appears and can advance to macroalbuminuria, eventually progressing to severe nephropathy. It is worthwhile to acknowledge that DKD is not always progressive and with timely and effective treatment, normoalbuminuria is possible to be achieved (de Boer et al., 2011). Furthermore, kidney-protective medication for patients with diabetes is recommended, angiotensin-converting enzyme (ACE) inhibitors, angiotensin-II-receptor (ATR) blocker and sodium-glucose co-transporter 2 (SGLT2) inhibitors have favorable outcomes in renal function (Arry et al., 2001; Zelniker et al., 2019). DKD is a leading cause of end-stage kidney disease (ESKD) and approximately 50% of cases are due to DKD (Vallon & Komers, 2011). Treatment consists of lifelong dialysis; however, kidney transplantation is a valid treatment option despite limited availability of donated kidneys (Oniscu et al., 2005).

2.2.3 Macrovascular complications of diabetes

CVDs are a group of conditions that affect heart or blood vessels anywhere in the body. Common complications are myocardial infarction and cerebrovascular stroke due to coronary arterial and cerebrovascular disease, respectively. These conditions are important to recognize because of the increased morbidity in patients with diabetes. Especially in T2D, CVDs are common and globally approximately 32% of all patients with T2D have been diagnosed with CVD (Einarson et al., 2018). In a recent Finnish study, Status of kidney disease in T2D and heart failure in Finnish primary care, it was concluded that out of patients suffering from T2D whom were being treated in primary care, over 60% had a very high risk for CVD (Metsärinne

et al., 2022). Furthermore, patients with T1D are also at risk for CVDs, which should be considered in the treatment of these patients (Cleary et al., 2005; Harjutsalo et al., 2021).

In the prevention and treatment of CVDs, a multifactorial approach is needed. The best risk reduction is achieved with intensive glycemic control, in addition to treating other risk factors including arterial hypertension, dyslipidemia, and smoking cessation (Kuusisto et al., 1994; Rawshani et al., 2018). For secondary prevention, low-dose acetylsalicylic acid is recommended to prevent adverse effects of CVDs and death (Baigent et al., 2002).

For the treatment of hyperglycemia, medication decreasing the risk of cardiovascular complications is recommended. The golden standard for the treatment is metformin, which decreases macrovascular complications and is also safe to be used during pregnancy (Brand et al., 2022; Kahn et al., 2006b). To decrease morbidity and mortality associated with CVDs, medications including SGLT2 inhibitors and the glucagon-like peptide 1 (GLP-1) receptor antagonists are recommended (Kanie et al., 2021; Steiner, 2016).

2.2.4 Diabetes and the nervous system

When a patient suffers from diabetes, the nervous system is affected by chronic hyperglycemia. Diabetic neuropathy is further divided into subgroups according to the affected parts in the nervous system. Distal symmetric polyneuropathy has a progressive nature and can affect peripheral sensations and eventually interfere with walking. It is the most common type of diabetic neuropathy with a 30–50% prevalence among patients with diabetes (Dyck et al., 1993; Young et al., 1993).

Autonomic neuropathy causes complications in the autonomic nervous system. Therefore gastroparesis, enteropathies and postural hypotension may occur (DCCT, 1998). Distal polyneuropathy and autonomic neuropathy cause damage to multiple nerves, but in addition to this, diabetic neuropathy can appear as mononeuropathy, affecting only an individual cranial or peripheral nerve (Dyck et al., 1993; DCCT, 1998).

Although neuropathies more commonly occur in the later stages of diabetes, distal polyneuropathies can be one of the very first complications of diabetes in its early stages. Frequently, the duration of diabetes and the level of hyperglycemia works as a risk factor for diabetic neuropathies (Pirart, 1978; Young et al., 1993); moreover, poorly treated arterial hypertension and dyslipidemia can affect the onset of neuropathy (Dyck et al., 1993; Tesfaye et al., 2005).

The pathophysiology of diabetic neuropathy is affected by hyperglycemia induced activation of cellular metabolism, which in turn, leads to formation of reactive oxygen species (ROS), consequently damaging neural cells (Callaghan et al., 2012; Feldman et al., 2017). Multiple metabolic pathways are affected. However, hyperglycemia is not solely responsible for the pathogenesis of neuropathy (Feldman et al., 2017). The damage in diabetic neuropathy is irreversible and causes excessive morbidity. Identifying patients with diabetic neuropathies is crucial to prevent the progression of neuropathy (Callaghan et al., 2012).

Diabetes is also associated with neurocognitive dysfunction, where the level of hyperglycemia illustrates one of the risk factors (Kodl & Seaquist, 2008). Memory problems decreased information processing and psychomotor deficiency are linked with diabetic cognitive dysfunction alongside visuoconstruction (Kodl & Seaquist, 2008; Ryan et al., 2003; Wessels et al., 2007). A recent meta-analysis showed a positive correlation between DR and cognitive dysfunction, with a conclusion that the state of DR is one of the tools with which it is possible to identify patients with potential cognitive dysfunction (Wu et al., 2022).

2.2.5 Diabetes and non-retinal ocular complications

Ocular motor nerve palsy

The extraocular muscles are responsible for the positioning and movement of the eye. The innervation of these muscles is derived from the cranial nerves III, IV and VI named oculomotorius, trochlear and abducens nerve, respectively. In addition, the oculomotor nerve (III) innervates the levator palpebrae superioris muscle responsible for the function of the upper eyelid and the pupillary sphincter constricting the pupil (Kung & van Stavern, 2015).

Diabetic mononeuropathies can cause isolated cranial nerve palsy responsible for the eye movements, upper eyelid and pupil constriction innervation. Clinical features of isolated cranial nerve palsy may consist of diplopia, ptosis and pupillary dysfunction, depending on the affected nerve (Brown et al., 1982; Watanabe et al., 1990). In some cases, orbital pain may be present (Wilker et al., 2009).

The isolated cranial nerve palsy is due to microvascular ischemia and no invasive treatment is needed. Arterial hypertension increases the risk of diabetic mononeuropathy, giving emphasis on multifactorial treatment and prevention. The

prognosis of a symptomatic isolated cranial nerve palsy is excellent and total recovery can be expected, although recurrences may occur (Sanders et al., 2002).

Diabetic keratopathy

The cornea is responsible for ocular surface maintenance and works as a transparent tissue with the required optical power necessary for visual function. As an avascular tissue, corneal metabolism is dependent on the aqueous humor in the anterior chamber and the exterior tear film. The prevalence of diabetic keratopathy is 47–70% (Ljubimov, 2017; Manaviat et al., 2008; Schultz et al., 1981).

Hyperglycemia causes changes in the lacrimal gland due to neural damage, and changes in the tear film and decreased tear secretion are often observed (Cousen et al., 2007; Eissa et al., 2016). Hence, diabetes can cause severe dry eye disease aggravated by a decreased blinking rate (Eissa et al., 2016).

In the diabetic milieu, the aqueous humour becomes hyperglycemic leading to an abnormal metabolism and accumulation of ROSs and AGEs. These end products cause the dysfunction of diabetic cornea, often leading to decreased corneal sensitivity and impaired wound healing due to impaired epithelial function (Rogell, 1980; Yu et al., 2022). Delayed wound healing causes corneal neurotrophic ulcers and persistent epithelial defects (Hyndiuk et al., 1977; Yu et al., 2022).

The treatment of diabetic keratopathy consists of traditional methods of eye lubrication with artificial tears, infection prophylaxis in case of epithelial defects with antibiotic drops, therapeutic contact lenses or temporary tarsorrhaphy (Yeung & Dwarakanathan, 2021).

Diabetic changes in the lens

Tissues in the lens are not sensitive to insulin, hence, during hyperglycemia the polyol pathway is activated. One of the symptoms of undiagnosed diabetes or poor glycemic control is fluctuating vision. These transient refractive changes are dependent on blood glucose levels (Lin et al., 2009; Mehdizadeh & Nowroozzadeh, 2010). After hyperglycemia passes, a hyperopic shift occurs and patients may become symptomatic with transient blurry vision (Lin et al., 2009; Okamoto et al., 2000).

Glucose is reduced to sorbitol by aldose reductase and the accumulation of sorbitol causes osmotic damage and swelling (Bron et al., 1993). This is postulated

in the pathophysiology of transient refractive changes and further diabetic cataract due to breakage of lens fibers secondary to swelling (A. Y. W. Lee et al., 1995).

Patients with diabetes are at a higher risk for cataract, lens opacification and deterioration of vision (Klein et al., 1985). Incidence for cortical cataract and subcapsular cataract were 8.8% and 8.1%, respectively, in a 4-year follow-up (Srinivasan et al., 2017). In another population-based prospective cohort study, the overall incidence of nuclear cataract was 9% and diabetes increased the risk almost 2 times higher (Leske et al., 2002). The cumulative 10-year incidence of cataract surgery was 8% and 25% in patients with T1D and T2D, respectively (Klein et al., 1995). Cataract surgery is a common procedure with good postoperative visual outcomes, although patients with diabetes have an increased risk for postoperative macular edema (Baker et al., 2013).

Diabetic papillopathy

Anterior ischemic optic neuropathy (AION) involves the anterior part of the optic nerve head and diabetes may appear as diabetic papillopathy (Barr et al., 1980; Hayreh & Zahoruk, 1981). Both T1D and T2D may predispose to diabetic papillopathy, however, the level of glycemic control does not seem to play a role in the pathogenesis nor does the duration of diabetes itself (Barr et al., 1980; Bayraktar et al., 2002). Up to 3% of patients with diabetes have been estimated to be affected by diabetic papillopathy (Hua et al., 2019).

Microvascular transient ischemia in the optic nerve head causes optic disc edema and symptomatic vision loss (Hayreh & Vaphiades, 2002; Hayreh & Zahoruk, 1981). Although optic disc edema may be bilateral, usually only one eye is symptomatic. Visual acuity does not markedly change, and mild distortion of vision may be present, albeit diabetic papillopathy may be an incidental finding (Bayraktar et al., 2002; Ostri et al., 2010). In the visual field, small enlargement of the blind spot and defects may be observed (Barr et al., 1980). In the case of bilateral optic disc edema, papilledema due to increased intracranial pressure is to be excluded by neuroimaging.

Spontaneous resolution of diabetic papillopathy occurs within several months and the visual prognosis is affected by underlying DME and PDR (Ho et al., 1995; Regillo et al., 1995). No large and high-quality studies are available considering the treatment of diabetic papillopathy. Administration of steroid therapy may be efficient, but the evidence is somewhat controversial (Al-Haddad et al., 2004; Hayreh & Zimmerman, 2007). After the resolution of diabetic papillopathy, mild

pallor of the optic disc may be present without significant papillary atrophy (Barr et al., 1980; Hayreh & Zahoruk, 1981). A schematic overview of diabetic ocular complications is presented in Figure 2 below.

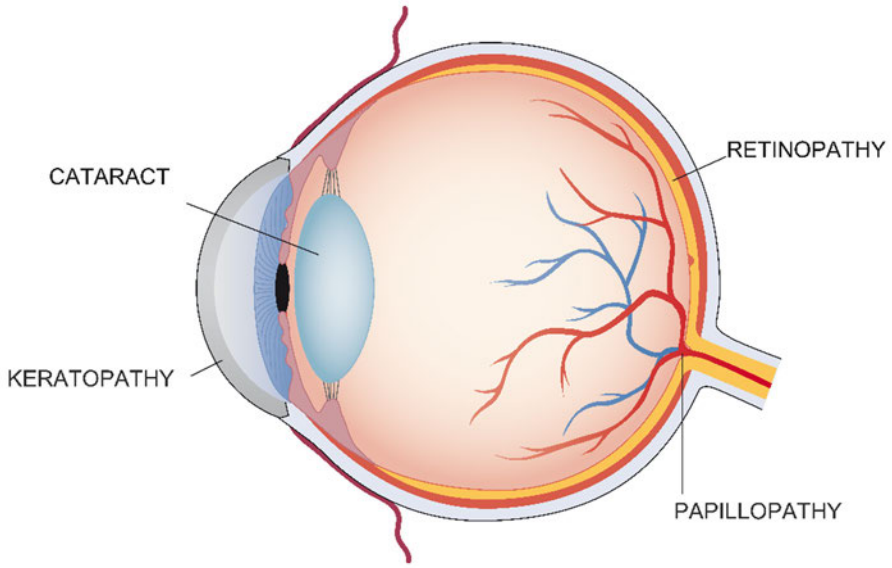


Fig. 2. Ocular complications observed in patients diagnosed with diabetes. In addition, extra-ocular muscles are affected by diabetes (not shown in the picture) (Modified with permission © 2023 The Finnish Medical Society Duodecim and Duodecim Publishing Company.

3 Diabetic retinopathy

3.1 Epidemiology

In 2021, 537 million people were estimated to have diabetes (Sun et al., 2022) and a recent meta-analysis concluded that over one out of five (22%) patients with diabetes had DR in 2020. The population with DR is increasing mainly due to growing number of patients with diabetes (Teo et al., 2021).

3.1.1 Prevalence and progression of diabetic retinopathy

Globally the prevalence of DR varies, being highest in Africa (36%), and lowest in South and Central America (13%) (Teo et al., 2021). Previous studies have reported a 29% prevalence for DR in the United States (Zhang et al., 2010) and a 19–26% prevalence in Europe (Li et al., 2020; Teo et al. 2021).

The prevalence of DR is higher among patients with T1D (54–77%) than in patients with T2D (25–52%) (Li et al., 2020; Yau et al., 2012) and the duration of diabetes significantly increases the prevalence of DR up to 94–98% in patients with T1D (Hautala et al., 2014; Klein et al., 1984a).

Patients with diabetes have a 4% prevalence for DME globally (Teo et al., 2021) and the prevalence with T1D patients is estimated to be 11–18% depending on age (Warwick et al., 2017). However, the prevalence of DME was 27% in patients with T2D (Romero-Aroca et al., 2009).

According to the Wisconsin epidemiologic study of DR (WESDR), the prevalence of DR varied depending on the age of the patients (Klein et al., 1984b, 1984a). Prevalence rates are summarized in Table 1. In a Finnish population-based study of patients with T1D under 17 years of age by Kubin et al, the prevalence was 87% and 13% for no DR and for mild DR, respectively (Kubin et al., 2011). In another Finnish study, the Oulu cohort study of DR, after more than 17 years of T1D at the age of 22–35, the prevalence was 6%, 17%, 30%, 11% and 38% for no retinopathy, mild, moderate, or severe non-PDR and PDR, respectively (Hautala et al., 2014).

Table 1. The prevalence of diabetic retinopathy according to the severity of diabetic retinopathy and age at onset of diabetes in the Wisconsin Epidemiologic study in diabetic retinopathy (Klein et al., 1984a, 1984b).

Severity	Prevalence (%)		
	Under 30 years[1]	Over 30 years[2]	
		Treated with insulin	Treated without insulin
No retinopathy	29	38	64
Non-proliferative diabetic retinopathy			
Mild	18	17	18
Moderate	12	13	8
Severe	17	21	7
Proliferative diabetic retinopathy	23	11	3

[1] Klein, R., Klein, B. E. K., Moss, S. E., Davis, M. D., & Demets, D. L. (1984a). The Wisconsin Epidemiologic Study of Diabetic Retinopathy: II. Prevalence and Risk of Diabetic Retinopathy When Age at Diagnosis Is Less Than 30 Years. Archives of Ophthalmology, 102(4), 520–526.

[2] Klein, R., Klein, B. E. K., Moss, S. E., Davis, M. D., & Demets, D. L. (1984b). The Wisconsin Epidemiologic Study of Diabetic Retinopathy: III. Prevalence and Risk of Diabetic Retinopathy When Age at Diagnosis Is 30 or More Years. Archives of Ophthalmology, 102(4), 527–532.

DR has a progressive nature over time, when the duration of diabetes increases, although improvement may occur (Klein et al., 2008). The risk of progression to PDR after one year is 5%, 12–27% and 52% for mild, moderate, and severe non-PDR, respectively (Aiello, 2003).

3.1.2 Risk factors

To measure the glycemic control, glycated hemoglobin (HbA1c) is obtained. HbA1c level of 48 mmol/mol is used to diagnose diabetes (WHO, 2011) and good glycemic control for prevention of DR is lower than 53 mmol/mol near the euglycemia according to Finnish Medical Society Duodecim Current Care Guidelines (Finnish Medical Society Duodecim, 2020).

Since glycemic control is a modifiable risk factor that can be affected by adequate treatment, it is important to provide emphasis on the treatment of diabetes to achieve satisfactory glycemic control (Hautala et al., 2014; DCCT, 1993; UKPDS Group, 1998a; Zhang et al., 2001).

It is worthwhile to recognize that the duration of diabetes has a great impact on DR and should be considered as one of the primary risk factors (Klein et al., 1984b; Zhang et al., 2001; Zhang et al., 2010). Furthermore, patients that have had the diagnosis of diabetes before puberty, have also an increased risk of DR (Olsen et al., 2004; Porta et al., 2001) (Table 2).

Table 2. Risk factors for development and progression of diabetic retinopathy.

Modifiable risk factors	Non-modifiable risk factors
Glycemic control	Duration of diabetes
Arterial hypertension	Onset of diabetes before puberty
Dyslipidemia	Low levels of C-peptide secretion
Abdominal obesity (waist-to-hip ratio)	Other microvascular complications (nephropathy, neuropathy)
Obstructive sleep apnea	Pregnancy

Other modifiable risk factors including arterial hypertension and dyslipidemia should be treated accordingly, keeping in mind the comorbidities and macrovascular complications (Chung et al., 2017; Klein et al., 1984b; Zhang et al., 2010). In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Eye Study the treatment of arterial hypertension did not influence DR progression but treatment of dyslipidemia with fenofibrate had favorable outcomes (Chew et al., 2014). In addition, abdominal obesity with a higher waist-to-hip ratio is linked to progression of DR to PDR (Porta et al., 2001; van Leiden et al., 2003) rather than just the body mass index (BMI) (Klein et al., 1984b; van Leiden et al., 2003).

Non-modifiable risk factors include other microvascular complications of diabetes besides retinopathy. Nephropathy (de Boer et al., 2011; Klein et al., 1984b) and neuropathy (Li et al., 2020) have been proven to be additional independent risk factors of DR. Furthermore, diabetes during pregnancy can exacerbate DR (Finnish Medical Society Duodecim, 2022). The progression of DR during pregnancy is associated with the baseline DR severity at the time of conception; patients with moderate to severe DR were more likely to develop PDR (Chew et al., 1995; Loukovaara et al., 2003). Although pregnancy can exacerbate DR, no long-term complications have been observed (DCCT, 2000; Kaaja & Loukovaara, 2007).

Besides proper glycemic control, treatment of arterial hypertension and lipid-lowering therapy, further protective factors against DR and its progression have been found. Actions against a sedentary lifestyle in terms of increased physical activity have been associated with ameliorating DR (Praidou et al., 2017).

Obstructive sleep apnea is also an independent risk factor for DR, furthermore, treatment with a continuous positive airway pressure device has been associated with decreased progression of DR (Altaf et al., 2017). In the DCCT study, even remaining pancreatic beta-cell activity and endogenous insulin production were related to a decreased incidence of DR (Steffes et al., 2003).

3.1.3 Visual impairment due to diabetic retinopathy

DR is one of the leading causes of new-onset blindness accounting for 3% of all cases of blindness globally (Leasher et al., 2016) and is responsible for vision-related functional burden with a 49% prevalence in patients with severe non-PDR or PDR (Willis et al., 2017). The prevalence of diabetes caused blindness has increased 15% globally and 45% in Southeast Asia throughout 1990–2020, however, in high income countries there is a declining trend with a 14% decrease in the prevalence of DR (Bourne et al., 2021).

For patients with T1D, PDR is the leading cause of visual loss. In contrast to this, patients with T2D result in vision loss more frequently due to DME (Cheung et al., 2010). In addition to visual impairment and blindness, PDR is associated with increased mortality (Klein et al., 2008).

A recent study by Purola et al. pooled data from the Finnish Registry of Visual Impairment to analyze visual impairment due to DR. Despite the increasing number of patients receiving treatment for diabetes, the visual impairment incidence decreased 102 to 6 per 100 000 and 40 to 7 per 100 000 in non-PDR versus PDR, respectively. In addition, the severity of visual impairment decreased during the 40-year period and the age of patients during the onset of visual impairment has increased (Purola et al., 2022). In Finland, efficient treatment of diabetes and DR has led to a decline in severe non-PDR in the past decades (Kytö et al., 2011).

3.1.4 Health-related quality of life

Diabetes is a chronic condition and requires active treatment. DR has been associated with increased diabetes-related stress alongside inadequate glycemic control and diabetes therapy regimen (Bhaskara et al., 2022). Diabetes-related comorbidities and impaired health-related quality of life (HRQoL) are also risk factors for loss to follow-up in PDR-treatment resulting in further vision loss (Abdelmotaal et al., 2020). Patients with diabetes have been reported to maintain

normal HRQoL, even though longer duration of diabetes has a deteriorating effect (Schanner et al., 2016).

Impaired HRQoL in patients with DR has been reported to result from poor self-reported visual functioning and overall well-being. Limitations include difficulties in reading and walking, furthermore, DR can significantly affect the ability to work and drive. The impaired HRQoL is further aggravated by an increase in DR severity (Cooper et al., 2020)

Health-related quality of life (HRQoL) is decreased by DR and is associated with severity of DR (Mazhar et al., 2011). Oulu cohort study of DR revealed that PDR is associated with lower education and 26% of young adults were unemployed or retired early (Hannula et al., 2015).

In another study from the same cohort, HRQoL was impaired in patients with PDR in addition to being equal to healthy controls in mild to severe non-PDR (Hannula et al., 2014). Although treatment of DR may be time-consuming, patients are willing to participate in treatment and laser photocoagulation has been reported to improve overall HRQoL (Sharma et al., 2005).

3.2 Pathophysiology

3.2.1 Hyperglycemia induced changes in glucose metabolism

DR is a multifactorial disease composed of several pathophysiological mechanisms. Hyperglycemia is the main factor in the pathogenesis of diabetes related complications (DCCT, 1993; UKPDS Group, 1998b).

An excessive amount of glucose causes metabolism in alternative pathways, resulting in production of ROSs as a resulting product. These ROSs mediate damage to the delicate structure of the retina. Although the exact pathophysiology of DR is yet to be studied, several metabolic pathways affecting anatomical and physiological changes in the retina and the surrounding tissues have been described (Figure 3).

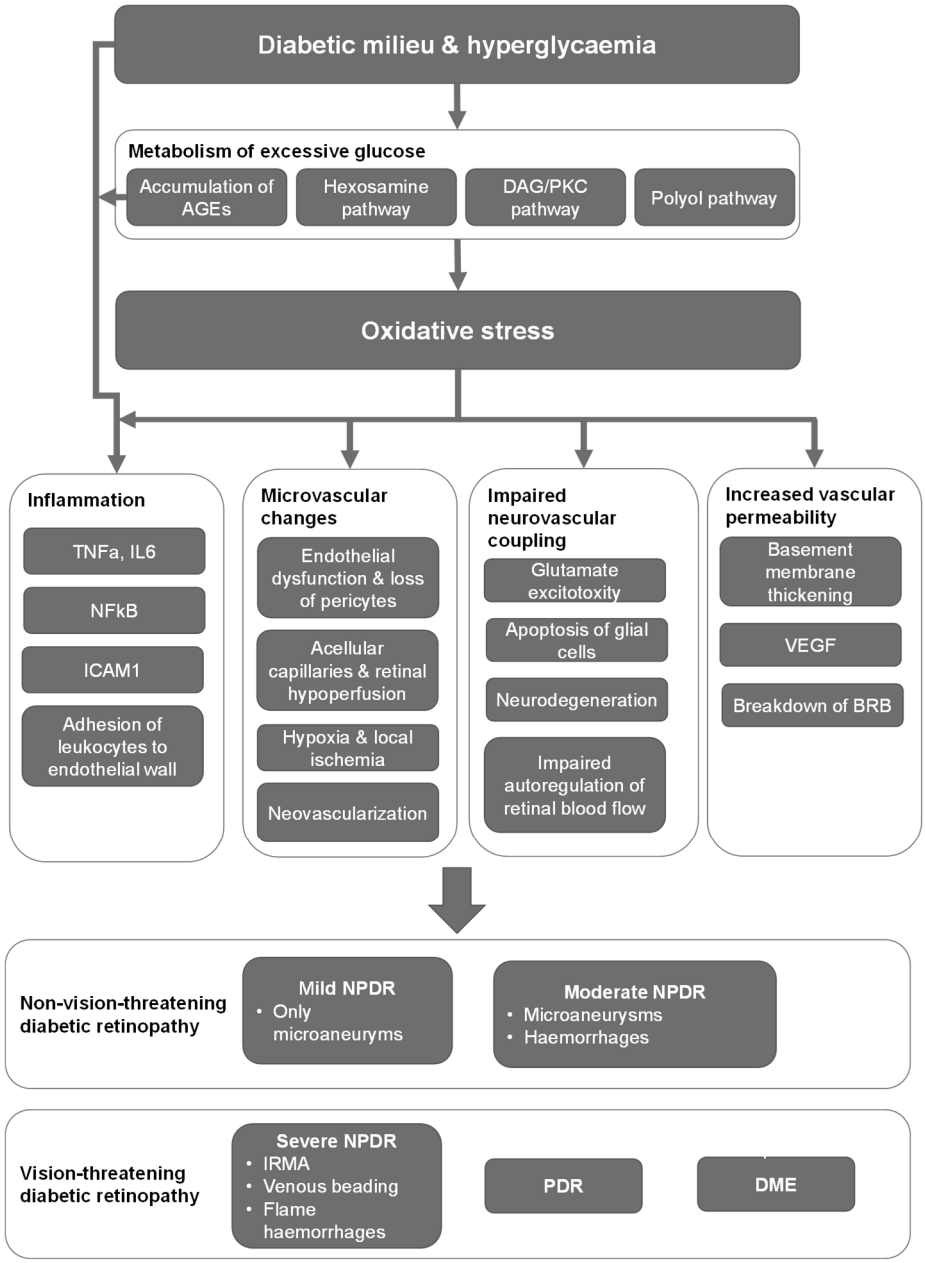


Fig. 3. Pathophysiology of diabetic retinopathy due to diabetes and chronic hyperglycemia.

Glucose is the main substrate of energy metabolism. In the process of glycolysis, glucose is converted to pyruvate for the citric acid cycle and further energy production, in other words for the production of adenosine triphosphate (ATP) (Kaneto et al., 2001). In the diabetic milieu, the first enzyme, hexokinase, converting glucose to glucose-6-phosphate (G6P) is oversaturated and the excess amount of glucose is metabolized in both the polyol pathway and hexosamine pathway.

Hexosamine pathway

Hyperglycemia causes increased flux through the hexosamine pathway, and eventually results in increasing oxidative stress (Du et al., 2003; Kaneto et al., 2001). The hexosamine pathway shares the two first steps of glycolysis and in hyperglycemic conditions, the enzyme responsible for limiting the hexosamine pathway, GFAT (glutamine: fructose-6-phosphate aminotransferase) is upregulated resulting in an increased flux. As a result, O-linked β-N-acetylglucosamine (O-GlcNAc) needed for post-translational modification of proteins is formed (Semba et al., 2014). Abnormal O-GlcNAc modification due to hyperglycemic condition is linked to apoptosis of retinal cells, including neural cells and pericytes (Gurel & Sheibani, 2018). Furthermore, O-ClcNAc modification is associated with pathogenesis of diabetogenesis and insulin resistance (Semba et al., 2014).

Polyol pathway

An abundant availability of glucose upregulates the polyol pathway responsible for the sorbitol production via the aldose reductase enzyme and further to fructose via the sorbitol dehydrogenase enzyme (Dagher et al., 2004). Sorbitol is disputed to cause osmotic damage as it accumulates inside cells due to cellular membrane impermeability (Lee et al., 1995).

On the other hand, fructose metabolism leads to the formation of AGEs. It is worthwhile to acknowledge that the production of sorbitol requires a coenzyme, nicotinamide adenine dinucleotide phosphate (NAPDH), and in euglycemic conditions NADPH prevents formation of oxygen radicals, hence the decreased availability of NADPH promotes oxidative stress (Nyengaard et al., 2004; Steinmetz et al., 1973).

Protein kinase C

Hyperglycemia is responsible for diacylglycerol (DAG) de-novo synthesis, which in turn activates protein kinase C (PKC) (Shiba et al., 1993). This DAG-PKC pathway causes several metabolic changes resulting in DR which is described in Table 3 (Idris & Donnelly, 2006; Way et al., 2001).

Table 3. The role of PKC activation in diabetic retinopathy.

Target	Mechanism
Vessels	Increased vascular permeability
	Neovascularization, VEGF upregulation
	Decreased retinal blood flow
	Thickening of capillary basement membranes by increased extra-cellular matrix production
Leukocytes	Promoting leukocyte adhesion
Cell metabolism	Increased amount of reactive oxygen species

PKC, protein kinase C; VEGF, vascular-endothelial growth factor

Accumulation of advanced glycation end products

AGEs are irreversible end-products of the non-enzymatic glycation of glucose. Hyperglycemia promotes increased glycation and accumulation of AGEs (Brownlee, 1994). In the capillary basement membranes AGEs cause increased collagen cross-linking, resulting in the thickening of basement membrane. AGEs can cause basement membrane thickening also by binding proteins into them, which in turn, promotes loss of pericytes (Brownlee, 1994; Hammes et al., 1991).

Some endothelial cells and macrophages have AGE receptors, and binding AGEs can cause the activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NFkB). The release of cytokines, endothelial dysfunction and coagulative activity are due to activation of NFkB contributing to DR pathogenesis and formation of ROSs (Hammes et al., 1991; Yamagishi et al., 2008). NFkB can also be activated due to PKC activation (Way et al., 2001).

3.2.2 Low-grade inflammation behind diabetic retinopathy

Patients with diabetes suffer from a low-grade inflammation which affects the retina (Tang & Kern, 2011). Inflammation has been argued to be part of the pathophysiology of diabetes and its complications for decades (Powell & Field,

1964; Tsalamandris et al., 2019). Receptors in the cell membrane can transduce inflammatory signals inside cells, for example, receptors of AGEs can activate proinflammatory NFkB (Tobon-Velasco et al., 2014). In addition, proinflammatory cytokines, such as interferons, interleukin-1-beta (IL-1β) and TNF-α, can trigger the inflammation process by activating NFkB (Li et al., 2021; Tang & Kern, 2011; Tsalamandris et al., 2019).

Inflammation in retinal capillary endothelial cells (ECs) is associated with vaso-occlusion resulting from the accumulation of leucocytes and apoptosis of ECs (Forrester et al., 2020). Inflammation promotes expression of intracellular adhesion molecule-1 (ICAM-1) and therefore adhesion of leukocytes to vascular endothelium (Lu et al., 1999; Zhang et al., 2022). A pro-inflammatory shift during VH has also been observed (Zeiner et al., 2019).

Leukocyte adhesion and transmigration induce the breakdown of the blood-retinal barrier (BRB) leading to vascular leakage (Noda et al., 2012). In addition, VEFG has been shown to increase ICAM-1 expression and works as an inflammation mediating agent (Forrester et al., 2020; Lu et al., 1999).

3.2.3 Changes in retinal function

DR has an asymptomatic nature, and only the late changes cause notable disturbance to the field of vision (ETDRS Research Group, 1991a). For further reading, see chapter 3.4 about the severity scales of DR.

DR has severe vision-threatening endpoints, although neural dysfunction in mild DR may be presented as visual functional changes. Impaired color sensitivity and microperimetry without decreased visual acuity is observed in patients with mild DR (McAnany et al., 2020). Stereopsis has been shown to be altered in patients with diabetes as well as in patients with no or mild DR compared to healthy subjects (Faraji et al., 2020). In no or mild DR, changes in electroretinogram and short-wavelength automated perimetry can be observed (Han et al., 2004) in addition to impaired dark adaptation (Drasdo et al., 2002).

Anatomical changes in the retina can be observed with Optical Coherence Tomography (OCT) (Huru et al., 2021; van Dijk et al., 2012). The thinning of retinal layers due to diabetes combined with mild DR is observed both in T1D and T2D patients as an early sign of diabetic neural damage (van Dijk et al., 2009, 2012). In a study from the Northern Finland Birth Cohort, neurodegenerative retinal changes were also observed in prediabetic patients, whose macula was significantly thinner compared to subjects with normal glucose metabolism (Huru et al., 2021).

Neurovascular coupling

The blood-retinal barrier (BRB) is responsible for the function of the retina by regulating the neurochemical environment. This connection is recognized as the neurovascular unit (Gardner & Davila, 2017). Endothelial cell tight junctions and pericytes are required for proper formation of the BRB, where neurovascular coupling occurs with surrounding neurons, microglia and astrocytes (Gardner & Davila, 2017; Spencer et al., 2020).

Hyperglycemia causes oxidative stress and inflammation eventually leading to apoptosis of neurons, and dysfunction of supporting microglia and astrocytes (Arroba & Valverde, 2017; Gardner & Davila, 2017). Microglia can further exacerbate inflammation by secretion of inflammatory cytokines including TNF-α and IL-1β (Abcouwer, 2017). Incidentally impaired glutamate metabolism and accumulation of extracellular glutamate causes glutamate excitotoxicity, a possible mechanism of retinal cell apoptosis (Barber et al., 2011).

Retinal blood flow is autoregulated due to the lack of autonomic innervation by neurovascular interactions and is impaired in patients with diabetes (Simó et al., 2018). The impaired autoregulation is present in patients with T1D even without DR and abnormal electroretinogram responses can be observed (Mandecka et al., 2009). Loss of retinal blood flow autoregulation further exacerbates the ischemia and hypoxemic conditions (Pournaras et al., 2008).

Microvascular changes

The first detectable microvascular changes in the retina are microaneurysms and small hemorrhages. The formation of microaneurysms is often thought to be related to elevated capillary pressure leading to the stretching of capillary walls with epithelial dysfunction and loss of pericytes (Gardiner et al., 2007).

Microaneurysms are saccular outpouchings of retinal capillaries and appear as small red dots in fundus photographs that are detectable in biomicroscopy (Curtis et al., 2009). Likewise, small intraretinal hemorrhages, so called dot and blot hemorrhages, can appear as small red dots which are slightly larger than microaneurysms (Garner, 1993; Tang & Kern, 2011). Hemorrhages alongside the ganglion nerve fiber layer appear horizontally and are referred to as flame hemorrhages (Kaur & Taylor, 1990).

The impaired BRB leads to excess fluid in the retina and development of DME (Idris & Donnelly, 2006). Leakage from retinal capillaries can leave hard

lipoprotein deposits in the inner retina, where these deposits called hard exudates, appear as small and yellow lesions in fundus examination (Otani & Kishi, 2001). In the Early Treatment Diabetic Retinopathy Study (ETDRS) dyslipidemia was associated with the formation of hard exudates and the decrease of serum lipid levels reduced the number of hard exudates (Chew et al., 1996).

Retinal hypoxia

Retinal microthrombosis due to leukocyte adhesion can cause leakage from the retinal capillaries and capillary occlusion (Tang & Kern, 2011). Retinal ischemia resulting from capillary occlusion leads to formation of cotton-wool spots (CWSs) characterized by a pale and feathery edged appearance visible in ophthalmological exams up to 8–12 months (Kohner et al., 1969). It is disputed if CWSs are due to retinal nerve fiber layer infarction or whether they are purely a sentinel of the underlying ischemic condition (McLeod, 2005).

Structural microvascular changes increase in accordance with the severity of the DR. The occurrence of intra-retinal microvascular abnormalities (IRMA) is a hallmark of severe non-PDR (Wilkinson et al., 2003a). After capillary occlusion, new shunt vessels and recanalization may occur in the ischemic retina, creating convoluted intraretinal IRMA vessels (Muraoka & Shimizu, 1984; Shimouchi et al., 2020).

In addition to IRMAs, in severe non-PDR, venous beading in terms of variation of venous caliber due to extensive retinal ischemia can occasionally be observed (Wilkinson et al., 2003a). The presence of both IRMAs and venous beading predicts the progression of DR to PDR (ETDRS Research Group, 1991b; Lee et al., 2017).

Endothelial cell dysfunction, inflammation, and adhesion of leukocytes with vascular hypoperfusion leads to local ischemia (Li et al., 2021; Zhang et al., 2022). In this hypoxic condition, VEGF is upregulated, and eventually retinal neovascularization occurs as DR progresses to its proliferative stage (Aiello et al., 1994; Idris & Donnelly, 2006). As neovascularization occurs, fibrous proliferation initiates (Davis, 1965; Faulborn & Bowald, 1985; Roy et al., 2016), the uncontrolled growth of fibrous tissues ultimately causes vitreoretinal adhesions, which can cause tractional retinal detachment, consecutively leading to hemorrhages from the neovascularized vessels (Roy et al., 2016).

3.3 Classification

DR can be classified based on anatomical findings and severity in accordance with probability of progression and clinical relevance (Wilkinson et al., 2003b; Wong et al., 2018;) (Figure 4).

Non-vision threatening DR (NVTDR) describes non-PDR stages from mild to moderate. These changes are marks of retinal damage due to DR, however, without immediate threat to vision (Finnish Medical Society Duodecim, 2014; Wilkinson et al., 2003b). Mild DR is characterized by microaneurysms which are the first detectable changes visible in DR (Curtis et al., 2009). Changes observed in moderate DR include retinal dot and blot hemorrhages in addition to flame hemorrhages, CWSs and hard exudates (Curtis et al., 2009; Garner, 1993; Kaur & Taylor, 1990; Otani & Kishi, 2001).

<table>
<tr><th>Diagnosis</th><th>Severity</th><th>Clinical relevance</th></tr>
<tr><td colspan="3">No diabetic retinopathy</td></tr>
<tr><td rowspan="3">Non-proliferative diabetic retinopathy</td><td>Mild diabetic retinopathy</td><td rowspan="2">Non-vision threatening diabetic retinopathy</td></tr>
<tr><td>Moderate diabetic retinopathy</td></tr>
<tr><td>Severe diabetic retinopathy</td><td rowspan="3">Vision threatening diabetic retinopathy</td></tr>
<tr><td colspan="2">Proliferative diabetic retinopathy</td></tr>
<tr><td colspan="2">Diabetic macular oedema</td></tr>
</table>

Fig. 4. Classification of diabetic retinopathy (Wilkinson et al., 2003a).

Vision-threatening stages of DR are severe non-PDR, PDR, and DME. In severe DR, the so called 4–2–1 rule is applied. Severe DR is classified as vision-threatening due to a markedly increased risk of progression to PDR (ETDRS Research Group, 1991b). One of the following 4–2–1 rule findings is used to define

severe DR: over 20 hemorrhages in every quadrant, venous beading in two quadrants or IRMAs in one quadrant without the presence of neovascularization. PDR includes neovascularization, and eventually preretinal or intravitreal hemorrhages, retinal tractional detachment and fibrovascular changes can occur (Finnish Medical Society Duodecim, 2014; Wilkinson et al., 2003b). DME can be present at any stage of DR with or without significant changes. In the presence of CI-DME, vision often becomes deteriorated, and DME is therefore classified as a vision-threatening stage of DR (Idris & Donnelly, 2006; Virgili et al., 2018).

3.4 Imaging and screening of diabetic retinopathy

Patients with diabetes are at a high risk for DR and are therefore screened to detect possible retinal changes (Hautala et al., 2014; Wong et al., 2018). The International Council of Ophthalmology has published guidelines for DR screening (Wong et al., 2018), whilst the management and screening of DR in Finland is carried out according to the Current Care Guidelines (Finnish Medical Society Duodecim, 2014) (Table 4).

Table 4. Diabetic retinopathy screening program based on The Finnish Medical Society Duodecim Current Care Guidelines (Finnish Medical Society Duodecim, 2014).

Diabetes type	Screening interval	
	No diabetic retinopathy	After diabetic retinopathy onset[1]
Type 1 diabetes	Every 2 years[2]	Every year
Type 2 diabetes	Every 3 years	Every 2 years (mild to moderate changes without DME) Every year (severe to PDR or in the presence of DME)
Patients with diabetes during pregnancy	When planning to become pregnant or early stage of pregnancy	
Gestational diabetes	No screening recommended	

DME, diabetic macular edema; PDR, proliferative diabetic retinopathy

[1]Screening according to the guidelines or more frequently, if necessary, based on clinical evaluation

[2]Screening begins at 10 years of age, if younger, the screening is postponed

In Oulu University Hospital District, the screening of DR is accomplished with mydriatic retinal fundus photography in the primary health care unit or mobile eye unit in rural areas (Hautala et al., 2009) (Figure 5). A table-top fundus camera is normally used. However, in a recent study, the performance of handheld fundus

camera was evaluated as sufficient for DR screening, for example in low-resource settings (Kubin et al., 2021). DR screening requires a lot of resources in order to be carried out properly (Savolainen & Lee, 1982). Therefore, DR screening should be in line with available resources for the screening and treatment (Hautala et al., 2014; Wong et al., 2018).

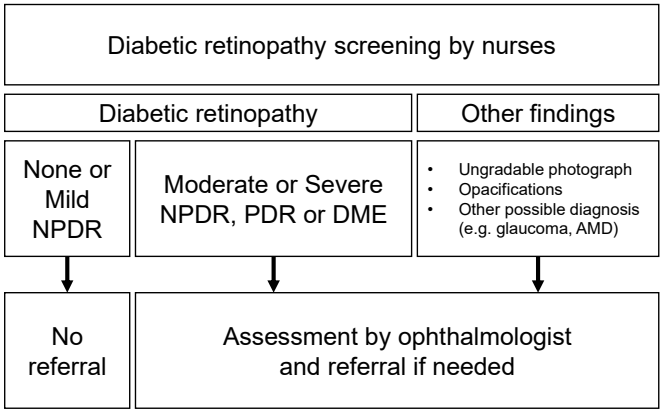


Fig. 5. Diabetic retinopathy screening protocol in Oulu University Hospital.

The use of only mydriatic fundus photography has been evaluated to be a sufficient tool in DR screening (Hutchinson et al., 2000) since it has been noted that mydriasis improves the quality of fundus photography and reduces the number of ungradable photographs from 26% to 5% (Murgatroyd et al., 2004). The usage of at least two 45-degree field fundus photographs (macular and nasal) in screening of DR is required (Aldington et al., 1995; Finnish Medical Society Duodecim, 2014). Conditions, such as cataract or dense VH can prevent the usage of some imaging techniques including fundus photography and OCT. In these cases, ophthalmologic ultrasonography can be used to evaluate whether VH is present (Lahham et al., 2019; Rabinowitz et al., 2004) and if retinal detachment has occurred (Lahham et al., 2019).

OCT is superior to fundus photography and slit-lamp examination when examining macular conditions. CI-DME is primarily defined based on the findings from OCT (Wong et al., 2018). However, the sole use of central retinal thickness (CRT) measured by OCT is not a reliable outcome measure when evaluating the status of DME, hence individual clinical evaluation is needed (Virgili et al., 2015).

The imaging of retinal circulation and vasculature in different phases of circulation is possible with fluorescein angiography (FAG) (ETDRS Research

Group, 1991a; Novotny & Alvis, 1961). Fluorescein is used as an intravenous dye which can be seen in the optic nerve head approximately 10 seconds after injection, whilst the whole examination takes close to 10 minutes. The fluorescein dye leakage from damaged vessels makes it is possible to detect changes once the fluorescein dye has passed the retina (Novotny & Alvis, 1961). FAG has an invasive nature and possible complications should be considered before imaging. The most common adverse effects include nausea, itching and vomiting. However, there is a rare risk for allergic reactions which, in the worst case, may lead to anaphylactic shock (Yannuzzi et al., 1986).

In 2014, a novel method to illustrate retinal vasculature was presented. Optical coherence tomography angiography (OCTA) is based on mapping reflections from moving red blood cells and combining several scans to form an angiogram (Koustenis et al., 2017). With OCTA, it is possible to detect vessels throughout the full depth of the retina, giving even more information about the vessel layers than traditional FAG. When imaging DR, OCTA can give information about neovascularization and nonperfused areas without applying the more invasive FAG using intravenous dye (Spaide, Klancnik, et al., 2015). It is worthwhile to acknowledge that artifacts in the angiogram due to the OCTA imaging technique requires expertise in the analysis of the results (Spaide, Fujimoto, et al., 2015).

New imaging modalities have not yet been established in DR screening. However, ultra-wide field fundus photographs have been developed with a 200-degree field that can cover greater areas than two 45-degree photographs, enabling observation of changes in the peripheral retina, which would have otherwise been missed (Neubauer et al., 2008; Price et al., 2015). Furthermore, evolving technologies such as machine learning, provides possible tools for DR screening in the future (Grzybowski et al., 2020) which has led to the first commercial products in the United States markets (Abràmoff et al., 2018).

3.5 Treatment

3.5.1 Retinal photocoagulation

For decades, the golden standard of DR treatment has been PRP (Grunwald et al., 1986). PRP is known for its ability to reduce the retinal oxygen demand and prevent further progression of DR, simultaneously reducing severe vision loss by at least 50%, therefore outweighing the possible adverse effects (DRS Research Group,

1981a). PRP is recommended for vision-threatening DR in order to reduce further complications and vision loss (DRS Research Group, 1981a; ETDRS Research Group, 1991a; Finnish Medical Society Duodecim, 2014). Treatment outcomes remain persistent even after 15 years (Blankenship, 1991). Adverse effects documented from PRP treatment include decreased visual field sensitivity, impaired night vision and dark adaptation in addition to impaired color vision and contrast sensitivity (Fong et al., 2007; Gross et al., 2015; Mäntyjärvi, 1989).

Focal photocoagulation treatment of clinically significant DME is recommended for extra-foveolar lesions (ETDRS Research Group, 1985; Schmidt-Erfurth et al., 2017). Focal treatment can aid in preventing vision loss and consequently leading to only minor impairment in the patients' color vision and visual fields (ETDRS Research Group, 1991a).

3.5.2 Anti-VEGF treatment

Vitreous concentration of VEGF is increased in patients with PDR whereas PRP is known to decrease the concentration (Aiello et al., 1994). In addition to PRP anti-VEGF treatment can be used to treat PDR to mitigate VEGF induced changes in retinal function (Simunovic & Maberley, 2015). Anti-VEGF drugs bind to VEGF receptors in the retinal blood vessels preventing neovascularization. Out of the anti-VEGF drugs, bevacizumab (Avastin) was originally designed as a humanized monoclonal antibody to treat cancer (Ferrara et al., 2005). It was first used in 2005 as an off-label intravitreal injection to treat age-related macular degeneration (Rosenfeld et al., 2005) and later to treat PDR (Avery et al., 2006).

Since then, several clinical trials have been established in order to determine long-term effects of anti-VEGF treatment in relation to DR (Brown et al., 2015; Gross et al., 2018; Maturi et al., 2023; Sivaprasad et al., 2018; Wells et al., 2016). A combination treatment of bevacizumab and PRP in treating PDR together with DME had superior visual and anatomical outcomes compared to PRP alone (Sameen et al., 2017).

A DRCR.net trial compared ranibizumab with PRP for 2-years. The trial underlined the noninferiority of ranibizumab compared to PRP. The results showed that treatment with ranibizumab was associated with less visual field loss and DME development compared to PRP (Gross et al., 2015). The trial outcomes after a 5-years illustrated improvement in visual acuity in both groups. However, patients treated in the PRP group suffered from considerable visual field losses and more frequent DME (Gross et al., 2018). In the PROTEUS study, a combination of

ranibizumab and PRP was compared to PRP alone. A more frequent regression of neovascularization was documented in the combination group, however, no differences between visual acuities were noted (Figueira et al., 2018).

Aflibercept was compared to PRP in the Clinical efficacy and mechanistic evaluation of aflibercept for proliferative diabetic retinopathy (CLARITY) trial, where it was demonstrated that one-year visual outcomes were better in patients receiving aflibercept (Sivaprasad et al., 2017). Patients receiving anti-VEGF had better visual outcomes and were more satisfied with the treatment than patients treated only with PRP. However, costs of anti-VEGF treatment are higher, and require more healthcare resources in contrast to PRP only (Sivaprasad et al., 2018).

Recent clinical trials including the DRCR.net Protocol W and The Study of the Efficacy and Safety of Intravitreal Aflibercept for the Improvement of Moderately Severe to Severe Non-proliferative Diabetic Retinopathy (PANORAMA) have presented benefits of early intervention with aflibercept during a 2-year follow-up period. In the Protocol W trial, a respective 14% and 33% of patients who received aflibercept treatment and sham injections, developed PDR during the trial (Maturi et al., 2021). Furthermore, in the PANORAMA trial, vision-threatening endpoints were less common in patients receiving aflibercept compared to sham injections, in addition to the severity of DR decreasing over time (Brown et al., 2021).

Treatment of PDR with anti-VEGF instead of PRP involves constant injections and follow-up, otherwise risking progression of PDR, resulting in possible vision loss (Maguire et al., 2021). As shown in a study by Wubben et al., the risks of inadvertent interruption of anti-VEGF treatment may lead to severe vision loss (Wubben et al., 2019). Patients with PDR are known to have a 16% rate of loss to follow-up, which is associated with lower visual acuity (Abdelmotaal et al., 2020). However, anti-VEGF treatment works as adjuvant therapy for PDR providing potentially better visual outcome and fewer vitrectomies compared to PRP (Yates et al., 2021).

The Cochrane systematic review (Virgili et al., 2018), evaluated the effect of anti-VEGF treatment for DME. After one year of treatment, aflibercept was found to be superior to bevacizumab or ranibizumab, however, the differences faded after 2 years of follow-up. In addition, aflibercept was associated with better visual outcomes than bevacizumab or ranibizumab after 2 years of follow-up, when the baseline visual acuity was 0.4 or worse. Moreover, all three anti-VEGF agents were shown to be superior compared with laser treatment after a one year of follow-up period (DRCR.net, 2015; Virgili et al., 2018).

Treatment of CI-DME with a mildly affected visual acuity of 0.8 or better, with aflibercept or focal photocoagulation, did not result in better visual outcomes in a 2-year follow-up, compared with observation (Baker et al., 2019). The DRCR.net clinical trial treating DME with either bevacizumab, ranibizumab or aflibercept, with non-PDR subjected to any anti-VEGF treatment, 22–31% of patients had improvement in DR severity and no differences were noted between the treatment groups during a 2-year follow-up period (Bressler et al., 2017).

Endophthalmitis is considered as one of the major adverse events of anti-VEGF treatment (DRCR.net, 2015; Virgili et al., 2018). However, when presented under one per a thousand cases, anti-VEGF treatment is considered to have an adequate safety profile when treating DME (Virgili et al., 2018) (Table 5).

Table 5. Adverse effects of intravitreal anti-VEGF treatment (DRCR.net, 2015; Virgili et al., 2018).

Tissue	Adverse effect
Conjunctiva	Conjunctival hemorrhage
	Eye irritation
Cornea	Corneal abrasion
Vitreous	Blurred vision
	Vitreous floaters
	Endophthalmitis
	Increased intraocular pressure

In conclusion, The European Society of Retina Specialists (EURETINA) has made a guideline for the management of DME and anti-VEGF treatment with bevacizumab, ranibizumab or aflibercept is recommended in CI-DME (Schmidt-Erfurth et al., 2017).

3.5.3 Corticosteroids in the treatment of diabetic macular edema

Triamcinolone (TA) is a corticosteroid that can be used intravitreally to treat DME (DRCR.net, 2008). However, after a 3-year follow-up, focal photocoagulation gave better visual outcomes compared to TA (Beck et al., 2009). Treatment with TA is associated with an increased risk of cataract and more frequent cataract surgery in addition to increased intraocular pressure (IOP) (Beck et al., 2009; DRCR.net, 2008).

However, it has been shown that corticosteroid therapy with fluocinolone acetonide has favorable visual outcomes in patients diagnosed with chronic DME

(Cunha-Vaz et al., 2014). Similarly, a clinical trial by Boyer et al. compared intravitreal dexamethasone implants and sham for three years. Improved visual and anatomical outcomes were documented in the dexamethasone group, even though dexamethasone was associated with cataract and increased IOP (Boyer et al., 2014).

The EURETINA guideline recommends that corticosteroids should be used as a second-line treatment, hence anti-VEGF non-responders may benefit from a switch to corticosteroids (Schmidt-Erfurth et al., 2017). Due to increased cataract formation, pseudophakic patients are more eligible for corticosteroid treatment. IOP must be followed in all patients subjected to corticosteroid treatment (Beck et al., 2009; Boyer et al., 2014; Schmidt-Erfurth et al., 2017).

3.5.4 Pars plana vitrectomy for persistent diabetic macular edema

Pars plana vitrectomy is a surgical treatment option for persistent DME in the presence of vitreomacular traction or posterior hyaloid attachment (Lewis et al., 1992; Pendergast et al., 2000). In a clinical trial by Thomas et al., primary vitrectomy versus laser in patients diagnosed with DME with a visual acuity of 0.5 or worse, presented that those patients undergoing vitrectomy had a slight improvement in visual acuity and anatomical outcomes compared to the laser group (Thomas et al., 2005). Furthermore, a study of vitrectomy for persistent DME with prior macular laser treatment showed improved visual acuity and decreased central macular thickness (Recchia et al., 2005).

3.6 Advanced proliferative diabetic retinopathy

3.6.1 Vitreous hemorrhage

PDR is characterized by neovascularization induced by retinal hypoxia and increased VEGF levels (Adamis et al., 1994; Idris & Donnelly, 2006). The formation of new vasculature is susceptible to hemorrhages and the risk of VH increases (Jonas et al., 2008; Park et al., 2021).

Rates for VHs in the general population varies from 7-50 per 100 000 people (Lindgren et al., 1995; Wang et al., 2017). However, up to 27% of patients with peripheral neovascularization will have a vitreous hemorrhage within 5 years if not properly treated (Turner et al., 1985). Treatment with PRP reduces the risk of severe vision loss by 50% (DRS Research Group, 1981a). Despite fully completed PRP,

VHs may still occur, though spontaneous reabsorption is possible (Park et al., 2021; Ziemianski et al., 1980). For persistent cases vitrectomy may be performed (DRVS, 1990; Jorge et al., 2021).

VH is a complication of DR, therefore additional PRP is needed (DRS Research Group, 1981a; Parikh et al., 2017). However, in some cases the VH may be so dense that there is no visibility to the retina and performing PRP is not possible or comprehensive PRP has already been performed. In these scenarios, administration of anti-VEGF treatment may speed up the clearance of VHs. Anti-VEGF treatment with bevacizumab (Huang et al., 2009; Jonas et al., 2008; Parikh et al., 2017; Park et al., 2021) or ranibizumab (Chelala et al., 2018) has been associated with the regression of VHs. Despite the benefits of anti-VEGF treatment, complete clearance of VHs is not always achieved, and vitrectomy is needed. Furthermore, vitrectomy rates are lower in anti-VEGF treatment than without (Chelala et al., 2018; Huang et al., 2009; Parikh et al., 2017; Park et al., 2021).

3.6.2 Neovascular glaucoma

In addition to retinal neovascularization, the iris can also be affected. Neovascularization of the iris is present in approximately 2% of patients with PDR and can be visible in a slit-lamp examination. Gonioscopy may further reveal the affected chamber angle (DRS Research Group, 1981b). Neovascular glaucoma occurs when the chamber angle is obstructed and IOP rises (Fernández-Vigo et al., 1997).

To treat neovascularization of the iris and PDR, PRP is needed (DRS Research Group, 1981a; Tasman et al., 1980). Additionally, treatment with bevacizumab has been shown to regress iris neovascularization rapidly (Avery et al., 2006; Jiang et al., 2009) and decrease the risk of neovascular glaucoma (Wakabayashi et al., 2008). Poor visual prognosis is associated with neovascular glaucoma: in the advanced disease retinal cryoablation or glaucoma surgery may be needed alongside medication in order to decrease IOP (Sivak-Callcott et al., 2001).

3.6.3 Tractional retinal detachment

Retinal neovascularization is combined with fibrous proliferation causing vitreoretinal adhesions, therefore, traction to the retina eventually progresses to retinal detachment (Davis, 1965). The natural course of PDR often includes risk for tractional retinal detachment (TRD). This is despite intensive treatment of PDR and

in the ETDRS trial, a 5-year cumulative rate for PPV was 5% out of which 46% were due to TRD (Flynn et al., 1992).

It has been disputed if patients with retinal neovascularization having anti-VEGF treatment may have an increased risk of tractional retinal detachment due to rapid regression of neovascular vessels (Arevalo et al., 2008). In a randomized clinical trial by the DRCR.net (Diabetic Retinopathy Clinical Research Network), out of patients with VHs treated with aflibercept or vitrectomy, 22% and 13% were diagnosed with TRD, respectively (Antoszyk et al., 2020). However, TRD is part of the natural course of PDR (Arevalo et al., 2008; Flynn et al., 1992) and a pooled analysis of DRCR.net trials did not find evidence of anti-VEGF treatment for PDR or DME being associated with an increased risk of TRD (N. M. Bressler et al., 2020).

4 Purpose of the research

The main purpose of this research was to evaluate the effects of DR in relation to patients' vision and the treatment outcomes of PDR and DME.

The specific purposes of the original publications are listed as follows:

I To evaluate the occurrence of VH secondary to PDR and the efficacy of IVB for resolution of VH and improvement of BCVA in a real-world study of five years.

II To evaluate functional vision including visual acuity, visual field and contrast sensitivity, in addition to HRQoL in patients with PDR after 35-year duration of T1D.

III To evaluate real-world visual outcomes of DME treatment in observation, macular laser, anti-VEGF and combination of anti-VEGF and macular laser in a cohort of patients with T1D after the initial DME episode combined with long-term follow-up in terms of BCVA improvement.

5 Materials and methods

5.1 Study design

This research was conducted at the Oulu University Hospital (OYS) in Oulu, Finland. All the study subjects lived in the Oulu area or in the Northern Ostrobothnia area. The research followed the tenets of the Declaration of Helsinki and was conducted with the approval of the Oulu University Hospital Research Committee (document number 175/2016). Studies I and III were retrospective in nature and carried out as register-based research, meaning they were carried out without direct involvement of patients; hence no written consent was obtained. A written consent was obtained from patients taking part in study II. Patient inclusion and exclusion criteria are presented in Table 6.

Table 6. Patient selection criteria for studies I–III.

Study	Inclusion criteria	Exclusion criteria
I–III	Diagnosis, treatment, and follow-up conducted in the Oulu University Hospital	No diagnosed diabetes
I	Patients with type 1 or type 2 diabetes Diagnosis of PDR 1.1.2011–31.12.2015 VH as a complication for PDR	Previously performed PPV VH for reasons other than PDR Follow-up time under 1 year
II	Previous participation to Oulu cohort study of diabetic retinopathy Patients with type 1 diabetes Diagnosis of PDR at study examination in 2007	No PDR
III	Patients with type 1 diabetes Diagnosis of DME 1.6.2006–31.12.2020 Central retinal thickness ≥300 µm	Other ocular conditions requiring retinal photocoagulation or anti-VEGF treatment Follow-up time under 6 months

DME = diabetic macular edema, PDR = proliferative diabetic retinopathy, PPV = pars plana vitrectomy, VEGF = vascular-endothelial growth factor, VH = vitreous hemorrhage

5.2 Intravitreal hemorrhage as a complication of proliferative diabetic retinopathy (I)

For this 5-year study (I), a total of 850 study subjects with either T1D or T2D and PDR, were screened for VH between 2011 and 2015 in order to evaluate real-world treatment outcomes of VH. The Oulu University Hospital electronic patient

database was used to select the study population based on the tenth revision of the International Classification of Diseases (ICD-10). Patients with type 1 or 2 diabetes, PDR and VH were selected for further analysis. Exclusion criteria included a follow-up time of under one year, previously performed PPV, and VH for other reasons than PDR. Baseline information of patients was gathered including gender, age at VH onset, prior PRP, history of iris neovascularization or DME, lens status, and previous treatment with intravitreal bevacizumab (IVB).

The treatment decision was made by a retina specialist based on the clinical status of the retina and the density of the VH. Patients were divided into treatment groups, IVB, PRP, PPV and observation, accordingly. Mild VHs with previously performed PRP were often observed. Patients with relatively good fundus visibility and mild VH were treated with PRP. Patients with dense VH decreasing visual acuity were treated mainly with IVB. Patients with dense VH without diagnostic fundus visibility underwent an ocular ultrasonography in order to exclude retinal detachment.

To evaluate the efficiency of the treatment, each individual case was evaluated for resolution of VH, and the best corrected visual acuity (BCVA) was recorded at the onset and after the resolution of the VH alongside IOP. Furthermore, the efficiency of IVB was compared with other treatments PRP, PPV, and observation for spontaneous resorption of VH.

5.3 Long-term visual outcomes of proliferative diabetic retinopathy (II)

The Oulu cohort study of diabetic retinopathy was a population-based cohort of children with T1D, first examined in 1989 and re-evaluated in 2007. During re-examination in 2007, 60 patients had been diagnosed with PDR. They were invited to participate in this prospective population-based study and second re-examination in 2019 (II). Our aim was to evaluate long-term effects of T1D and PDR on visual function and HRQoL. Out of the 60 patients, 29 patients were able to participate, 26 patients were not able to participate due to long distance, one patient had incomplete participation and eight patients had deceased.

The re-evaluation in 2019 consisted of a full ophthalmological examination including a mydriatic biomicroscopy, measurement of BCVA and IOP, fundus photography and OCT. Clinical characteristics including blood pressure and laboratory blood testing (HbA1c, high-density lipoprotein [HDL] and low-density lipoprotein [LDL] cholesterols, triglyceride, natrium, kalium, albumin and

creatinine) were recorded. The 15D instrument was used to evaluate the HRQoL of patients in 2019 and to compare results to those obtained from the same individuals in 2007.

Evaluation of visual field sensitivities, contrast sensitivity and reaction time was performed using the Ocusweep device (Ocuspecto LTD., Turku, Finland) in order to measure the functional vision of patients. The results were compared to 3046 age-matched, healthy control groups from the measurements completed by the vision test manufacturer. A standard automated perimetry method by Ocusweep was used to determine the central and peripheral visual field sensitivities in decibels (dB). Bilateral contrast sensitivity utilizing sine wave gratings at one cycle per degree (cpd), with the Ocusweep algorithm detecting the lowest contrast sensitivity threshold, was used. Reaction time measurements were completed by the Ocusweep reaction time perimetry test.

5.4 Treatment of diabetic macular edema in a real-world setting (III)

All patients diagnosed with T1D complicated by clinically significant DME in the Northern Ostrobothnia Hospital District area between 2006 and 2020 were included in this population-based cohort study (III). The Oulu University Hospital electronic patient database was used for retrospective data collection. Patients with ICD-10 codes for T1D (E10.3) and DME (H36.1) were reviewed. Only patients with a CRT of ≥300 μm were considered to have clinically significant DME and were included in the study. Patients with other ocular conditions requiring retinal photocoagulation or anti-VEGF treatment, in addition patients with a follow-up time of under six months were excluded. Patient characteristics that were recorded included sex, age at onset of T1D and DME as well as DR severity at the onset of DME.

Patients were divided into groups based on selected treatment: macular laser, anti-VEGF injection, combination of macular laser and anti-VEGF or observation. Patients with an extrafoveal DME located ≥500 μm from the central fovea were either observed or received macular laser depending on the location and amount of intraretinal or subretinal fluid. Patients with central DME within 500 μm from the central fovea received anti-VEGF treatment as a primary treatment. A combination of macular laser and anti-VEGF was chosen if the patient had both central and extrafoveal DME. The number of anti-VEGF injections and the selected anti-VEGF agent was recorded. In Finland, bevacizumab is commonly used as the first-line

intravitreal drug for DME, and for selected cases, aflibercept or corticosteroid may be used.

Real-world outcomes were analyzed within the groups based on changes in vision at the onset of DME and after the initial episode or at the end of follow-up period. Any recurrences of DME were recorded. The status of visual impairment was recorded at the onset of DME and after the follow-up period. The patients with BCVA of less than 0.3 were classified as visually impaired.

5.5 Statistical analysis

The statistical analysis was performed using the IBM SPSS Statistics software (versions 23, 25 and 26, IBM Corp, Armonk, NY, USA) and SAS (version 9.4, SAS Institute Inc. Cary, NC, USA). For the statistical analysis, the best corrected visual acuity was either changed from Snellen to logarithm of the minimum angle of resolution (logMAR) units (study I) or ETDRS letters (studies II, III). The number of cases and percentages were used to describe the characteristics of the data. Summary statistics were presented as a means with standard deviation (SD) if not otherwise stated, with minimum and maximum values. Two-tailed p-values under 0.05 were considered as statistically significant.

In the study comparing visual outcomes of anti-VEGF treatment of VH (I), the generalized estimation equation (GEE) was used to evaluate the change in BCVA during and after VH in different treatment groups. The GEE with exchangeable structure made it possible to take intraindividual correlation into account. Diabetes type, prior PRP, prior IVB, PPV and baseline BCVA were set as covariates. In addition, to analyze clearance and duration of VH, Kaplan-Meier survival analysis was used to compare outcomes between treatment groups. Furthermore, the chi-square ($\chi 2$) test was used to detect differences between categorical variables and the independent t-test for continuous variables. The Pearson correlation was calculated in order to find correlations between continuous variables.

The cohort's results from the previous visit in 2007 between the study visit in 2019 (II) were compared using the paired samples t-test and the results were presented with 95% confidence interval. Ophthalmologic outcomes, visual field, contrast sensitivity and reaction time were compared to healthy subjects by use of linear mixed models, age as an adjusted factor. The Pearson correlation coefficient was used to evaluate the relationship between CRT, BCVA, contrast sensitivity and sensitivity of the central visual field.

Comparison of visual outcomes within the groups of patients with DME (III) was conducted with linear mixed models, after the first DME episode and after the follow-up period. Both the patient and the eye were used as variables in order to take intra- and interindividual correlation into account. The adjusting factors included sex, age and the duration of T1D. The results were presented with a 95% confidence interval.

6 Results

6.1 Characteristics of the study population

The number of study participants and included eyes with basic characteristics are reported in Table 7.

Table 7. Characteristic information of the study population.

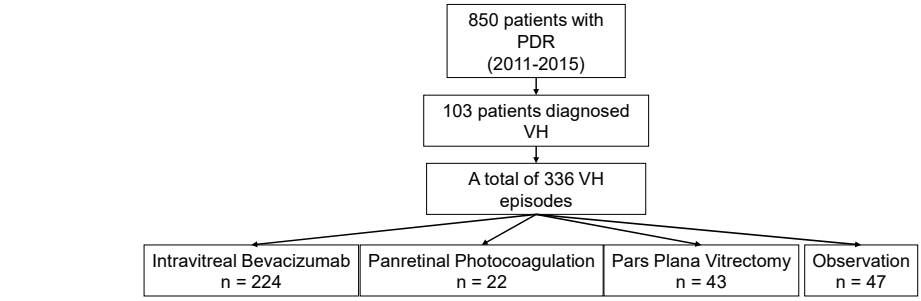
Study	Participants, n	Eyes, n	Sex, males, n (%)	Age, years	Duration of diabetes, years	non-PDR, n	PDR, n
I	103	140	54 (52)	54±15	-	0	103 (100)
II	29	58	18 (62)	41±3	35±4	0	29 (100)
III	206	304	121 (59)	47±14	24±12	155 (75)	51 (25)

PDR = proliferative diabetic retinopathy

6.2 Anti-VEGF treatment for intravitreal hemorrhage (I)

A total of 103 study subjects were diagnosed with VH during the 5-year period between 2011 and 2015. This population included 12% of the total 850 patients with T1D (n=351, 41%) or T2D (n=499, 59%) complicated by PDR (Figure 6). VH occurred in 16% and 9% of patients with T1D or T2D, respectively. 52% of the study subjects were males (54/103). Patients diagnosed with T1D were 44±13 years old at the time of VH and patients with T2D were 66±7 years old.

PRP had been performed prior to the VH in 88% of the patients (91 patients, 121 eyes). Out of a total of 140 eyes diagnosed with VH, 25% had a history of DME (35/140). In addition, 14% of the study eyes had been affected by iris neovascularization (20/140).



BCVA (logMAR†)				
- Baseline	1.15 ± 0.70	0.55 ± 0.57	0.39 ± 0.43	0.24 ± 0.33
- After	0.42 ± 0.42	0.19 ± 0.21	0.75 ± 0.62	0.26 ± 0.34
VH duration (days†)	57 ± 46	76 ± 54	103 ± 84	81 ± 42

† mean ± SD
BCVA = best corrected visual acuity, logMAR = logarithm of the minimun angle of resolution,
PDR = proliferative diabetic retinopathy, VH = vitreous haemorrhage

Fig. 6. Flowchart of patient selection and the main results, visual outcomes, and vitreous hemorrhage duration in treatment groups.

A total of 336 VH episodes out of which 196 (58%) were recurrent VHs were recorded in 140 eyes during the study period. Treatments were divided as follows; 224 (67%) VH episodes were initially treated with IVB in 97 eyes, other treatments included PRP in 22 (6%) and PPV in 43 (13%) episodes, and 47 (14%) VH episodes were observed without any treatment.

A statistically significant difference of VH duration was noted between the groups. A staggering 92% of the 224 VHs had cleared in less than three months in study subjects receiving IVB treatment, compared to other treatment groups (PRP, PPV, observation) where a clear vitreous was observed in only 61% of the 112 episodes ($p<0.0001$, $\chi 2$ test).

The median estimate for the clearance of VH was 46±2 days in the study subjects receiving IVB and 70±6 days in the other treatment groups ($p<0.0001$, 95% confidence interval (CI) 42.3 to 49.7, Kaplan-Meier) (Figure 7). The duration of VH was 57±46 days in the IVB group, and 46±54, 103±84, 81±42 days in episodes treated with PRP, PPV, or observation, respectively. In all groups 2.2±2.7 VH recurrences were noted during the 5-year study period.

Study subjects receiving IVB had a total of 376 injections, with the rate of 1.7±1.1 injections per VH episode, to clear the vitreous with a minimum of one and maximum of seven injections. These injections were given with a 7.2±3.9-week

interval. Only 4% of the cases had contraindications for IVB (14/336). The contraindications included pregnancy, the refusal of the patient, acute ocular infections, and preceding cardiovascular complications in 3, 3, 3 and 5 patients, respectively. No severe adverse effects of IVB, including TRD or endophthalmitis were noted.

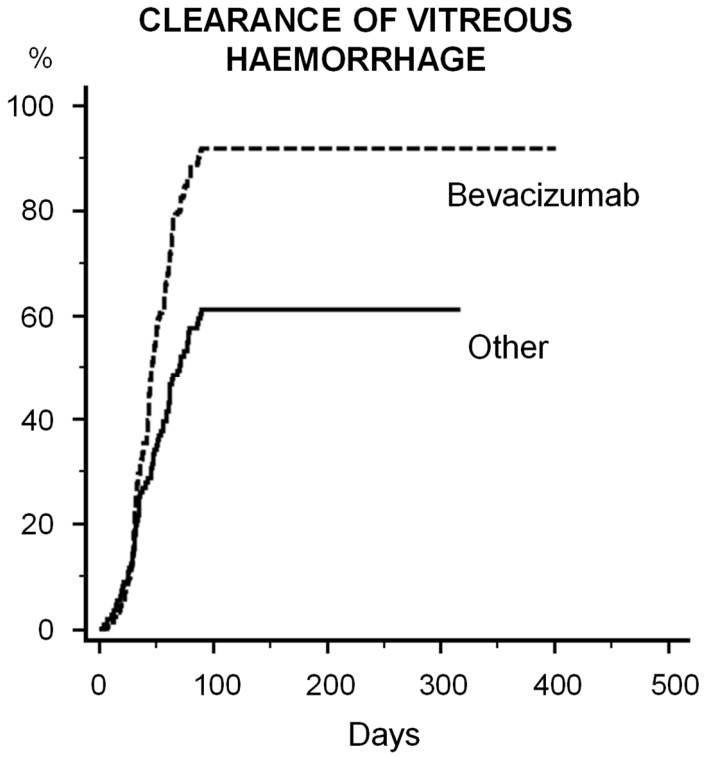


Fig. 7. Kaplan-Meier estimates for the clearance of vitreous hemorrhage when treated with bevacizumab or other treatments (Modified from the original, CC BY 4.0 from the Study I © 2019).

Patients receiving IVB treatment had a statistically significant BCVA improvement of 0.73±0.04 logMAR units (p=0.0004, General Estimating Equations). The defined confounding factors were not significantly associated with the improvement of the BCVA; diabetes type (E=0.03, SD±0.02, p=0.223), prior PRP (E=-0.01, SD±0.01, p=0.538) or prior PPV (E=0.10, SD±0.08, p=0.228).

Furthermore, an improvement of ≥15 letters were noted in 66% and 59% of episodes treated with IVB or other treatments, respectively.

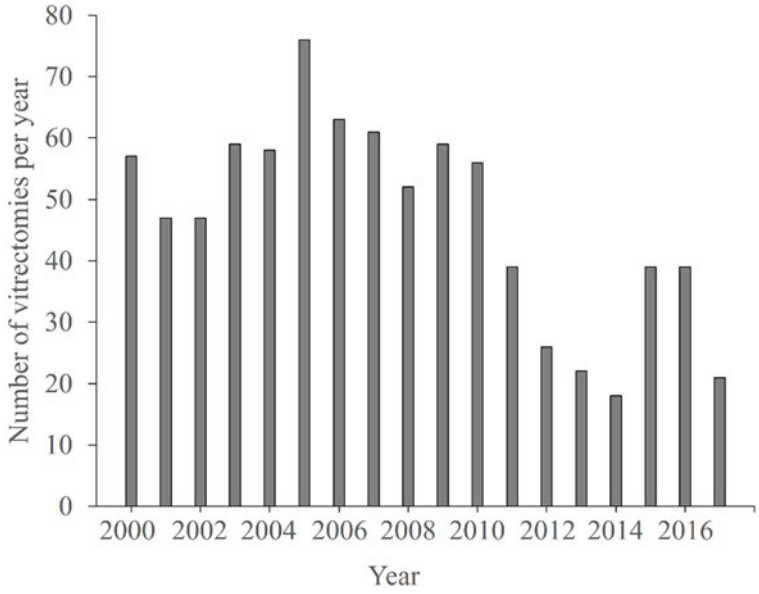


Fig. 8. Number of diabetic vitrectomies in the Oulu University Hospital during 2000–2017 (CC BY 4.0 from the Study I © 2019).

During the years 1993–2005, the number of diabetic vitrectomies increased, however, in 2006 after the initiation of IVB treatment for VHs, the number of diabetic vitrectomies has declined 72% between 2005–2017 (IRR=0.90, Poisson regression model, 95% CI 0.88 to 0.92, $p<0.001$, Pearson $\chi 2$) (Figure 8.)

6.3 Long-term effects of proliferative diabetic retinopathy on visual function (II)

Out of the original cohort (n=2016), 60/172 (35%) patients with T1D who participated in the evaluation in 2007 had PDR and were invited for re-examination in 2019. A total of 29 (48%) of these patients with T1D and PDR participated in this study. There were 18 (62%) males participating in this study, the mean age during the onset of diabetes was 6.0±4.2 years and mean age at the time of the examination was 41±3.4 years. Patients had been diagnosed with PRD for 15.4±2.8 years at the time of the study (Table 8).

Table 8. Patient characteristics and clinical outcomes in 2007 and 2019 (Reprinted with permission from the Study II © 2023.

Patient characteristics	2007	2019	p[1]
General characteristics			
Age at examination, years, mean (SD) [min-max]	30.0 (2.7) [23–35]	41.0 (3.4) [34–46]	
Males, n (%)		18.0 (62)	
Diabetes duration, years, mean (SD) [min-max]	24.0 (3.7) [17–29]	35.0 (3.9) [29–41]	
Age at diabetes onset, years, mean (SD) [min-max]		6.0 (4.2) [1–16]	
Diabetic retinopathy duration, years, mean, (SD) [min-max]	9 (6.5) [0–21]	11.0 (5.0) [3–22]	
Years to diabetic retinopathy after diabetes onset, years, mean, (SD) [min-max]	21.0 (4.0) [12–26]		
Clinical characteristics			
Transdermal glucose monitoring, n (%)	0	22 (76)	
Best-corrected visual acuity, ETDRS, mean (SD) [min-max]			
Right eye	61.9 (38.2) [0–95]	76.7 (16) [5–92]	0.057
Left eye	79.6 (17.6) [35–100]	73.3 (14) [36–91]	0.011
Visual impairment, n (%)	1 (3)	2 (7)	
Intraocular pressure, mmHg, mean (SD) [min-max]			
Right eye	14.1 (2.7) [10–19]	16 (3.8) [9–22]	0.029
Left eye	14.2 (2.6) [10–18]	16.4 (4.4) [10–26]	0.041
Lens opacifications			
Eyes with no opacifications, n (%)		47 (87)	
Eyes with cataract, n (%)		7 (13)	
Systolic blood pressure, mmHg, mean (SD) [min-max]	141.6 (18.7) [107–191]	139.8 (12.4) [114–160]	0.28
Diastolic blood pressure, mmHg, mean (SD) [min-max]	87.9 (11.0) [68–114]	83.5 (6.5) [65–95]	0.099
Heart beats per minute, mean (SD) [min-max]		77 (9.7) [60–100]	
Ophthalmology clinic visits, mean (SD) [min-max]	13.4 (15.6) [1–72]	24.2 (18.5) [1–82]	
Panretinal Photocoagulation visits, mean (SD) [min-max]	4.9 (3.7) [1–10]	2.9 (2.9) [0–12]	
Eyes that have undergone Pars plana vitrectomy, n (%)	4 (7)	15 (26)	
Laboratory characteristics[2]			

Patient characteristics	2007	2019	p[1]
HbA1c, mmol/mol, mean (SD) [min-max]	80.1 (17.0) [49–118]	63.6 (14.1) [24–90]	<0.001
High-density lipoprotein, mmol/l, mean (SD) [min-max]	1.4 (0.4) [0.9–2.9]	1.5 (0.4) [0.9–2.5]	0.44
Low-density lipoprotein, mmol/l, mean (SD) [min-max]	2.1 (0.7) [0.16–3.7]	2.3 (0.7) [1.2–3.9]	>0.9
Triglyceride, mmol/l, mean (SD) [min-max]	1.3 (0.9) [0.4–4.2]	1.2 (0.8) [0.5–4.8]	>0.9
Natrium, mmol/l, mean (SD) [min-max]		138.8 (3.0) [132–146]	
Potassium, mmol/l, mean (SD) [min-max]		4.2 (0.4) [3.4–5.3]	
Albumin, g/l, mean (SD) [min-max]		38.8 (4.2) [30–44]	
Creatinine, µmol/l, mean (SD) [min-max]		108 (188.1) [49–1080]	

[1]Paired samples t-test

[2]Laboratory reference ranges in healthy adults: HbA1c 20–42 mmol/mol, HDL female >1.2 and male >1.0 mmol/l, LDL <3.0 mmol/l, triglycerides <1.7 mmol/l, natrium 137–144 mmol/l, potassium 3.5–4.8 mmol/l, albumin 36–48 g/l, creatinine female 50–90 and male 60–100 µmol/l

Patients had diabetes related complications such as neuropathy (3%), nephropathy (34%) and cardiovascular diseases (10%) alongside other ocular complications such as DME in 5 (17%) and VHs in 16 (57%) patients. Medication other than insulin used by the patients consisted of ACE inhibitors or ATR blockers in 16 (55%), statins in 15 (52%), other antihypertensive agents in 9 (31%), and acetylsalicylic acid in 3 (10%) patients (Table 9).

Table 9. Medication, diabetes complications and concomitant diseases of the study population at 2019 (n=29) (Reprinted with permission from the Study II © 2023).

Medical characteristics	n
Acetylsalicylic acid, n (%)	3 (10)
Statin, n (%)	15 (52)
ACE inhibitor or ATR blocker, n (%)	16 (55)
Antihypertensive, n (%)	9 (31)
Diabetes complications	
Neuropathy	1 (3)
Nephropathy	10 (34)
Chronic kidney disease, n (%)	6 (21)
Dialysis, n (%)	1 (3)
Renal transplant, n (%)	3 (10)
Renal-pancreas transplant, n (%)	2 (7)
Cardiovascular disease	3 (10)

Medical characteristics	n
Arterial hypertension, n (%)	18 (62)
Diabetic macular edema, n (%)	5 (17)
Anti-VEGF-injections given, mean (SD) [min-max]	2,6 (8,0) [0-36]
Intravitreal hemorrhage, n (%)	16 (57)
Anti-VEGF-injections given, mean (SD) [min-max]	2,9 (5,4) [0-18]
Concomitant diseases, n (%)	
Autoimmune thyroiditis	5 (17)
Coeliac disease	2 (7)
Bronchial asthma	4 (14)
Sarcoidosis	2 (7)
Psychiatric disease	3 (10)

Patients underwent laboratory blood testing. The average HbA1c had decreased from 9.5% (80.1 mmol/mol) in 2007 to 8.0% (63.6 mmol/mol) in 2019 ($p<0.001$). After the 2007 visit, 22 (76%) patients had transdermal flash glucose monitoring in use. The values of HDL, LDL, and triglyceride had remained stable between the years 2007–2019 (HDL 1.4±0.4 vs. 1.5±0.4, $p=0.44$, LDL 21±0.7 vs 2.3±0.7, $p>0.9$, and triglyceride 1.3 ±0.9 vs 1.2±0.8, $p>0.9$).

The average visual acuity was a respective 77 and 73 ETDRS letters in the right and left eye and an additional two patients (7%) were visually impaired. The patients Ocusweep test results, visual field sensitivities, contrast sensitivity and reaction time were compared to 3046 age-matched, healthy control group patients provided by the manufacturer. Patients diagnosed with PDR had lower visual field sensitivities measured using the SAP method by Ocusweep, compared to the healthy control group, a central sensitivity of -3.7 dB (23.2±3.9 dB vs. 26.9±1.0 dB, 95% CI -4.1 to -3.3, $p<0.001$) and peripheral sensitivity of -6.1 dB (14.9±5.6 dB vs. 21.0±2.0 dB, 95% CI -6.8 to -5.3, $p<0.001$) were measured, respectively. In addition, the reaction time in the Ocusweep reaction time perimetry test was 27.6 ms longer in patients with PDR than healthy controls (490.5±62.9 ms vs. 462.8±48.8 ms, 95% CI 9.1 to 46.2, $p=0.004$). However, there was no statistical difference in contrast sensitivity between patients diagnosed with PDR compared to the healthy control group (2.1±0.2 vs. 2.1±0.2, difference -0.05, 95% CI -0.14 to 0.05, $p=0.32$).

The mean CRT was 236±41 μm at the study visit in 2019. There was no statistically significant correlation between CRT and binocular visual acuity (r=-

0.30, p=0.124), contrast sensitivity (r=0.50, p=0.20) or central visual field sensitivity (r=0.43, p=0.23).

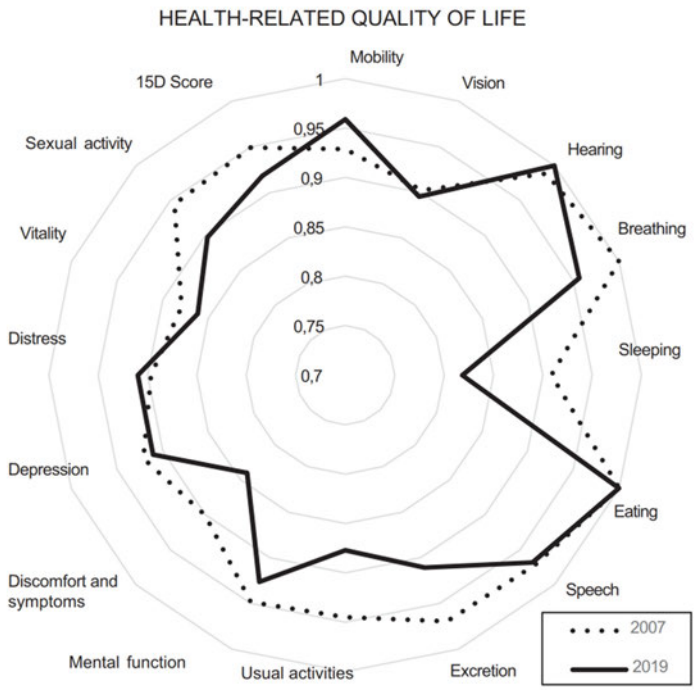


Fig. 9. The health-related quality of life measurements by the 15D instrument in patients with type 1 diabetes since childhood in 2007 and 2019 (Reprinted with permission from the Study II © 2023).

The HRQoL was measured using the 15D instrument (Figure 9). Dimensions concerning sleeping, usual activities, discomfort and symptoms and sexual activity in 2019 had slightly decreased among the participants compared to the results in 2007. An improvement was noted in dimensions concerning mobility and distress. The dimensions for vision remained unchanged during the follow-up. The total score of 15D was adjusted for age and sex, and a reduction of 0.04 from 0.95 in 2007 to 0.92 in 2019 (p=0.015) was observed.

6.4 Diabetic macular edema treatment in patients with type 1 diabetes (III)

A total of 206 patients with 304 eyes were included in this study, out of which all patients had T1D in addition to DME. The mean follow-up time was 65.2±44.9 months (a range of 6–235 months). Out of the study population, 121 (59%) were males and the mean age of the study participants was 23.4±16.5 years at the time of T1D diagnosis. After T1D had lasted for 16.9±9.7 and 24.1±11.8 years, DR and DME occurred, respectively. The mean age during the onset of DME was 47.4±14.4 years.

During the study period between 2006 and 2020, there were 304 initial and 193 recurrent DME episodes. DME was bilateral in 68% of the patients. At the time of the onset of DME 155 (75%) patients had been diagnosed with non-PDR and 51 (25%) had been diagnosed with PDR.

Out of the 304 initial episodes of DME, 45 (15%) were observed without any treatment, 100 (33%) were subjected to macular laser, 124 (41%) received anti-VEGF treatment and 35 (12%) received a combination of laser and anti-VEGF. The average BCVA during the onset of DME was 76.4±12.6 ETDRS letters, and five patients (2.4%) were visually impaired according to the WHO classification of visual impairment. After the follow-up, only two patients (1.0%) were still visually impaired despite treatment of DME.

Table 10. DME treatment outcomes in observation, macular laser, anti-VEGF and combination of macular laser and anti-VEGF groups (CC BY 4.0 from the Study III © 2022).

Outcome	All n=304	Observation n=45	Macular laser n=100	Anti-VEGF n=124	Macular laser and anti-VEGF n=35
Age at DME onset[1], mean (SD)	47.4 (14.4)	47.5 (16.1)	43.0 (12.1)	49.9 (14.5)	44.7 (13.2)
Given anti-VEGF-injections, mean (SD)				6.0 (4.2)	6.5 (6.5)
Visual impaired eyes, n (%)					
at DME onset	22 (7.2)	4 (8.9)	3 (3.0)	11 (8.9)	4 (11.4)
after the first DME	16 (5.3)	3 (6.7)	4 (4.0)	7 (5.6)	2 (5.7)
at the end of follow-up	7 (2.3)	2 (4.4)	3 (3.0)	2 (1.6)	0 (0)
Recurrence of DME, n (%)	193 (63.5)	41 (91.1)	59 (59)	80 (64.5)	13 (37.1)
BCVA , mean (SD)					
at DME onset	76.4 (12.5)	81.6 (8.8)	80.8 (13.1)	72.8 (11.1)	72.4 (13.2)
at the end of first episode	79.7 (11.5)	80.8 (12.6)	80.7 (13.7)	78.9 (9.9)	78.5 (8.9)
at the end of follow-up	78.9 (12.2)	78.3 (17.7)	80.2 (13.4)	78.3 (10.1)	78.7 (9.0)
ETDRS letters gain after first episode, mean (95% CI)	2.9 (2.1 to 3.8)	0.1 (-3.6 to 3.8)	0.4 (-1.9 to 1.1)	4.9 (3.9 to 6.0)	5.5 (2.9 to 8.1)
p-value	<0.001*	>0.90	0.61	<0.001*	<0.001*
ETDRS letters gain at the end of follow-up, mean (95% CI)	1.8 (1.0 to 2.7)	-3.7 (-7.4 to 0.04)	-1.1 (-2.7 to 0.4)	4.1 (3.1 to 5.2)	5.1 (2.5 to 7.8)
p-value	<0.001*	>0.90	0.14	<0.001	<0.001

VEGF = vascular endothelial growth factor, DME = diabetic macular edema, BCVA = best corrected visual acuity with ETDRS letters, SD = standard deviation, CI = confidence interval

[1]No statistical significance between groups (p = 0.38, ANOVA)

* Statistical significance (p-value < 0.05)

Patients with DME who were observed or received macular laser treatment had no statistically significant change in BCVA. The change was noted to be 0.1 and -0.4 ETDRS letters after the first DME episode (95% CI -3.6 to 3.8, p>0.90 and 95% CI -1.9 to 1.1, p=0.61), respectively. At the end of the follow-up, the change was -3.7 and -1.1 ETDRS letters (95% CI -7.4 to 0.04, p>0.90 and 95% CI -2.7 to 0.4, p=0.14) for observation and macular laser treatment, respectively. In the anti-VEGF group and combination group, the statistically significant gain after the first DME episode was a respective 4.9 and 5.5 ETDRS letters (95% CI 3.9 to 6.0,

p<0.0001 and 95% CI 2.9 to 8.1, p<0.001). These outcomes sustained after the follow-up and gain were 4.1 and 5.1 ETDRS letters (95% CI 3.1 to 5.2, p<0.0001 and 95% CI 2.5 to 7.8, p<0.0001), respectively (Table 10).

During the onset of DME, five patients with T1D (2.4%) were visually impaired according to the classification of visual impairment by WHO. However, treatment of DME improved the BCVA in several cases, and at the end of the follow-up, only two of these patients (1.0%) met the criteria of visual impairment.

In the anti-VEGF and combination group, a respective 6.0±4.2 and 6.5±6.5 injections were given during the first DME episode. Bevacizumab was the first chosen anti-VEGF agent in 158/159 (99.4%) DME episodes treated with anti-VEGF only or with a combination of macular laser and anti-VEGF. In one case only (0.6%) aflibercept was the first choice of treatment. None of the patients received intravitreal corticosteroids or underwent vitrectomy, and no adverse effects of anti-VEGF treatment were observed.

7 Discussion

7.1 Efficient treatment of intravitreal hemorrhage (I)

BCVA can be very close to normal or severely impaired in patients diagnosed with advanced PRD, depending on the severity of the VH (Chelala et al., 2018; Turner et al., 1985; Wang et al., 2017). Prolonged VH can result in impaired visual acuity and treatment is usually needed (Ahmadieh et al., 2009; Antoszyk et al., 2020; Chelala et al., 2018; DRVS, 1990). In this study, our aim was to research how anti-VEGF treatment performed with IVB can affect VH in a real-world setting and whether it expedites the clearance of the vitreous compared to PRP, vitrectomy and spontaneous resolution of VH. Our results showed that IVB improves the clearance of VH and visual outcomes in patients with PDR. The mean duration of VH was only 57±46 days, and 66% of the patients had a ≥15 letter improvement in their BCVA. The CLARITY trial has shown that anti-VEGF treatment can result in increased BCVA improvement compared to PRP only in patients diagnosed with PDR (Sivaprasad et al., 2017). Moreover, DRCR.net Protocol W, a randomized clinical trial comparing anti-VEGF treatment and sham treatment, showed that anti-VEGF treatment is efficient to prevent vision-threatening complications of DR (Maturi et al., 2021).

In our study we found that VH was more frequent in patients with T1D. Out of all the patients diagnosed with PDR, 16% had T1D and 9% had T2D. Out of these patients 25% developed VH during the 5-year study period. This result agrees with the previous studies showing that complications related to DR are more common in patients diagnosed with T1D (Hautala et al., 2014; Yau et al., 2012) and patients diagnosed with T1D suffer vision loss due to PDR more often than patients diagnosed with T2D (Cheung et al., 2010). In addition, the patients diagnosed with T1D in this study were younger at the time of the onset of the VH (44±13 years) compared to patients diagnosed with T2D (66±7 years). One of the main reasons for this may be that the duration of diabetes is regarded as an independent risk factor for DR (Klein et al., 1984a; Yau et al., 2012; Zhang et al., 2010).

Previous PRP had been performed in 88% of the study patients before the onset of the VH, hence, the PDR progressed despite prior treatment. DRCR.net Protocol S showed that anti-VEGF treatment or PRP are efficient ways to treat PDR, and after 5-year follow-up BCVA was similar between groups. However, these groups had a similar rate of VHs during the study period with a cumulative

probability of 58% for the anti-VEGF group and 54% for the PRP group (Gross et al., 2018).

The analysis identified that IVB improved visual acuity in patients and BCVA increased 0.73±0.04 logMAR units. In agreement with our results, several studies have shown that anti-VEGF treatment for VHs can improve BCVA (Huang et al., 2009; Jonas et al., 2008; Park et al., 2021). In contrast to this, there is evidence that IVB is not superior to other treatments such as PPV (Jorge et al., 2021). However, this may be due to the fact that PPV favors short-term outcomes in comparison to IVB. In addition, PPV is a surgical intervention, whereas IVB is merely an injection, resulting in more convenient and efficient treatment. In order to clear the vitreous an average of 1.7±1.1 injections for one VH episode in our study were needed. Our results are in line with previous studies, which have shown that one to three IVB injections are needed to clear the vitreous (Jonas et al., 2008; Jorge et al., 2021; Park et al., 2021). The median estimate for VH clearance was 57±46 days in the IVB group and 70±6 days for other treatments, and some patients reported that the VH cleared within a few days to 1–2 weeks after the IVB. Park et al. compared IVB to observation of VHs. Their patients were followed for 20 months resulting in data where the time it took for the clearance of VH to be 7 vs. 13 months, respectively (Park et al., 2021). In accordance with our results, even shorter times between 2–4 months for VH clearance with IVB have been reported (Huang et al., 2009; Jonas et al., 2008).

Only 7% of the patients treated with IVB needed PPV during the follow-up. Furthermore, other studies have gained evidence supporting results that patients receiving anti-VEGF treatment have lower vitrectomy rates compared to control groups (Chelala et al., 2018; Huang et al., 2009). Furthermore, a recent meta-analysis showed that monotherapy with anti-VEGF resulted in lower rates of VHs and PPVs compared to PRP (Yates et al., 2021), which supports the idea of anti-VEGF as a conjunctive therapy for PDR. All patients in the IVB group in our study received bevacizumab, which is the primary anti-VEGF drug commonly used in Finland. Studies with ranibizumab (Chelala et al., 2018; Figueira et al., 2018) and aflibercept (Antoszyk et al., 2020; Glassman et al., 2021) have also proven efficient when treating VH due to PDR and regression of retinal neovascularization.

Our results indicate that IVB can be used to efficiently treat VH due to PDR and an average of 1 to 2 injections is needed for the clearance of the vitreous in less than 3 months. Patients in our study presented no serious side effects of IVB, such as endophthalmitis or TRD, suggesting the safety of the treatment, which is further in line with the results presented by the long follow-up period. The safety of IVB

for VH has also been demonstrated in other studies (Gross et al., 2018; Jorge et al., 2021; Park et al., 2021).

This study has several limitations. The study was not randomized, and it was uncontrolled and retrospective in nature. The timing of the control visits after IVB varied and the clearance of VH was observed only at the time of the control visit. The specific time of the appearance of the VH was often available, but the exact time of the clearance of the vitreous was dependent on the time when the patient had their scheduled control visit, leading to a possible negative effect in the results. In addition, the treatment criteria were not pre-defined and depended on the decision made by a retina specialist. Bevacizumab was the only intravitreal drug that had been used, therefore effects of other anti-VEGF drugs, such as ranibizumab or aflibercept, could not be assessed. The number of VH episodes in the IVB group was considerably higher than in PRP, PPV or observation groups. Estimates for clearance of VH were made between the IVB group and combination of other treatment groups in order to match the group sizes. Therefore, conclusions regarding the clearance of VH with IVB cannot be compared to the PRP, PPV and observation groups individually.

Despite the limitations and the retrospective nature, our study illustrates population-based results of advanced PDR with VH. In addition, a long 5-year follow-up period in a real-world setting might be considered as a strength of the study. This enabled the study to determine the rate of VH recurrences and the need for reinjections in a longer time frame. Further research is needed to evaluate which patients benefit the most from anti-VEGF treatment and if there is an adequate treatment protocol to be adapted for patients with VH. For example, a previous DRCR.net study revealed no difference in vitrectomy rates between patients treated with ranibizumab or saline injections, although BCVA offered greater improvement and fever VH recurrences were noted in the ranibizumab group (Bhavsar et al., 2013). Moreover, findings from this study may help ophthalmologists when making treatment decisions for patients with VH.

7.2 Proliferative diabetic retinopathy effects on visual function (II)

In this population-based cohort study, all patients had been diagnosed with T1D since childhood and had developed PDR, which had lasted for 15.4±2.8 years at the time of the study. The Diabetic Retinopathy Study research group concluded that with timely treatment with PRP a significant reduction in risk of vision loss is noted (DRS Research Group, 1981a). Based on this, all study patients had

completed full PRP. Even when treated with PRP, the risk for vision loss is present and PDR may progress (Park et al., 2021). In this study, DME or VHs were seen in 17% and 57% of patients with PDR, despite fully completed PRP. In the DRCR.net Protocol S study there were similar results in regard to the occurrence of VH; after 5 years 46% of patients with PDR treated with PRP had VH (Gross et al., 2018).

However, PRP is an inherently destructive approach and has some adverse effects (Fong et al., 2007; Hautala et al., 2014). In our study, both central and peripheral visual field sensitivities were lower in patients with PDR compared to healthy controls, matching previously reported results on visual field defects due to PRP (Gross et al., 2015; Sivaprasad et al., 2018).

Contrast sensitivity is also known to be affected due to PRP (Fong et al., 2007; Hautala et al., 2018), however, in our study there was no difference in contrast sensitivity between study patients and healthy controls. During the time of the patients' previous visit in 2007, 63% of patients were reported to have decreased contrast sensitivity (Hautala et al., 2018). In contrast to this, our results disagree with the previously reported results. This may be due the different procedure to evaluate the contrast sensitivity. In 2007 the measurements were made by using the Vistech chart at five spatial frequencies whereas in the current study, the Ocusweep algorithm used only one spatial frequency to evaluate the contrast sensitivity of the patients. This may also be explained with the possibility that the algorithm which used one spatial frequency at one cycle per degree was not sensitive enough to detect differences between the study patients and healthy controls. Furthermore, in the current study, binocular contrast sensitivity was measured whereas the same measurement was performed monocularly in the previous study, thus affecting the results. This may highlight the importance of binocularity in overall visual function.

The Ocusweep reaction time perimetry test was also performed on the patients, leading to a 26.2 millisecond slower reaction time compared to the healthy controls. It can be assumed that reaction time may be impaired because of overall neuropathy (Ryan et al., 2003) and even cognitive dysfunction (Wu et al., 2022) due to T1D. However, only one study patient was diagnosed with neuropathy secondary to T1D, thus not completely explaining the slower reaction time.

After 35±3.9 years of life with T1D, patients obtained a relatively good visual function; their BCVA was 73–77 ETDRS letters and only two patients were visually impaired due to PDR. This may be explained by the efficient management of T1D and PDR. The patients also showed an improvement in glycemic control during the follow-up from 2007 to 2019. Another factor to be considered is the fact that several patients started using transdermal glucose monitoring system after their visit in

2007. In a recent meta-analysis, the usage of transdermal glucose monitoring systems has been associated with improved glycemic control in patients diagnosed with T1D an T2D (Liang et al., 2022). In addition, the lipid profile and blood pressure of the study patients remained stable during the follow-up.

Efficient management of PDR after the fully completed PRP has included anti-VEGF treatment for DME and VH if applicable. Data from two meta-analyses have shown that treatment of PDR with PRP and anti-VEGF has beneficial effects on treatment stability and visual outcomes (Fallico et al., 2021; Yates et al., 2021).

HRQoL measured with the 15D instrument decreased slightly during the follow-up, however, the overall HRQoL remained good and the 15D dimension concerning vision remained unchanged. During the follow-up, dimensions concerning mobility and distress improved which might be explained by the implementation of new transdermal glucose monitoring. Flash glucose sensors able patients to measure blood glucose levels effortlessly and in a non-invasive manner, thus, motivating and encouraging more frequent blood glucose level monitoring. Patients with diabetes have been shown to have an emotional and social impact on patients with an impaired HRQoL (Graham-Rowe et al., 2018; Selenius et al., 2020). However, in a previous study analyzing HRQoL of Finnish patients diagnosed with diabetes, it was sown that HRQoL was similar to the general population and only the duration of diabetes seemed to have a negative impact on HRQoL (Schanner et al., 2016). Furthermore, PDR has been associated with impaired HRQoL in these cohort patients in the previous study visit in 2007 (Hannula et al., 2014).

We acknowledge several limitations in this study. The study population was relatively small in size and only 57% of patients diagnosed with PDR in 2007 were able to participate in the re-evaluation in 2019 (excluding deaths and one patient with incomplete participation). Also, measurements of functional vision require proper usage of the Ocusweep device. The measurements can be affected by other conditions, for example defects in hand-eye coordination, causing impairment in the reaction time perimetry test. In addition, decreased reaction time might not only be a result of PDR, but also be caused by diabetic neuropathy which should be considered when interpretating the results. Furthermore, the Ocusweep algorithm measuring contrast sensitivity is based on only one spatial frequency and is a source of positive bias leading to higher spatial frequencies possibly being neglected.

In the current study, we evaluated HRQoL providing us with information about the overall quality of life instead of vision related QoL. The 15D instrument was chosen because the evaluation in 2007 contained measurements of HRQoL with the 15D instrument because aimed to compare HRQoL results between the two re-

evaluation visits in 2007 and 2019. To acquire more detailed information about vision-related QoL, for example National Eye Institute Visual Function Questionnaire 25 would have been used.

The prospective nature, long follow-up time and 35-year duration of T1D are the strengths of this study. All the patients were evaluated in 2007 so that results in BCVA and glycemic control could be compared to the re-evaluation in 2019. Also, functional vision test results with the Ocusweep device were compared to healthy, age-matched Finnish controls with a 1:105 relationship to provide high-quality reference data. Although study patients had suffered from T1D for 35 years and had PDR treated with PRP, they had maintained good visual outcomes and HRQoL comparable to healthy age-matched controls. Furthermore, the rate of visual impairment was low. These findings support the fact that with timely and effective treatment, patients can remain relatively good visual function despite PDR and associated treatments encouraging ophthalmologists to make effective treatment choices.

In the future, more research is needed to evaluate the treatment of VTDR and especially PDR after fully completed PRP. Additional information is needed in order to assess the importance of glycemic control in patients with T1D to prevent further progression of PDR. Novel transdermal glucose monitoring systems provide information about the glycemic control by evaluating the time-in-range instead of long-time glycemic control measured with HbA1c (Liang et al., 2022; Yapanis et al., 2022). This information can provide us with new treatment strategies for patients with T1D and vison-threatening complications (Lu et al., 2018; Yapanis et al., 2022). Moreover, anti-VEGF treatment provides an efficient way to reduce vision loss in patients with DME, VH or progressing neovascularization after fully completed PRP (Yates et al., 2021). Also, recently published four-year outcomes of DRCR.net Protocol W study showed that anti-VEGF therapy may prevent non-PDR progression to PDR (Maturi et al., 2023). Therefore, anti-VEGF treatment should be considered as an adjuvant therapy to PRP in patients diagnosed with PDR.

7.3 Treatment of diabetic macular edema preserves vision (III)

Treatment of DME has revolutionized due to the availability of anti-VEGF therapy, leading to visual impairment caused by DR to markedly reduce (Purola et al., 2022; Schmidt-Erfurth et al., 2017; Wong et al., 2018). Previously focal macular photocoagulation has been the only treatment for DME (ETDRS Research Group, 1985), however, anti-VEGF therapy is currently considered the primary treatment

for CI-DME (Schmidt-Erfurth et al., 2017; Zhang et al., 2022). In our study, patients with T1D and DME were either observed, treated with macular laser, they received anti-VEGF monotherapy or a combination of macular laser and anti-VEGF. As recognized (Hautala et al., 2014; Yau et al., 2012) and observed in our previous study (I), patients diagnosed with T1D have more DR related complications, such as VHs, compared to patients diagnosed with T2D, suggesting different risk profiles for DR related complications in these patients. Therefore, our third study focused on DME treatment outcomes in patients diagnosed with T1D exclusively.

Anti-VEGF agents, bevacizumab, ranibizumab and aflibercept seem to have similar long-term visual outcomes when treating DME (DRCR.net, 2015). However, both ranibizumab (Vader et al., 2020) and aflibercept (DRCR.net, 2015; Wells et al., 2016) have been shown to have better visual outcomes when compared with bevacizumab with poor BCVA at the time of the onset of DME. Bevacizumab is typically used as a first-line anti-VEGF agent in Finland when treating DME or neovascular age-related macular degeneration. In our study, patients received bevacizumab as the first anti-VEGF in all but one case. It is known that the effect of anti-VEGF treatment may be late due to partial response in patients, and at times, some patients are non-responders to the treatment (Ashraf et al., 2016). During the follow-up, 15% of the DME episodes required a switch to aflibercept due to an inadequate response to bevacizumab.

Patients with center-involved DME (CI-DME) were treated with only anti-VEGF or a combination of macular laser and anti-VEGF. Previous clinical trials have shown that with anti-VEGF therapy offers a long-term significant improvement of ≥15 ETDRS letters in BCVA, which can be achieved in more than one third of the patients (Brown et al., 2015; DRCR.net, 2015). Our study agrees with these previous results of the benefits of anti-VEGF treatment for DME. Our study demonstrated the benefit of anti-VEGF therapy in DME during the 65±45-month follow-up in a real-world setting. A statistically significant improvement of 4.9–5.5 ETDRS letters was documented after the first DME episode and these results sustained during the follow-up, leading to a long-term improvement of BCVA measuring at 4.1–5.1 ETDRS letters. Furthermore, a clinical trial comparing bevacizumab and laser therapy for DME showed that after two years 32% of the patients gained ≥15 ETDRS letters, hence supporting the finding that bevacizumab was superior to macular laser, since only 4% of patients treated with macular laser gained ≥15 ETDRS letters (Rajendram et al., 2012). Considering this, patients with DME that were observed or treated by macular laser in our study had no statistically

significant change in BCVA after the first DME episode or during the follow-up. A previous ETDRS study has demonstrated the beneficial effect of focal laser treatment in preventing vision loss (ETDRS Research Group, 1985).

Beyond VEGF, the presence of inflammation is known to affect the pathogenesis of DME (Forrester et al., 2020) and intravitreal corticosteroids may be used to treat DME (Beck et al., 2009; Gao et al., 2021). In our study, none of the patients with DME received intravitreal corticosteroids. Most of the study patients, at the average age of 47 years, might have been assumed to not have their BCVA impaired by cataract, and anti-VEGF treatment with a safer profile may have been chosen to avoid cataract formation which has been associated with administration of intravitreal corticosteroids alongside an increased IOP (Beck et al., 2009; Gao et al., 2021).

At the onset of DME 75% and 25% of the patients had non-PDR and PDR, respectively, after an average of 24±12 years of life with T1D. In a meta-analysis pooling data from five different clinical trials evaluating DME treatment with anti-VEGF, it was shown that DME resolution was faster in patients with more severe DR at the baseline. However, after a 2-year follow-up there were no differences between different DR severities (Talcott et al., 2023). In our study, the duration of T1D had no statistically significant effects on BCVA improvement after the DME resolution. However, the effect of the severity of DR was not assessed. Moreover, we have an agreement with previously stated results, that the prevalence of PDR rises with the duration of T1D even though the prevalence of DME reaches a plateau after 10 years with T1D (Warwick et al., 2017).

Our study has some limitations. Treatment groups were based on real-world treatment decisions made by ophthalmologists and had different clinical features at the baseline, therefore resulting in groups being heterogenic, which in turn, affected the outcomes. For example, there was no pre-defined BCVA-level for each treatment. Taking these features of the data into consideration, only intragroup analysis for BCVA improvement after the first DME episode and after the long-term follow-up was performed. Thus, our study provides information of different treatment results, but no intergroup comparison was made because of this. We also reported long-term BCVA improvement among patients, however, the presence of cataract was not evaluated, as well as any intraocular lens surgery prior or during the follow-up was not included. The main reason for this being that the patients in the study cohort were relatively young and cataract is not common in this patient population, this is still a limitation to be considered. In addition, glycemic control was not defined prior to or during the follow-up, hence the effect of glycemic

control on visual outcomes was not assessed. All patients except one received bevacizumab as a first-line anti-VEGF agent, so no results are available about other anti-VEGF agents such as ranibizumab and aflibercept. In addition, no patients received intravitreal corticosteroids.

This study was a population-based cohort with a long follow-up time giving strong real-world data and treatment results. In addition, one of the strengths of this study is that only patients diagnosed with T1D were included, in contrast to previous studies reporting DME treatment outcomes for both patients diagnosed with T1D and T2D. Patients were treated mainly with bevacizumab which is also the first-line anti-VEGF agent in Finland, thus giving reliable results on intravitreal bevacizumab for DME.

Future research of treatment outcomes between patients diagnosed with T1D and T2D in addition to DME is needed in order to evaluate the possible differences in the visual outcomes and treatment protocols for both patient groups. The efficiency of anti-VEGF treatment is well known; however, more research is needed to establish more individualized treatment protocols. Our study supports the fact that with anti-VEGF treatment for DME it is possible to maintain good visual function even in long-term follow-up.

7.4 Future diagnostics and treatments for diabetic retinopathy offers answers regarding associated burden

Management of DR, in terms of screening and the need for ophthalmic treatment, cause an increasing burden to the healthcare system (Bourne et al., 2021; Teo et al., 2021; Willis et al., 2017). Furthermore, in industrialized countries, for example in Europe including Finland, the population has an increasing median age and WHO has estimated that by 2050, there will be double the number of 60-years olds compared to today (WHO, 2015). Screening and ophthalmic treatment requires high resources and a strong public healthcare sector to cover all patients adequately in order to prevent vision loss (Hautala et al., 2014; Wong et al., 2018). The visual prognosis of DR has markedly improved since the anti-VEGF era, not to mention PRP (Purola et al., 2022; Wong et al., 2018).

PRP will remain as a standard treatment of VTDR alongside anti-VEGF therapy. However, novel methods of applying these treatments are needed to respond to the increasing burden. Telemedicine will provide some answers. In Northern Finland, DR screening is already carried out with a mobile screening unit – screening fundus photographs are instantly available for ophthalmologist referral

via 4G wireless network (Hautala et al., 2014; Hautala et al., 2009). Machine learning based algorithms for DR screening are already available in open markets and research is being carried out to evaluate these algorithms in a real-life setting (Grzybowski et al., 2020; Ngiam & Khor, 2019). Studies are also being conducted to evaluate the possibility of real-time retinal photocoagulation via wireless networks, which can help to cover even more patients living in vast, rural areas (Chen et al., 2021; Kozak et al., 2017).

Novel anti-VEGF agents are also being studied with new application methods. For example, the United States Food and Drug Administration has approved ocular implants continuously releasing anti-VEGF for age-related wet macular degeneration (Chang et al., 2022). These new innovations can profoundly advance the treatment of patients in need of anti-VEGF therapy. The role of anti-VEGF therapy will most likely increase and be applied after fully completed PDR as a form of adjuvant therapy (Maturi et al., 2023; Yates et al., 2021). In the future, modern technologies will provide resource saving methods to reduce the burden caused by the management of DR.

8 Conclusions

I Treatment of VH with IVB is superior to other treatments including PRP, PPV and observation in clearing the vitreous, improving visual outcomes and preventing recurrences of VHs.

II Long-term visual prognosis and HRQoL remained good, despite the declined functional vision caused by PDR, due to efficient treatment of DR and an improved glycemic balance in the cohort of patients with 35-year duration of T1D.

III Anti-VEGF treatment alone or in combination with macular laser seems to be an efficient treatment for patients with T1D and central-involved DME in terms of improvement in visual outcomes even in long-term follow-up.

References

Abcouwer, S. F. (2017). Müller cell–microglia cross talk drives neuroinflammation in diabetic retinopathy. *Diabetes*, *66*(2), 261. https://doi.org/10.2337/DBI16-0047

Abdelmotaal, H., Ibrahim, W., Sharaf, M., & Abdelazeem, K. (2020). Causes and clinical impact of loss to follow-up in patients with proliferative diabetic retinopathy. *Journal of Ophthalmology*, *2020*. https://doi.org/10.1155/2020/7691724

Abràmoff, M. D., Lavin, P. T., Birch, M., Shah, N., & Folk, J. C. (2018). Pivotal trial of an autonomous AI-based diagnostic system for detection of diabetic retinopathy in primary care offices. *Npj Digital Medicine 2018 1:1*, *1*(1), 1–8. https://doi.org/10.1038/s41746-018-0040-6

Adamis, A. P., Miller, J. W., Bernal, M. T., D'Amico, D. J., Folkman, J., Yeo, T. K., & Yeo, K. T. (1994). Increased vascular endothelial growth factor levels in the vitreous of eyes with proliferative diabetic retinopathy. *American Journal of Ophthalmology*, *118*(4), 445–450. https://doi.org/10.1016/S0002-9394(14)75794-0

Ahmadieh, H., Shoeibi, N., Entezari, M., & Monshizadeh, R. (2009). Intravitreal bevacizumab for prevention of early postvitrectomy hemorrhage in diabetic patients: a randomized clinical trial. *Ophthalmology*, *116*(10), 1943–1948. https://doi.org/10.1016/J.OPHTHA.2009.07.001

Aiello, L. M. (2003). Perspectives on diabetic retinopathy. *American Journal of Ophthalmology*, *136*(1), 122–135. https://doi.org/10.1016/S0002-9394(03)00219-8

Aiello, L. P., Avery, R. L., Arrigg, P. G., Keyt, B. A., Jampel, H. D., Shah, S. T., Pasquale, L. R., Thieme, H., Iwamoto, M. A., Park, J. E., Nguyen, H. v., Aiello, L. M., Ferrara, N., & King, G. L. (1994). Vascular endothelial growth factor in ocular fluid of patients with diabetic retinopathy and other retinal disorders. *The New England Journal of Medicine*, *331*(22), 1480–1487. https://doi.org/10.1056/NEJM199412013312203

Aiello, L. P., Beck, R. W., Bressler, N. M., Browning, D. J., Chalam, K. v., Davis, M., Ferris, F. L., Glassman, A. R., Maturi, R. K., Stockdale, C. R., & Topping, T. M. (2011). Rationale for the diabetic retinopathy clinical research network treatment protocol for center-involved diabetic macular edema. *Ophthalmology*, *118*(12). https://doi.org/10.1016/J.OPHTHA.2011.09.058

Aldington, S. J., Kohner, E. M., Meuer, S., Klein, R., & SjØlie, A. K. (1995). Methodology for retinal photography and assessment of diabetic retinopathy: the EURODIAB IDDM complications study. *Diabetologia*, *38*(4), 437–444. https://doi.org/10.1007/BF00410281

Al-Haddad, C. E., Jurdi, F. A., & Bashshur, Z. F. (2004). Intravitreal triamcinolone acetonide for the management of diabetic papillopathy. *American Journal of Ophthalmology*, *137*(6), 1151–1153. https://doi.org/10.1016/j.ajo.2004.01.032

Altaf, Q. A., Dodson, P., Ali, A., Raymond, N. T., Wharton, H., Fellows, H., Hampshire-Bancroft, R., Shah, M., Shepherd, E., Miah, J., Barnett, A. H., & Tahrani, A. A. (2017). Obstructive sleep apnea and retinopathy in patients with type 2 diabetes. a longitudinal study. *American Journal of Respiratory and Critical Care Medicine*, *196*(7), 892–900. https://doi.org/10.1164/RCCM.201701-0175OC

American Diabetes Association Professional Practice Committee, Draznin, B., Aroda, V. R., Bakris, G., Benson, G., Brown, F. M., Freeman, R., Green, J., Huang, E., Isaacs, D., Kahan, S., Leon, J., Lyons, S. K., Peters, A. L., Prahalad, P., Reusch, J. E. B., & Young-Hyman, D. (2021). 9. Pharmacologic approaches to glycemic treatment: standards of medical care in diabetes—2022. *Diabetes Care*, *45*(Supplement_1), S125–S143. https://doi.org/10.2337/dc22-S009

Antoszyk, A. N., Glassman, A. R., Beaulieu, W. T., Jampol, L. M., Jhaveri, C. D., Punjabi, O. S., Salehi-Had, H., Wells, J. A., Maguire, M. G., Stockdale, C. R., Martin, D. F., & Sun, J. K. (2020). Effect of intravitreous aflibercept vs vitrectomy with panretinal photocoagulation on visual acuity in patients with vitreous hemorrhage from proliferative diabetic retinopathy: a randomized clinical trial. *JAMA*, *324*(23), 2383–2395. https://doi.org/10.1001/JAMA.2020.23027

Arevalo, J. F., Maia, M., Flynn, H. W., Saravia, M., Avery, R. L., Wu, L., Eid Farah, M., Pieramici, D. J., Berrocal, M. H., & Sanchez, J. G. (2008). Tractional retinal detachment following intravitreal bevacizumab (Avastin) in patients with severe proliferative diabetic retinopathy. *The British Journal of Ophthalmology*, *92*(2), 213–216. https://doi.org/10.1136/BJO.2007.127142

Arffman, M., Ilanne-Parikka, P., Keskimäki, I., Kurkela, O., Lindström, J., Sund, R., & Winell, K. (2020). Tyypin 1 ja 2 diabeteksen ja niiden lisäsairauksien ilmaantuvuus ja esiintyvyys Suomessa vuosina 2000-2017. *The Finnish Institute for Health and Welfare*. https://urn.fi/URN:ISBN:978-952-343-501-8

Arroba, A. I., & Valverde, Á. M. (2017). Modulation of microglia in the retina: new insights into diabetic retinopathy. *Acta Diabetologica*, *54*(6), 527–533. https://doi.org/10.1007/S00592-017-0984-Z/FIGURES/1

Arry, B., Renner, M. B., Ark, M., Ooper, E. C., Eane, I. F. K., AH Enrik, H., Arving, P., Iuseppe, G., Emuzzi, R., Hang, H. Z., Hahnaz, S., Hahinfar, S., Tudy, S., & Nvestigators, I. (2001). Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *345*(12), 861–869. https://doi.org/10.1056/nejmoa011161

Ashraf, M., Souka, A., & Adelman, R. (2016). Predicting outcomes to anti-vascular endothelial growth factor (VEGF) therapy in diabetic macular oedema: a review of the literature. *The British Journal of Ophthalmology*, *100*(12), 1596–1604. https://doi.org/10.1136/BJOPHTHALMOL-2016-308388

Avery, R. L., Pearlman, J., Pieramici, D. J., Rabena, M. D., Castellarin, A. A., Nasir, M. A., Giust, M. J., Wendel, R., & Patel, A. (2006). Intravitreal bevacizumab (Avastin) in the treatment of proliferative diabetic retinopathy. *Ophthalmology*, *113*(10). https://doi.org/10.1016/J.OPHTHA.2006.05.064

Bach, J.-F. O., & Chatenoud, L. (2012). The hygiene hypothesis: an explanation for the increased frequency of insulin-dependent diabetes. *Cold Spring Harb Perspect Med.*, *2*(2), a007799. https://doi.org/10.1101/cshperspect.a007799

Baekkeskov, S., Aanstoot, H. J., Christgai, S., Reetz, A., Solimena, M., Cascalho, M., Folli, F., Richter-Olesen, H., & Camilli, P. de. (1990). Identification of the 64K autoantigen in insulin-dependent diabetes as the GABA-synthesizing enzyme glutamic acid decarboxylase. *Nature*, *347*(6289), 151–156. https://doi.org/10.1038/347151A0

Baigent, C., Blackwell, L., Emberson, J., Holland, L. E., Reith, C., Bhala, N., Peto, R., Barnes, E. H., Keech, A., Simes, J., Collins, R., de Lemos, J., Braunwald, E., Blazing, M., Murphy, S., Downs, J. R., Gotto, A., Clearfield, M., Holdaas, H., Sourjina, T. (2010). Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet (London, England)*, *376*(9753), 1670–1681. https://doi.org/10.1016/S0140-6736(10)61350-5

Baigent, C., Sudlow, C., Collins, R., & Peto, R. (2002). Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ*, *324*(7329), 71–86. https://doi.org/10.1136/BMJ.324.7329.71

Baker, C. W., Almukhtar, T., Bressler, N. M., Glassman, A. R., Grover, S., Kim, S. J., Murtha, T. J., Rauser, M. E., & Stockdale, C. (2013). Macular edema after cataract surgery in eyes without preoperative central-involved diabetic macular edema. *JAMA Ophthalmology*, *131*(7), 870–879. https://doi.org/10.1001/JAMAOPHTHALMOL.2013.2313

Baker, C. W., Glassman, A. R., Beaulieu, W. T., Antoszyk, A. N., Browning, D. J., Chalam, K. v., Grover, S., Jampol, L. M., Jhaveri, C. D., Melia, M., Stockdale, C. R., Martin, D. F., & Sun, J. K. (2019). Effect of initial management with aflibercept vs laser photocoagulation vs observation on vision loss among patients with diabetic macular edema involving the center of the macula and good visual acuity: a randomized clinical trial. *JAMA*, *321*(19), 1880–1894. https://doi.org/10.1001/JAMA.2019.5790

Barber, A. J., Gardner, T. W., & Abcouwer, S. F. (2011). The significance of vascular and neural apoptosis to the pathology of diabetic retinopathy. *Investigative Ophthalmology & Visual Science*, *52*(2), 1156–1163. https://doi.org/10.1167/IOVS.10-6293

Barr, C. C., Glaser, J. S., & Blankenship, G. (1980). Acute disc swelling in juvenile diabetes. Clinical profile and natural history of 12 cases. *Archives of Ophthalmology (Chicago, Ill. : 1960)*, *98*(12), 2185–2192. https://doi.org/10.1001/ARCHOPHT.1980.01020041037006

Bayraktar, Z., Alacali, N., & Bayraktar, S. (2002). Diabetic papillopathy in type II diabetic patients. *Retina (Philadelphia, Pa.)*, *22*(6), 752–758. https://doi.org/10.1097/00006982-200212000-00011

Beck, R. W., Edwards, A. R., Aiello, L. P., Bressler, N. M., Ferris, F., Glassman, A. R., Hartnett, M. E., Ip, M. S., Kim, J. E., & Kollman, C. (2009). Three-year follow-up of a randomized trial comparing focal/grid photocoagulation and intravitreal triamcinolone for diabetic macular edema. *Archives of Ophthalmology (Chicago, Ill. : 1960)*, *127*(3), 245–251. https://doi.org/10.1001/ARCHOPHTHALMOL.2008.610

Beck-Nielsen, H., & Groop, L. C. (1994). Metabolic and genetic characterization of prediabetic states. Sequence of events leading to non-insulin-dependent diabetes mellitus. *The Journal of Clinical Investigation*, *94*(5), 1714–1721. https://doi.org/10.1172/JCI117518

Bhaskara, G., Budhiarta, A. A. G., Gotera, W., Saraswati, M. R., Dwipayana, I. M. P., Semadi, I. M. S., Nugraha, I. B. A., Wardani, I. A. K., & Suastika, K. (2022). Factors associated with diabetes-related distress in type 2 diabetes mellitus patients. *Diabetes, Metabolic Syndrome and Obesity : Targets and Therapy*, *15*, 2077–2085. https://doi.org/10.2147/DMSO.S363431

Bhavsar, A. R., Torres, K., Beck, R. W., Bressler, N. M., Ferris, F. L., Friedman, S. M., Glassman, A. R., Maturi, R. K., Melia, M., Singer, M. A., & Stockdale, C. R. (2013). Randomized clinical trial evaluating intravitreal ranibizumab or saline for vitreous hemorrhage from proliferative diabetic retinopathy. *JAMA Ophthalmology*, *131*(3), 283–293. https://doi.org/10.1001/JAMAOPHTHALMOL.2013.2015

Blankenship, G. W. (1991). Fifteen-year Argon Laser and Xenon Photocoagulation Results of Bascom Palmer Eye Institute's Patients Participating in the Diabetic Retinopathy Study. *Ophthalmology*, *98*(2), 125–128. https://doi.org/10.1016/S0161-6420(91)32326-1

Bourne, R. R. A., Steinmetz, J. D., Saylan, M., Mersha, A. M., Weldemariam, A. H., Wondmeneh, T. G., Sreeramareddy, C. T., Pinheiro, M., Yaseri, M., Yu, C., Zastrozhin, M. S., Zastrozhina, A., Zhang, Z. J., Zimsen, S. R. M., Yonemoto, N., Tsegaye, G. W., Vu, G. T., Vongpradith, A., Renzaho, A. M. N., … Vos, T. (2021). Causes of blindness and vision impairment in 2020 and trends over 30 years, and prevalence of avoidable blindness in relation to VISION 2020: the Right to Sight: an analysis for the Global Burden of Disease Study. *The Lancet. Global Health*, *9*(2), e144–e160. https://doi.org/10.1016/S2214-109X(20)30489-7

Boyer, D. S., Yoon, Y. H., Belfort, R., Bandello, F., Maturi, R. K., Augustin, A. J., Li, X. Y., Cui, H., Hashad, Y., & Whitcup, S. M. (2014). Three-year, randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with diabetic macular edema. *Ophthalmology*, *121*(10), 1904–1914. https://doi.org/10.1016/J.OPHTHA.2014.04.024

Brand, K. M. G., Saarelainen, L., Sonajalg, J., Boutmy, E., Foch, C., Vääräsmäki, M., Morin-Papunen, L., Schlachter, J., Hakkarainen, K. M., Korhonen, P., Vehkala, M., Thorén, R., & Svanström, H. (2022). Metformin in pregnancy and risk of adverse long-term outcomes: a register-based cohort study. *BMJ Open Diabetes Research and Care*, *10*(1), e002363. https://doi.org/10.1136/BMJDRC-2021-002363

Bressler, N. M., Beaulieu, W. T., Bressler, S. B., Glassman, A. R., Melia, B. M., Jampol, L. M., Jhaveri, C. D., Salehi-Had, H., Velez, G., & Sun, J. K. (2020). Anti-vascular endothelial growth factor therapy and risk of traction retinal detachment in eyes with proliferative diabetic retinopathy: pooled analysis of five drcr retina network randomized clinical trials. *Retina (Philadelphia, Pa.)*, *40*(6), 1021–1028. https://doi.org/10.1097/IAE.0000000000002633

Bressler, S. B., Liu, D., Glassman, A. R., Blodi, B. A., Castellarin, A. A., Jampol, L. M., Kaufman, P. L., Melia, M., Singh, H., & Wells, J. A. (2017). change in diabetic retinopathy through 2 years: secondary analysis of a randomized clinical trial comparing aflibercept, bevacizumab, and ranibizumab. *JAMA Ophthalmology*, *135*(6), 558–568. https://doi.org/10.1001/JAMAOPHTHALMOL.2017.0821

Bron, A. J., Sparrow, J., Brown, N. A. P., Harding, J. J., & Blakytny, R. (1993). The lens in diabetes. *Eye (London, England)*, *7 (Pt2)* (2), 260–275. https://doi.org/10.1038/EYE.1993.60

Brown, D. M., Schmidt-Erfurth, U., Do, D. v., Holz, F. G., Boyer, D. S., Midena, E., Heier, J. S., Terasaki, H., Kaiser, P. K., Marcus, D. M., Nguyen, Q. D., Jaffe, G. J., Slakter, J. S., Simader, C., Soo, Y., Schmelter, T., Yancopoulos, G. D., Stahl, N., Vitti, R., … Korobelnik, J. F. (2015). Intravitreal aflibercept for diabetic macular edema: 100-week results from the VISTA and VIVID Studies. *Ophthalmology*, *122*(10), 2044–2052. https://doi.org/10.1016/J.OPHTHA.2015.06.017

Brown, D. M., Wykoff, C. C., Boyer, D., Heier, J. S., Clark, W. L., Emanuelli, A., Higgins, P. M., Singer, M., Weinreich, D. M., Yancopoulos, G. D., Berliner, A. J., Chu, K., Reed, K., Cheng, Y., & Vitti, R. (2021). Evaluation of intravitreal aflibercept for the treatment of severe nonproliferative diabetic retinopathy: results from the PANORAMA randomized clinical trial. *JAMA Ophthalmology*, *139*(9), 946–955. https://doi.org/10.1001/JAMAOPHTHALMOL.2021.2809

Brown, M. R., Dyck, P. J., McClearn, G. E., Sima, A. A., Powell, H. C., & Porte, D. (1982). Central and peripheral nervous system complications. *Diabetes*, *31*(Suppl 1 Pt 2), 65–70. https://doi.org/10.2337/DIAB.31.1.S65

Brownlee, M. (1994). Glycation and Diabetic Complications. *Diabetes*, *43*(6), 836–841. https://doi.org/10.2337/DIAB.43.6.836

Callaghan, B. C., Cheng, H. T., Stables, C. L., Smith, A. L., & Feldman, E. L. (2012). Diabetic neuropathy: clinical manifestations and current treatments. *The Lancet Neurology*, *11*(6), 521–534. https://doi.org/10.1016/S1474-4422(12)70065-0

Chang, M. A., Kapre, A., Kaufman, D., Kardatzke, D. R., Rabena, M., Patel, S., Bobbala, A., Gune, S., Fung, A., & Wallenstein, G. (2022). Patient preference and treatment satisfaction with a port delivery system for ranibizumab vs intravitreal injections in patients with neovascular age-related macular degeneration: a randomized clinical trial. *JAMA Ophthalmology*, *140*(8), 771–778. https://doi.org/10.1001/JAMAOPHTHALMOL.2022.1091

Chelala, E., Nehme, J., el Rami, H., Aoun, R., Dirani, A., Fadlallah, A., & Jalkh, A. (2018). Efficacy of intravitreal ranibizumab injections in the treatment of vitreous hemorrhage related to proliferative diabetic retinopathy. *Retina*, *38*(6), 1127–1133. https://doi.org/10.1097/IAE.0000000000001673

Chen, H., Pan, X., Yang, J., Fan, J., Qin, M., Sun, H., Liu, J., Li, N., Ting, D. S. W., & Chen, Y. (2021). Application of 5g technology to conduct real-time teleretinal laser photocoagulation for the treatment of diabetic retinopathy. *JAMA Ophthalmology*, *139*(9), 975–982. https://doi.org/10.1001/JAMAOPHTHALMOL.2021.2312

Cheung, N., Mitchell, P., & Wong, T. Y. (2010). Diabetic retinopathy. *Lancet (London, England)*, *376*(9735), 124–136. https://doi.org/10.1016/S0140-6736(09)62124-3

Chew, E. Y., Davis, M. D., Danis, R. P., Lovato, J. F., Perdue, L. H., Greven, C., Genuth, S., Goff, D. C., Leiter, L. A., Ismail-Beigi, F., & Ambrosius, W. T. (2014). The effects of medical management on the progression of diabetic retinopathy in persons with type 2 diabetes: the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Eye Study. *Ophthalmology*, *121*(12), 2443–2451. https://doi.org/10.1016/J.OPHTHA.2014.07.019

Chew, E. Y., Klein, M. L., Ferris, F. L., Remaley, N. A., Murphy, R. P., Chantry, K., Hoogwerf, B. J., & Miller, D. (1996). Association of elevated serum lipid levels with retinal hard exudate in diabetic retinopathy. Early Treatment Diabetic Retinopathy Study (ETDRS) Report 22. *Archives of Ophthalmology (Chicago, Ill. : 1960)*, *114*(9), 1079–1084. https://doi.org/10.1001/ARCHOPHT.1996.01100140281004

Chew, E. Y., Mills, J. L., Metzger, B. E., Remaley, N. A., Jovanovic-Peterson, L., Knopp, R. H., Conley, M., Rand, L., Simpson, J. L., Holmes, L. B., & Aarons, J. H. (1995). Metabolic control and progression of retinopathy. The diabetes in early pregnancy study. National institute of child health and human development diabetes in early pregnancy study. *Diabetes Care*, *18*(5), 631–637. https://doi.org/10.2337/DIACARE.18.5.631

Choudhury, A. A., & Devi Rajeswari, V. (2021). Gestational diabetes mellitus - A metabolic and reproductive disorder. *Biomedicine & Pharmacotherapy = Biomedecine & Pharmacotherapie*, *143*. https://doi.org/10.1016/J.BIOPHA.2021.112183

Chung, Y. R., Park, S. W., Choi, S. Y., Kim, S. W., Moon, K. Y., Kim, J. H., & Lee, K. (2017). Association of statin use and hypertriglyceridemia with diabetic macular edema in patients with type 2 diabetes and diabetic retinopathy. *Cardiovascular Diabetology*, *16*(1). https://doi.org/10.1186/S12933-016-0486-2

Cleary, A., Backlund, J.-Y. C., Ge-nuth, S. M., Lachin, J. M., Orchard, T. J., Raskin, P., & Zinman, B. (2005). Intensive Diabetes Treatment and Cardiovascular Disease in Patients with Type 1 Diabetes. *Https://Doi.Org/10.1056/NEJMoa052187*, *353*(25), 2643–2653. https://doi.org/10.1056/NEJMOA052187

Cooper, O. A. E., Taylor, D. J., Crabb, D. P., Sim, D. A., & McBain, H. (2020). Psychological, social and everyday visual impact of diabetic macular oedema and diabetic retinopathy: a systematic review. *Diabetic Medicine : A Journal of the British Diabetic Association*, *37*(6), 924–933. https://doi.org/10.1111/DME.14125

Cousen, P., Cackett, P., Bennett, H., Swa, K., & Dhillon, B. (2007). Tear production and corneal sensitivity in diabetes. *Journal of Diabetes and Its Complications*, *21*(6), 371–373. https://doi.org/10.1016/J.JDIACOMP.2006.05.008

Cunha-Vaz, J., Ashton, P., Iezzi, R., Campochiaro, P. A., Dugel, P. U., Holz, F. G., Weber, M., Danis, R. P., Kuppermann, B. D., Bailey, C., Billman, K., Kapik, B., Kane, F., Green, K., Brown, D. M., & Pearson, A. (2014). Sustained delivery fluocinolone acetonide vitreous implants: long-term benefit in patients with chronic diabetic macular edema. *Ophthalmology*, *121*(10), 1892–1903.e3. https://doi.org/10.1016/J.OPHTHA.2014.04.019

Curtis, T. M., Gardiner, T. A., & Stitt, A. W. (2009). Microvascular lesions of diabetic retinopathy: clues towards understanding pathogenesis? *Eye (London, England)*, *23*(7), 1496–1508. https://doi.org/10.1038/EYE.2009.108

Dagher, Z., Park, Y. S., Asnaghi, V., Hoehn, T., Gerhardinger, C., & Lorenzi, M. (2004). Studies of rat and human retinas predict a role for the polyol pathway in human diabetic retinopathy. *Diabetes*, *53*(9), 2404–2411. https://doi.org/10.2337/DIABETES.53.9.2404

D'Angeli, M. A., Merzon, E., Valbuena, L. F., Tirschwell, D., Paris, C. A., & Mueller, B. A. (2010). Environmental factors associated with childhood-onset type 1 diabetes mellitus: an exploration of the hygiene and overload hypotheses. *Archives of Pediatrics & Adolescent Medicine*, *164*(8), 732–738. https://doi.org/10.1001/ARCHPEDIATRICS.2010.115

Davis, M. D. (1965). Vitreous contraction in proliferative diabetic retinopathy. *Archives of Ophthalmology (Chicago, Ill.: 1960)*, *74*(6), 741–751. https://doi.org/10.1001/ARCHOPHT.1965.00970040743003

de Boer, I. H., Rue, T. C., Cleary, P. A., Lachin, J. M., Molitch, M. E., Steffes, M. W., Sun, W., Zinman, B., Brunzell, J. D., & Group, D. C. and C. T. of D. I. and C. S. R. (2011). Long-term renal outcomes of patients with type 1 diabetes mellitus and microalbuminuria: an analysis of the diabetes control and complications trial/epidemiology of diabetes interventions and complications cohort. *Archives of Internal Medicine*, *171*(5), 412–420. https://doi.org/10.1001/archinternmed.2011.16

Delvecchio, M., Pastore, C., & Giordano, P. (2020). Treatment options for mody patients: a systematic review of literature. *Diabetes Therapy*, *11*(8), 1667–1685. https://doi.org/10.1007/S13300-020-00864-4

Deshpande, A. D., Harris-Hayes, M., & Schootman, M. (2008). Epidemiology of diabetes and diabetes-related complications. *Physical Therapy*, *88*(11), 1254. https://doi.org/10.2522/PTJ.20080020

Diabetes Control and Complications Trial Research Group. (2000). Effect of pregnancy on microvascular complications in the diabetes control and complications trial. The Diabetes Control and Complications Trial Research Group. *Diabetes Care*, *23*(8), 1084–1091. https://doi.org/10.2337/DIACARE.23.8.1084

Drasdo, N., Chiti, Z., Owens, D. R., & North, R. v. (2002). Effect of darkness on inner retinal hypoxia in diabetes. *Lancet*, *359*(9325), 2251–2253. https://doi.org/10.1016/S0140-6736(02)09265-6

DRCR.net. (2008). A randomized trial comparing intravitreal triamcinolone acetonide and focal/grid photocoagulation for diabetic macular edema. *Ophthalmology*, *115*(9). https://doi.org/10.1016/J.OPHTHA.2008.06.015

DRCR.net. (2015). Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema. *New England Journal of Medicine*, *372*(13), 1193–1203. https://doi.org/10.1056/NEJMOA1414264/SUPPL_FILE/NEJMOA1414264_DISCLOSURES.PDF

DRS Research Group. (1978). Photocoagulation treatment of proliferative diabetic retinopathy: the second report of diabetic retinopathy study findings. *Ophthalmology*, *85*(1), 82–106. https://doi.org/10.1016/S0161-6420(78)35693-1

DRS Research Group. (1981a). Photocoagulation treatment of proliferative diabetic retinopathy. Clinical application of Diabetic Retinopathy Study (DRS) findings, DRS Report Number 8. The Diabetic Retinopathy Study Research Group. *Ophthalmology*, *88*(7), 583–600.

DRS Research Group. (1981b). Diabetic retinopathy study. Report number 6. Design, methods, and baseline results. Report Number 7. A modification of the Airlie House classification of diabetic retinopathy. Prepared by the Diabetic Retinopathy. *Investigative Ophthalmology & Visual Science*, *21*(1), 147–226.

DRVS. (1990). Early vitrectomy for severe vitreous hemorrhage in diabetic retinopathy. Four-year results of a randomized trial: Diabetic Retinopathy Vitrectomy Study Report 5. *Archives of Ophthalmology (Chicago, Ill. : 1960)*, *108*(7), 958–964. https://doi.org/10.1001/ARCHOPHT.1990.01070090060040

Du, X., Matsumura, T., Edelstein, D., Rossetti, L., Zsengellér, Z., Szabó, C., & Brownlee, M. (2003). Inhibition of GAPDH activity by poly(ADP-ribose) polymerase activates three major pathways of hyperglycemic damage in endothelial cells. *Journal of Clinical Investigation*, *112*(7), 1049–1057. https://doi.org/10.1172/JCI18127

Dyck, P. J., Kratz, K. M., Karnes, J. L., Litchy, W. J., Klein, R., Pach, J. M., Wilson, D. M., O'Brien, P. C., & Melton, L. J. (1993). The prevalence by staged severity of various types of diabetic neuropathy, retinopathy, and nephropathy in a population-based cohort: the Rochester Diabetic Neuropathy Study. *Neurology*, *43*(4), 817–824. https://doi.org/10.1212/WNL.43.4.817

Einarson, T. R., Acs, A., Ludwig, C., & Panton, U. H. (2018). Prevalence of cardiovascular disease in type 2 diabetes: a systematic literature review of scientific evidence from across the world in 2007–2017. *Cardiovascular Diabetology 2018 17:1*, *17*(1), 1–19. https://doi.org/10.1186/S12933-018-0728-6

Eissa, I. M., Khalil, N. M., & El-Gendy, H. A. (2016). A controlled study on the correlation between tear film volume and tear film stability in diabetic patients. *Journal of Ophthalmology*, *2016*. https://doi.org/10.1155/2016/5465272

Elsayed, N. A., Aleppo, G., Aroda, V. R., Bannuru, R. R., Brown, F. M., Bruemmer, D., Collins, B. S., Hilliard, M. E., Isaacs, D., Johnson, E. L., Kahan, S., Khunti, K., Leon, J., Lyons, S. K., Perry, M. Lou, Prahalad, P., Pratley, R. E., Seley, J. J., Stanton, R. C., & Gabbay, R. A. (2023). 8. Obesity and Weight Management for the Prevention and Treatment of Type 2 Diabetes: Standards of Care in Diabetes—2023. *Diabetes Care*, *46*(Suppl 1), S128. https://doi.org/10.2337/DC23-S008

Emanuele, N. v., Swade, T. F., & Emanuele, M. A. (1998). Consequences of Alcohol Use in Diabetics. *Alcohol Health and Research World*, *22*(3), 211. /pmc/articles/PMC6761899/

ETDRS Research Group. (1985). Photocoagulation for Diabetic Macular Edema: Early Treatment Diabetic Retinopathy Study Report Number 1 Early Treatment Diabetic Retinopathy Study Research Group. *Archives of Ophthalmology*, *103*(12), 1796–1806. https://doi.org/10.1001/ARCHOPHT.1985.01050120030015

ETDRS Research Group. (1991a). Early photocoagulation for diabetic retinopathy: ETDRS report number 9. *Ophthalmology*, *98*(5), 766–785. https://doi.org/10.1016/S0161-6420(13)38011-7

ETDRS Research Group. (1991b). Fundus photographic risk factors for progression of diabetic retinopathy: ETDRS report number 12. *Ophthalmology*, *98*(5), 823–833. https://doi.org/10.1016/S0161-6420(13)38014-2

Eze, I. C., Hemkens, L. G., Bucher, H. C., Hoffmann, B., Schindler, C., Künzli, N., Schikowski, T., & Probst-Hensch, N. M. (2015). Association between ambient air pollution and diabetes mellitus in Europe and North America: systematic review and meta-analysis. *Environmental Health Perspectives*, *123*(5), 381–389. https://doi.org/10.1289/EHP.1307823

Fajans, S. S., & Bell, G. I. (2011). MODY: History, genetics, pathophysiology, and clinical decision making. *Diabetes Care*, *34*(8), 1878–1884. https://doi.org/10.2337/dc11-0035

Fallico, M., Maugeri, A., Lotery, A., Longo, A., Bonfiglio, V., Russo, A., Avitabile, T., Pulvirenti, A., Furino, C., Cennamo, G., Barchitta, M., Agodi, A., & Reibaldi, M. (2021). Intravitreal anti-vascular endothelial growth factors, panretinal photocoagulation and combined treatment for proliferative diabetic retinopathy: a systematic review and network meta-analysis. *Acta Ophthalmologica*, *99*(6), e795–e805. https://doi.org/10.1111/AOS.14681

Faraji, M., Kangari, H., Majidi, A., & Tabatabaee, S. M. (2020). Stereopsis in Early Diabetic Retinopathy. *Clinical Optometry*, *12*, 1. https://doi.org/10.2147/OPTO.S232312

Faulborn, J., & Bowald, S. (1985). Microproliferations in proliferative diabetic retinopathy and their relationship to the vitreous: corresponding light and electron microscopic studies. *Graefe's Archive for Clinical and Experimental Ophthalmology = Albrecht von Graefes Archiv Fur Klinische Und Experimentelle Ophthalmologie*, *223*(3), 130–138. https://doi.org/10.1007/BF02148888

Feldman, E. L., Nave, K. A., Jensen, T. S., & Bennett, D. L. H. (2017). New Horizons in Diabetic Neuropathy: Mechanisms, Bioenergetics, and Pain. *Neuron*, *93*(6), 1296–1313. https://doi.org/10.1016/J.NEURON.2017.02.005

Fernández-Vigo, J., Castro, J., & Macarro, A. (1997). Diabetic iris neovascularization. Natural history and treatment. *Acta Ophthalmologica Scandinavica*, *75*(1), 89–93. https://doi.org/10.1111/J.1600-0420.1997.TB00258.X

Ferrara, N., Hillan, K. J., & Novotny, W. (2005). Bevacizumab (Avastin), a humanized anti-VEGF monoclonal antibody for cancer therapy. *Biochemical and Biophysical Research Communications*, *333*(2), 328–335. https://doi.org/10.1016/J.BBRC.2005.05.132

Figueira, J., Fletcher, E., Massin, P., Silva, R., Bandello, F., Midena, E., Varano, M., Sivaprasad, S., Eleftheriadis, H., Menon, G., Amaro, M., Ayello Scheer, S., Creuzot-Garcher, C., Nascimento, J., Alves, D., Nunes, S., Lobo, C., & Cunha-Vaz, J. (2018). Ranibizumab plus panretinal photocoagulation versus panretinal photocoagulation alone for high-risk proliferative diabetic retinopathy (PROTEUS study). *Ophthalmology*, *125*(5), 691–700. https://doi.org/10.1016/J.OPHTHA.2017.12.008

Finnish Medical Society Duodecim. (2014). *Diabetic retinopathy: current care guidelines*.

Finnish Medical Society Duodecim. (2018). *Insulin-deficient diabetes: current care guidelines*.

Finnish Medical Society Duodecim. (2020). *Type 2 diabetes: current care guidelines*.

Finnish Medical Society Duodecim. (2022). *Gestational diabetes: current care guidelines*.

Fiorentino, M., Bolignano, D., Tesar, V., Pisano, A., van Biesen, W., Tripepi, G., D'Arrigo, G., & Gesualdo, L. (2017). Renal biopsy in patients with diabetes: a pooled meta-analysis of 48 studies. *Nephrology Dialysis Transplantation*, *32*(1), 97–110. https://doi.org/10.1093/NDT/GFW070

Flaxel, C. J., Adelman, R. A., Bailey, S. T., Fawzi, A., Lim, J. I., Vemulakonda, G. A., & Ying, G. shuang. (2020). Diabetic Retinopathy Preferred Practice Pattern®. *Ophthalmology*, *127*(1), P66–P145. https://doi.org/10.1016/J.OPHTHA.2019.09.025

Flynn, H. W., Chew, E. Y., Simons, B. D., Barton, F. B., Remaley, N. A., & Ferris, F. L. (1992). Pars Plana Vitrectomy in the Early Treatment Diabetic Retinopathy Study: ETDRS Report Number 17. *Ophthalmology*, *99*(9), 1351–1357. https://doi.org/10.1016/S0161-6420(92)31779-8

Fong, D. S., Girach, A., & Boney, A. (2007). Visual side effects of successful scatter laser photocoagulation surgery for proliferative diabetic retinopathy: A literature review. *Retina*, *27*(7), 816–824. https://doi.org/10.1097/IAE.0B013E318042D32C

Forrester, J. v., Kuffova, L., & Delibegovic, M. (2020). The role of inflammation in diabetic retinopathy. *Frontiers in Immunology*, *11*, 2644. https://doi.org/10.3389/FIMMU.2020.583687/BIBTEX

Gao, L., Zhao, X., Jiao, L., & Tang, L. (2021). Intravitreal corticosteroids for diabetic macular edema: a network meta-analysis of randomized controlled trials. *Eye and Vision*, *8*(1), 1–13. https://doi.org/10.1186/S40662-021-00261-3/FIGURES/4

Gardiner, T. A., Archer, D. B., Curtis, T. M., & Stitt, A. W. (2007). Arteriolar involvement in the microvascular lesions of diabetic retinopathy: implications for pathogenesis. *Microcirculation*, *14*(1), 25–38. https://doi.org/10.1080/10739680601072123

Gardner, T. W., & Davila, J. R. (2017). The neurovascular unit and the pathophysiologic basis of diabetic retinopathy. *Graefe's Archive for Clinical and Experimental Ophthalmology*, *255*(1), 1–6. https://doi.org/10.1007/S00417-016-3548-Y/FIGURES/5

Garner, A. (1993). Histopathology of diabetic retinopathy in man. *Eye 1993 7:2*, *7*(2), 250–253. https://doi.org/10.1038/eye.1993.58

Gillies, C. L., Lambert, P. C., Abrams, K. R., Sutton, A. J., Cooper, N. J., Hsu, R. T., Davies, M. J., & Khunti, K. (2008). Different strategies for screening and prevention of type 2 diabetes in adults: cost effectiveness analysis. *BMJ (Clinical Research Ed.)*, *336*(7654), 1180–1184. https://doi.org/10.1136/BMJ.39545.585289.25

Glassman, A. R., Beaulieu, W. T., Maguire, M. G., Antoszyk, A. N., Chow, C. C., Elman, M. J., Jampol, L. M., Salehi-Had, H., & Sun, J. K. (2021). Visual acuity, vitreous hemorrhage, and other ocular outcomes after vitrectomy vs aflibercept for vitreous hemorrhage due to diabetic retinopathy: a secondary analysis of a randomized clinical trial. *JAMA Ophthalmology*, *139*(7), 725–733. https://doi.org/10.1001/JAMAOPHTHALMOL.2021.1110

Graham-Rowe, E., Lorencatto, F., Lawrenson, J. G., Burr, J. M., Grimshaw, J. M., Ivers, N. M., Presseau, J., Vale, L., Peto, T., Bunce, C., & J Francis, J. (2018). Barriers to and enablers of diabetic retinopathy screening attendance: a systematic review of published and grey literature. *Diabetic Medicine : A Journal of the British Diabetic Association*, *35*(10), 1308–1319. https://doi.org/10.1111/DME.13686

Gross, J. G., Glassman, A. R., Jampol, L. M., Inusah, S., Aiello, L. P., Antoszyk, A. N., Baker, C. W., Berger, B. B., Bressler, N. M., Browning, D., Elman, M. J., Ferris, F. L., Friedman, S. M., Marcus, D. M., Melia, M., Stockdale, C. R., Sun, J. K., & Beck, R. W. (2015). Panretinal photocoagulation vs intravitreous ranibizumab for proliferative diabetic retinopathy: a randomized clinical trial. *JAMA*, *314*(20), 2137–2146. https://doi.org/10.1001/JAMA.2015.15217

Gross, J. G., Glassman, A. R., Liu, D., Sun, J. K., Antoszyk, A. N., Baker, C. W., Bressler, N. M., Elman, M. J., Ferris, F. L., Gardner, T. W., Jampol, L. M., Martin, D. F., Melia, M., Stockdale, C. R., & Beck, R. W. (2018). Five-year outcomes of panretinal photocoagulation vs intravitreous ranibizumab for proliferative diabetic retinopathy: a randomized clinical trial. *JAMA Ophthalmology*, *136*(10), 1138–1148. https://doi.org /10.1001/JAMAOPHTHALMOL.2018.3255

Grunwald, J. E., Riva, C. E., Brucker, A. J., Sinclair, S. H., & Petrig, B. L. (1986). Effect of panretinal photocoagulation on retinal blood flow in proliferative diabetic retinopathy. *Ophthalmology*, *93*(5), 590–595. https://doi.org/10.1016/S0161-6420(86)33691-1

Grzybowski, A., Brona, P., Lim, G., Ruamviboonsuk, P., Tan, G. S. W., Abramoff, M., & Ting, D. S. W. (2020). Artificial intelligence for diabetic retinopathy screening: a review. *Eye (London, England)*, *34*(3), 451–460. https://doi.org/10.1038/S41433-019-0566-0

Gurel, Z., & Sheibani, N. (2018). O-Linked β-N-acetylglucosamine (O-GlcNAc) Modification: a new pathway to decode pathogenesis of diabetic retinopathy. *Clinical Science (London, England : 1979)*, *132*(2), 185. https://doi.org/10.1042/CS20171454

Hammes, H. P., Martin, S., Federlin, K., Geisen, K., & Brownlee, M. (1991). Aminoguanidine treatment inhibits the development of experimental diabetic retinopathy. *Proceedings of the National Academy of Sciences of the United States of America*, *88*(24), 11555. https://doi.org/10.1073/PNAS.88.24.11555

Han, Y., Adams, A. J., Bearse, M. A., & Schneck, M. E. (2004). Multifocal electroretinogram and short-wavelength automated perimetry measures in diabetic eyes with little or no retinopathy. *Archives of Ophthalmology (Chicago, Ill. : 1960)*, *122*(12), 1809–1815. https://doi.org/10.1001/ARCHOPHT.122.12.1809

Hannula, V., Hautala, N. M., Falck, A. A., & Tossavainen, P. (2015). Social well-being of young adults with type 1 diabetes since childhood. The Oulu cohort study of diabetic retinopathy. *Scandinavian Journal of Public Health*, *43*(6), 623–628. https://doi.org/10.1177/1403494815588423

Hannula, V., Hautala, N., Sintonen, H., & Falck, A. (2014). Health-related quality of life--using the 15D instrument--of young adults with type 1 diabetes since childhood. Population-based Oulu cohort study of diabetic retinopathy. *Acta Ophthalmologica*, *92*(3), 205–208. https://doi.org/10.1111/AOS.12122

Harjutsalo, V., Pongrac Barlovic, D., & Groop, P. H. (2021). Long-term population-based trends in the incidence of cardiovascular disease in individuals with type 1 diabetes from Finland: a retrospective, nationwide, cohort study. *The Lancet Diabetes & Endocrinology*, *9*(9), 575–585. https://doi.org/10.1016/S2213-8587(21)00172-8

Hautala, N., Aikkila, R., Korpelainen, J., Keskitalo, A., Kurikka, A., Falck, A., Bloigu, R., & Alanko, H. (2014). Marked reductions in visual impairment due to diabetic retinopathy achieved by efficient screening and timely treatment. *Acta Ophthalmologica*, *92*(6), 582–587. https://doi.org/10.1111/AOS.12278

Hautala, N., Hannula, V., Palosaari, T., Ebeling, T., & Falck, A. (2014). Prevalence of diabetic retinopathy in young adults with type 1 diabetes since childhood: the Oulu cohort study of diabetic retinopathy. *Acta Ophthalmologica*, *92*(8), 749–752. https://doi.org/10.1111/AOS.12426

Hautala, N., Hyytinen, P., Saarela, V., Hägg, P., Kurikka, A., Runtti, M., & Tuulonen, A. (2009). A mobile eye unit for screening of diabetic retinopathy and follow-up of glaucoma in remote locations in northern Finland. *Acta Ophthalmologica*, *87*(8), 912–913. https://doi.org/10.1111/J.1755-3768.2009.01570.X

Hautala, N., Siiskonen, M., Hannula, V., Järvinen, K., & Falck, A. (2018). Early glycaemic control for maintaining visual function in type 1 diabetes: The Oulu cohort study of diabetic retinopathy. *European Journal of Ophthalmology*, *28*(6), 684–689. https://doi.org/10.1177/1120672117750053/ASSET/IMAGES/LARGE/10.1177_1120672117750053-FIG1.JPEG

Hayreh, S. S., & Vaphiades, M. (2002). Diabetic papillopathy and nonarteritic anterior ischemic optic neuropathy (multiple letters). *Survey of Ophthalmology*, *47*(6), 600–602. https://doi.org/10.1016/S0039-6257(02)00358-2

Hayreh, S. S., & Zahoruk, R. M. (1981). Anterior Ischemic Optic Neuropathy. *Ophthalmologica*, *182*(1), 13–28. https://doi.org/10.1159/000309084

Hayreh, S. S., & Zimmerman, M. B. (2007). Incipient nonarteritic anterior ischemic optic neuropathy. *Ophthalmology*, *114*(9), 1763–1772. https://doi.org/10.1016/J.OPHTHA.2006.11.035

Hemminki, K., Li, X., Sundquist, J., & Sundquist, K. (2009). Familial association between type 1 diabetes and other autoimmune and related diseases. *Diabetologia*, *52*(9), 1820–1828. https://doi.org/10.1007/S00125-009-1427-3/TABLES/4

Hemminki, K., Li, X., Sundquist, K., & Sundquist, J. (2010a). Familial risks for type 2 diabetes in Sweden. *Diabetes Care*, *33*(2), 293–297. https://doi.org/10.2337/DC09-0947

Hivert, M. F., Jablonski, K. A., Perreault, L., Saxena, R., McAteer, J. B., Franks, P. W., Hamman, R. F., Kahn, S. E., Haffner, S., Meigs, J. B., Altshuler, D., Knowler, W. C., & Florez, J. C. (2011). Updated genetic score based on 34 confirmed type 2 diabetes Loci is associated with diabetes incidence and regression to normoglycemia in the diabetes prevention program. *Diabetes*, *60*(4), 1340–1348. https://doi.org/10.2337/DB10-1119

Ho, A. C., Maguire, A. M., Yannuzzi, L. A., Fisher, Y. L., Galetta, S. L., & Sergott, R. C. (1995). Rapidly progressive optic disk neovascularization after diabetic papillopathy. *American Journal of Ophthalmology*, *120*(5), 673–675. https://doi.org/10.1016/S0002-9394(14)72218-4

Hua, R., Qu, L., Ma, B., Yang, P., Sun, H., & Liu, L. (2019). Diabetic optic neuropathy and its risk factors in chinese patients with diabetic retinopathy. *Investigative Ophthalmology & Visual Science*, *60*(10), 3514–3519. https://doi.org/10.1167/IOVS.19-26825

Huang, Y. H., Yeh, P. T., Chen, M. S., Yang, C. H., & Yang, C. M. (2009). Intravitreal bevacizumab and panretinal photocoagulation for proliferative diabetic retinopathy associated with vitreous hemorrhage. *Retina (Philadelphia, Pa.)*, *29*(8), 1134–1140. https://doi.org/10.1097/IAE.0B013E3181B094B7

Huru, J. M., Leiviskä, I., Saarela, V., & Johanna Liinamaa, M. (2021). Prediabetes influences the structure of the macula: thinning of the macula in the Northern Finland Birth Cohort. *The British Journal of Ophthalmology*, *105*(12), 1731–1737. https://doi.org/10.1136/BJOPHTHALMOL-2020-317414

Hutchinson, A., McIntosh, A., Peters, J., O'Keeffe, C., Khunti, K., Baker, R., & Booth, A. (2000). Effectiveness of screening and monitoring tests for diabetic retinopathy--a systematic review. *Diabetic Medicine : A Journal of the British Diabetic Association*, *17*(7), 495–506. https://doi.org/10.1046/J.1464-5491.2000.00250.X

Hyndiuk, R. A., Kazarian, E. L., Schultz, R. O., & Seideman, S. (1977). Neurotrophic corneal ulcers in diabetes mellitus. *Archives of Ophthalmology*, *95*(12), 2193–2196. https://doi.org/10.1001/ARCHOPHT.1977.04450120099012

Hyttinen, V., Kaprio, J., Kinnunen, L., Koskenvuo, M., & Tuomilehto, J. (2003). Genetic liability of type 1 diabetes and the onset age among 22,650 young Finnish twin pairs: a nationwide follow-up study. *Diabetes*, *52*(4), 1052–1055. https://doi.org/10.2337/DIABETES.52.4.1052

Idris, I., & Donnelly, R. (2006). Protein kinase C beta inhibition: A novel therapeutic strategy for diabetic microangiopathy. *Diabetes & Vascular Disease Research*, *3*(3), 172–178. https://doi.org/10.3132/DVDR.2006.026

Ilonen, J., Kiviniemi, M., Lempainen, J., Simell, O., Toppari, J., Veijola, R., & Knip, M. (2016). Genetic susceptibility to type 1 diabetes in childhood – estimation of HLA class II associated disease risk and class II effect in various phases of islet autoimmunity. *Pediatric Diabetes*, *17*, 8–16. https://doi.org/10.1111/PEDI.12327

Ip, M. S., Domalpally, A., Sun, J. K., & Ehrlich, J. S. (2015). Long-term effects of therapy with ranibizumab on diabetic retinopathy severity and baseline risk factors for worsening retinopathy. *Ophthalmology*, *122*(2), 367–374. https://doi.org/10.1016/J.OPHTHA.2014.08.048

Jiang, Y., Liang, X., Li, X., Tao, Y., & Wang, K. (2009). Analysis of the clinical efficacy of intravitreal bevacizumab in the treatment of iris neovascularization caused by proliferative diabetic retinopathy. *Acta Ophthalmologica*, *87*(7), 736–740. https://doi.org/10.1111/J.1755-3768.2008.01353.X

Jonas, J. B., Libondi, T., von Baltz, S., & Vossmerbaeumer, U. (2008). Intravitreal bevacizumab for vitreous haemorrhage. *Acta Ophthalmologica*, *86*(5), 585–586. https://doi.org/10.1111/J.1600-0420.2007.01107.X

Jones, A. G., & Hattersley, A. T. (2013). The clinical utility of C-peptide measurement in the care of patients with diabetes. *Diabet. Med*, *30*, 803–817. https://doi.org/10.1111/dme.12159

Jorge, D. M., Tavares Neto, J. E. da S., Poli-Neto, O. B., Scott, I. U., & Jorge, R. (2021). Intravitreal bevacizumab (IVB) versus IVB in combination with pars plana vitrectomy for vitreous hemorrhage secondary to proliferative diabetic retinopathy: a randomized clinical trial. *International Journal of Retina and Vitreous*, *7*(1). https://doi.org/10.1186/S40942-021-00296-7

Kaaja, R., & Loukovaara, S. (2007). Progression of retinopathy in type 1 diabetic women during pregnancy. *Current Diabetes Reviews*, *3*(2), 85–93. https://doi.org/10.2174/157339907780598252

Kahn, R. (1997). Report of the Expert Committee on the diagnosis and classification of diabetes mellitus. *Diabetes Care*, *20*(7), 1183–1197. https://doi.org/10.2337/diacare.20.7.1183

Kahn, S. E., Haffner, S. M., Heise, M. A., Herman, W. H., Holman, R. R., Jones, N. P., Kravitz, B. G., Lachin, J. M., O'Neill, M. C., Zinman, B., & Viberti, G. (2006a). Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. *The New England Journal of Medicine*, *355*(23), 2427–2443. https://doi.org/10.1056/NEJMOA066224

Kahn, S. E., Haffner, S. M., Heise, M. A., Herman, W. H., Holman, R. R., Jones, N. P., Kravitz, B. G., Lachin, J. M., O'Neill, M. C., Zinman, B., & Viberti, G. (2006b). Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. *New England Journal of Medicine*, *355*(23), 2427–2443. https://doi.org/10.1056/NEJMOA066224/SUPPL_FILE/NEJMOA066224SA1.PDF

Kaneto, H., Xu, G., Song, K. H., Suzuma, K., Bonner-Weir, S., Sharma, A., & Weir, G. C. (2001). Activation of the hexosamine pathway leads to deterioration of pancreatic β-cell function through the induction of oxidative stress. *Journal of Biological Chemistry*, *276*(33), 31099–31104. https://doi.org/10.1074/JBC.M104115200

Kanie, T., Mizuno, A., Takaoka, Y., Suzuki, T., Yoneoka, D., Nishikawa, Y., Tam, W. W. S., Morze, J., Rynkiewicz, A., Xin, Y., Wu, O., Providencia, R., & Kwong, J. S. W. (2021). Dipeptidyl peptidase-4 inhibitors, glucagon-like peptide 1 receptor agonists and sodium-glucose co-transporter-2 inhibitors for people with cardiovascular disease: a network meta-analysis. *The Cochrane Database of Systematic Reviews*, *10*(10). https://doi.org/10.1002/14651858.CD013650.PUB2

Kaur, B., & Taylor, D. (1990). Retinal haemorrhages. *Archives of Disease in Childhood*, *65*(12), 1369–1372. https://doi.org/10.1136/ADC.65.12.1369

Khaw, K. T., Wareham, N., Bingham, S., Luben, R., Welch, A., & Day, N. (2004). Association of hemoglobin A1c with cardiovascular disease and mortality in adults: the European prospective investigation into cancer in Norfolk. *Annals of Internal Medicine*, *141*(6). https://doi.org/10.7326/0003-4819-141-6-200409210-00006

Klein, B. E. K., Klein, R., & Moss, S. E. (1985). Prevalence of cataracts in a population-based study of persons with diabetes mellitus. *Ophthalmology*, *92*(9), 1191–1196. https://doi.org/10.1016/S0161-6420(85)33877-0

Klein, B. E. K., Klein, R., & Moss, S. E. (1995). Incidence of cataract surgery in the Wisconsin Epidemiologic Study of Diabetic Retinopathy. *American Journal of Ophthalmology*, *119*(3), 295–300. https://doi.org/10.1016/S0002-9394(14)71170-5

Klein, B., Klein, R., Moss, S., & Cruickshanks, K. (1996). Parental history of diabetes in a population-based study. *Diabetes Care*, *19*(8), 827–830. https://doi.org/10.2337/DIACARE.19.8.827

Klein, R., Klein, B. E. K., & Moss, S. E. (1995). The Wisconsin Epidemiologic Study of Diabetic Retinopathy. XVI. The relationship of C-peptide to the incidence and progression of diabetic retinopathy. *Diabetes*, *44*(7), 796–801. https://doi.org/10.2337/DIAB.44.7.796

Klein, R., Klein, B. E. K., Moss, S. E., Davis, M. D., & Demets, D. L. (1984a). The Wisconsin Epidemiologic Study of Diabetic Retinopathy: II. Prevalence and risk of diabetic retinopathy when age at diagnosis is less than 30 years. *Archives of Ophthalmology*, *102*(4), 520–526. https://doi.org/10.1001/ARCHOPHT.1984.01040030398010

Klein, R., Klein, B. E. K., Moss, S. E., Davis, M. D., & Demets, D. L. (1984b). The Wisconsin Epidemiologic Study of Diabetic Retinopathy: III. prevalence and risk of diabetic retinopathy when age at diagnosis is 30 or more years. *Archives of Ophthalmology*, *102*(4), 527–532. https://doi.org/10.1001/ARCHOPHT.1984.01040030405011

Klein, R., Klein, B. E. K., Moss, S. E., Davis, M. D., & Demets, D. L. (1988). Glycosylated hemoglobin predicts the incidence and progression of diabetic retinopathy. *JAMA*, *260*(19), 2864–2871. https://doi.org/10.1001/JAMA.1988.03410190112033

Klein, R., Knudtson, M. D., Lee, K. E., Gangnon, R., & Klein, B. E. K. (2008). The Wisconsin Epidemiologic Study of Diabetic Retinopathy XXII. the twenty-five-year progression of retinopathy in persons with type 1 diabetes. *Ophthalmology*, *115*(11), 1859–1868. https://doi.org/10.1016/j.ophtha.2008.08.023

Klinker, M. W., Schiller, J. J., Magnuson, V. L., Wang, T., Basken, J., Veth, K., Pearce, K. I., Kinnunen, L., Harjutsalo, V., Wang, X., Tuomilehto, J., Sarti, C., & Ghosh, S. (2010). Single-nucleotide polymorphisms in the IL2RA gene are associated with age at diagnosis in late-onset Finnish type 1 diabetes subjects. *Immunogenetics*, *62*(2), 101–107. https://doi.org/10.1007/S00251-009-0417-4

Kodl, C. T., & Seaquist, E. R. (2008). Cognitive dysfunction and diabetes mellitus. *Endocrine Reviews*, *29*(4), 494. https://doi.org/10.1210/ER.2007-0034

Kohner, E. M., Dollery, C. T., & Bulpitt, C. J. (1969). Cotton-wool spots in diabetic retinopathy. *Diabetes*, *18*(10), 691–704. https://doi.org/10.2337/DIAB.18.10.691

Koustenis, A., Harris, A., Gross, J., Januleviciene, I., Shah, A., & Siesky, B. (2017). Optical coherence tomography angiography: an overview of the technology and an assessment of applications for clinical research. *The British Journal of Ophthalmology*, *101*(1), 16–20. https://doi.org/10.1136/BJOPHTHALMOL-2016-309389

Kozak, I., Payne, J. F., Schatz, P., Al-Kahtani, E., & Winkler, M. (2017). Teleophthalmology image-based navigated retinal laser therapy for diabetic macular edema: a concept of retinal telephotocoagulation. *Graefe's Archive for Clinical and Experimental Ophthalmology = Albrecht von Graefes Archiv Fur Klinische Und Experimentelle Ophthalmologie*, *255*(8), 1509–1513. https://doi.org/10.1007/S00417-017-3674-1

Kubin, A. M., Wirkkala, J., Keskitalo, A., Ohtonen, P., & Hautala, N. (2021). Handheld fundus camera performance, image quality and outcomes of diabetic retinopathy grading in a pilot screening study. *Acta Ophthalmologica*, *99*(8), e1415–e1420. https://doi.org/10.1111/AOS.14850

Kubin, M., Tossavainen, P., Hannula, V., Lahti, S., Hautala, N., & Falck, A. (2011). Prevalence of retinopathy in Finnish children and adolescents with type 1 diabetes: a cross-sectional population-based retrospective study. *Archives of Disease in Childhood*, *96*(10), 963–968. https://doi.org/10.1136/ADC.2011.210807

Kung, N. H., & van Stavern, G. P. (2015). Isolated Ocular Motor Nerve Palsies. *Seminars in Neurology*, *35*(5), 539–548. https://doi.org/10.1055/S-0035-1563568/ID/JR0027-29

Kuusisto, J., Mykkänen, L., Pyörälä, K., & Laakso, M. (1994). NIDDM and its metabolic control predict coronary heart disease in elderly subjects. *Diabetes*, *43*(8), 960–967. https://doi.org/10.2337/DIAB.43.8.960

Kytö, J. P., Harjutsalo, V., Forsblom, C., Hietala, K., Summanen, P. A., & Groop, P. H. (2011). Decline in the cumulative incidence of severe diabetic retinopathy in patients with type 1 diabetes. *Diabetes Care*, *34*(9), 2005–2007. https://doi.org/10.2337/DC10-2391

Laakso, M. (2011). Onko diabeteksen geenidiagnostiikasta hyötyä potilastyössä? *Suom Lääkärilehti*, *66*(1–2), 37–42.

Lahham, S., Shniter, I., Thompson, M., Le, D., Chadha, T., Mailhot, T., Kang, T. L., Chiem, A., Tseeng, S., & Fox, J. C. (2019). Point-of-care ultrasonography in the diagnosis of retinal detachment, vitreous hemorrhage, and vitreous detachment in the emergency department. *JAMA Network Open*, *2*(4), e192162. https://doi.org/10.1001/jamanetworkopen.2019.2162

Lammi, N., Blomstedt, P. A., Moltchanova, E., Eriksson, J. G., Tuomilehto, J., & Karvonen, M. (2008). Marked temporal increase in the incidence of type 1 and type 2 diabetes among young adults in Finland. *Diabetologia*, *51*(5), 897–899. https://doi.org/10.1007/s00125-008-0952-9

Lean, M. E., Leslie, W. S., Barnes, A. C., Brosnahan, N., Thom, G., McCombie, L., Peters, C., Zhyzhneuskaya, S., Al-Mrabeh, A., Hollingsworth, K. G., Rodrigues, A. M., Rehackova, L., Adamson, A. J., Sniehotta, F. F., Mathers, J. C., Ross, H. M., McIlvenna, Y., Stefanetti, R., Trenell, M., … Taylor, R. (2018). Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial. *Lancet (London, England)*, *391*(10120), 541–551. https://doi.org/10.1016/S0140-6736(17)33102-1

Leasher, J. L., Bourne, R. R. A., Flaxman, S. R., Jonas, J. B., Keeffe, J., Naidoo, K., Pesudovs, K., Price, H., White, R. A., Wong, T. Y., Resnikoff, S., & Taylor, H. R. (2016). Global estimates on the number of people blind or visually impaired by diabetic retinopathy: a meta-analysis from 1990 to 2010. *Diabetes Care*, *39*(9), 1643–1649. https://doi.org/10.2337/DC15-2171

Lee, A. Y. W., Chung, S. K., & Chung, S. S. M. (1995). Demonstration that polyol accumulation is responsible for diabetic cataract by the use of transgenic mice expressing the aldose reductase gene in the lens. *Proceedings of the National Academy of Sciences of the United States of America*, *92*(7), 2780–2784. https://doi.org/10.1073/PNAS.92.7.2780

Lee, C. S., Lee, A. Y., Baughman, D., Sim, D., Akelere, T., Brand, C., Crabb, D. P., Denniston, A. K., Downey, L., Fitt, A., Khan, R., Mahmood, S., Mandal, K., Mckibbin, M., Menon, G., Lobo, A., Kumar, B. V., Natha, S., Varma, A., … Kumar, V. (2017). The United Kingdom Diabetic retinopathy electronic medical record users group: report 3: baseline retinopathy and clinical features predict progression of diabetic retinopathy. *American Journal of Ophthalmology*, *180*, 64–71. https://doi.org/10.1016/J.AJO.2017.05.020

Leske, M. C., Wu, S. Y., Nemesure, B., & Hennis, A. (2002). Risk factors for incident nuclear opacities. *Ophthalmology*, *109*(7), 1303–1308. https://doi.org/10.1016/S0161-6420(02)01094-1

Lewis, H., Abrams, G. W., Blumenkranz, M. S., & Campo, R. v. (1992). Vitrectomy for diabetic macular traction and edema associated with posterior hyaloidal traction. *Ophthalmology*, *99*(5), 753–759. https://doi.org/10.1016/S0161-6420(92)31901-3

Li, B.-Y., Tan, W., Zou, J.-L., He, Y., Yoshida, S., Jiang, B., & Zhou, Y.-D. (2021). Role of interferons in diabetic retinopathy. *12*(7), 939–953. https://doi.org/10.4239/WJD.V12.I7.939

Li, J. Q., Welchowski, T., Schmid, M., Letow, J., Wolpers, C., Pascual-Camps, I., Holz, F. G., & Finger, R. P. (2020). Prevalence, incidence and future projection of diabetic eye disease in Europe: a systematic review and meta-analysis. *European Journal of Epidemiology*, *35*(1), 11–23. https://doi.org/10.1007/S10654-019-00560-Z

Liang, B., Koye, D. N., Hachem, M., Zafari, N., Braat, S., & Ekinci, E. I. (2022). Efficacy of flash glucose monitoring in type 1 and type 2 diabetes: a systematic review and meta-analysis of randomised controlled trials. *Frontiers in Clinical Diabetes and Healthcare*, *3*, 5. https://doi.org/10.3389/FCDHC.2022.849725

Lin, S. F., Lin, P. K., Chang, F. L., & Tsai, R. K. (2009). Transient hyperopia after intensive treatment of hyperglycemia in newly diagnosed diabetes. *Ophthalmologica. Journal International d'ophtalmologie. International Journal of Ophthalmology. Zeitschrift Fur Augenheilkunde*, *223*(1), 68–71. https://doi.org/10.1159/000173714

Lindgren, G., Sjödell, L., & Lindblom, B. (1995). A prospective study of dense spontaneous vitreous hemorrhage. *American Journal of Ophthalmology*, *119*(4), 458–465. https://doi.org/10.1016/S0002-9394(14)71232-2

Lindström, J., Peltonen, M., Eriksson, J. G., Ilanne-Parikka, P., Aunola, S., Keinänen-Kiukaanniemi, S., Uusitupa, M., & Tuomilehto, J. (2013). Improved lifestyle and decreased diabetes risk over 13 years: long-term follow-up of the randomised Finnish Diabetes Prevention Study (DPS). *Diabetologia*, *56*(2), 284–293. https://doi.org/10.1007/S00125-012-2752-5

Lindström, J., & Tuomilehto, J. (2003). The diabetes risk score: a practical tool to predict type 2 diabetes risk. *Diabetes Care*, *26*(3), 725–731. https://doi.org/10.2337/DIACARE.26.3.725

Ljubimov, A. v. (2017). Diabetic complications in the cornea. *Vision Research*, *139*, 138. https://doi.org/10.1016/J.VISRES.2017.03.002

Look AHEAD Research Group, Wing, R. R., Bolin, P., Brancati, F. L., Bray, G. A., Clark, J. M., Coday, M., Crow, R. S., Curtis, J. M., Egan, C. M., Espeland, M. A., Evans, M., Foreyt, J. P., Ghazarian, S., Gregg, E. W., Harrison, B., Hazuda, H. P., Hill, J. O., Horton, E. S., … Yanovski, S. Z. (2013). Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. *The New England Journal of Medicine*, *369*(2), 145–154. https://doi.org/10.1056/NEJMOA1212914

Loukovaara, S., Immonen, I., Teramo, K. A., & Kaaja, R. (2003). Progression of retinopathy during pregnancy in type 1 diabetic women treated with insulin lispro. *Diabetes Care*, *26*(4), 1193–1198. https://doi.org/10.2337/DIACARE.26.4.1193

Lu, J., Ma, X., Zhou, J., Zhang, L., Mo, Y., Ying, L., Lu, W., Zhu, W., Bao, Y., Vigersky, R. A., & Jia, W. (2018). Association of time in range, as assessed by continuous glucose monitoring, with diabetic retinopathy in type 2 diabetes. *Diabetes Care*, *41*(11), 2370–2376. https://doi.org/10.2337/DC18-1131

Lu, M., Perez, V. L., Ma, N., Miyamoto, K., Peng, H. B., Liao, J. K., & Adamis, A. P. (1999). VEGF increases retinal vascular ICAM-1 expression in vivo. *Investigative Ophthalmology & Visual Science*, *40*(8), 1808–1812.

Maguire, M. G., Liu, D., Bressler, S. B., Friedman, S. M., Melia, M., Stockdale, C. R., Glassman, A. R., & Sun, J. K. (2021). Lapses in care among patients assigned to ranibizumab for proliferative diabetic retinopathy: a post hoc analysis of a randomized clinical trial. *JAMA Ophthalmology*, *139*(12), 1266–1273. https://doi.org/10.1001/JAMAOPHTHALMOL.2021.4103

Mallare, J. T., Cordice, C. C., Ryan, B. A., Carey, D. E., Kreitzer, P. M., & Frank, G. R. (2003). Identifying risk factors for the development of diabetic ketoacidosis in new onset type 1 diabetes mellitus. *Clinical Pediatrics*, *42*(7), 591–597. https://doi.org/10.1177/000992280304200704

Manaviat, M. R., Rashidi, M., Afkhami-Ardekani, M., & Shoja, M. R. (2008). Prevalence of dry eye syndrome and diabetic retinopathy in type 2 diabetic patients. *BMC Ophthalmology*, *8*(1), 1–5. https://doi.org/10.1186/1471-2415-8-10/FIGURES/2

Mandecka, A., Dawczynski, J., Vilser, W., Blum, M., Müller, N., Kloos, C., Wolf, G., & Müller, U. A. (2009). Abnormal retinal autoregulation is detected by provoked stimulation with flicker light in well-controlled patients with type 1 diabetes without retinopathy. *Diabetes Research and Clinical Practice*, *86*(1), 51–55. https://doi.org/10.1016/J.DIABRES.2009.06.017

Mäntyjärvi, M. (1989). Colour vision and dark adaptation in diabetic patients after photocoagulation. *Acta Ophthalmologica*, *67*(2), 113–118. https://doi.org/10.1111/J.1755-3768.1989.TB00738.X

Maruyama, T., Nakagawa, T., Kasuga, A., & Murata, M. (2011). Heterogeneity among patients with latent autoimmune diabetes in adults. *Diabetes/Metabolism Research and Reviews*, *27*(8), 971–974. https://doi.org/10.1002/DMRR.1238

Maturi, R. K., Glassman, A. R., Josic, K., Antoszyk, A. N., Blodi, B. A., Jampol, L. M., Marcus, D. M., Martin, D. F., Melia, M., Salehi-Had, H., Stockdale, C. R., Punjabi, O. S., & Sun, J. K. (2021). Effect of intravitreous anti-vascular endothelial growth factor vs sham treatment for prevention of vision-threatening complications of diabetic retinopathy: The Protocol W randomized clinical trial. *JAMA Ophthalmology*, *139*(7), E1–E12. https://doi.org/10.1001/JAMAOPHTHALMOL.2021.0606

Maturi, R. K., Glassman, A. R., Josic, K., Baker, C. W., Gerstenblith, A. T., Jampol, L. M., Meleth, A., Martin, D. F., Melia, M., Punjabi, O. S., Rofagha, S., Salehi-Had, H., Stockdale, C. R., Sun, J. K., Network, D. R., Browning, D., Allen, J. B., Antoszyk, A. N., Wilson, A. H., … Wisniewski, S. (2023). Four-year visual outcomes in the protocol w randomized trial of intravitreous aflibercept for prevention of vision-threatening complications of diabetic retinopathy. *JAMA*, *329*(5), 376–385. https://doi.org/10.1001/JAMA.2022.25029

Mazhar, K., Varma, R., Choudhury, F., McKean-Cowdin, R., Shtir, C. J., & Azen, S. P. (2011). Severity of diabetic retinopathy and health-related quality of life: the Los Angeles Latino Eye Study. *Ophthalmology*, *118*(4), 649–655. https://doi.org/10.1016/J.OPHTHA.2010.08.003

McAnany, J. J., Park, J. C., Liu, K., Liu, M., Chen, Y. F., Chau, F. Y., & Lim, J. I. (2020). Contrast sensitivity is associated with outer-retina thickness in early-stage diabetic retinopathy. *Acta Ophthalmologica*, *98*(2), e224–e231. https://doi.org/10.1111/AOS.14241

McLeod, D. (2005). Why cotton wool spots should not be regarded as retinal nerve fibre layer infarcts. *British Journal of Ophthalmology*, *89*(2), 229–237. https://doi.org/10.1136/BJO.2004.058347

Mehdizadeh, M., & Nowroozzadeh, M. H. (2010). Transient hyperopia and diabetes. *Ophthalmologica*, *224*(1), 63–63. https://doi.org/10.1159/000235728

Metsärinne, K., Pietilä, M., Kantola, I., Stenman, L. K., Hätinen, O. P., Vesikansa, A., Poussa, T., & Niskanen, L. (2022). The majority of type 2 diabetic patients in Finnish primary care are at very high risk of cardiovascular events: A cross-sectional chart review study (STONE HF). *Primary Care Diabetes*, *16*(1), 135–141. https://doi.org/10.1016/J.PCD.2021.12.012

Muraoka, K., & Shimizu, K. (1984). Intraretinal Neovascularization in Diabetic Retinopathy. *Ophthalmology*, *91*(12), 1440–1446. https://doi.org/10.1016/S0161-6420(84)34125-2

Murgatroyd, H., Ellingford, A., Cox, A., Binnie, M., Ellis, J. D., MacEwen, C. J., & Leese, G. P. (2004). Effect of mydriasis and different field strategies on digital image screening of diabetic eye disease. *The British Journal of Ophthalmology*, *88*(7), 920–924. https://doi.org/10.1136/BJO.2003.026385

Nambam, B., Aggarwal, S., & Jain, A. (2010). Latent autoimmune diabetes in adults: A distinct but heterogeneous clinical entity. *World Journal of Diabetes*, *1*(4), 111. https://doi.org/10.4239/WJD.V1.I4.111

Neubauer, A. S., Kernt, M., Haritoglou, C., Priglinger, S. G., Kampik, A., & Ulbig, M. W. (2008). Nonmydriatic screening for diabetic retinopathy by ultra-widefield scanning laser ophthalmoscopy (Optomap). *Graefe's Archive for Clinical and Experimental Ophthalmology 246*(2), 229–235. https://doi.org/10.1007/S00417-007-0631-4

Ngiam, K. Y., & Khor, I. W. (2019). Big data and machine learning algorithms for health-care delivery. *The Lancet Oncology*, *20*(5), e262–e273. https://doi.org/10.1016/S1470-2045(19)30149-4

Noda, K., Nakao, S., Ishida, S., & Ishibashi, T. (2012). Leukocyte adhesion molecules in diabetic retinopathy. *Journal of Ophthalmology*, *2012*. https://doi.org/10.1155/2012/279037

Novotny, H., & Alvis, D. (1961). A method of photographing fluorescence in circulating blood in the human retina. *Circulation*, *24*(1), 82–86. https://doi.org/10.1161/01.CIR.24.1.82

Nyengaard, J. R., Ido, Y., Kilo, C., & Williamson, J. R. (2004). Interactions between hyperglycemia and hypoxia: implications for diabetic retinopathy. *Diabetes*, *53*(11), 2931–2938. https://doi.org/10.2337/DIABETES.53.11.2931

Nyenwe, E. A., & Kitabchi, A. E. (2016). The evolution of diabetic ketoacidosis: An update of its etiology, pathogenesis and management. *Metabolism: Clinical and Experimental*, *65*(4), 507–521. https://doi.org/10.1016/J.METABOL.2015.12.007

Ogurtsova, K., Guariguata, L., Barengo, N. C., Ruiz, P. L. D., Sacre, J. W., Karuranga, S., Sun, H., Boyko, E. J., & Magliano, D. J. (2022). IDF diabetes Atlas: Global estimates of undiagnosed diabetes in adults for 2021. *Diabetes Research and Clinical Practice*, *183*. https://doi.org/10.1016/J.DIABRES.2021.109118

Okamoto, F., Sone, H., Nonoyama, T., & Hommura, S. (2000). Refractive changes in diabetic patients during intensive glycaemic control. *The British Journal of Ophthalmology*, *84*(10), 1097–1102. https://doi.org/10.1136/BJO.84.10.1097

Olsen, B. S., Sjølie, A. K., Hougaard, P., Johannesen, J., Marinelli, K., Jacobsen, B. B., & Mortensen, H. B. (2004). The significance of the prepubertal diabetes duration for the development of retinopathy and nephropathy in patients with type 1 diabetes. *Journal of Diabetes and Its Complications*, *18*(3), 160–164. https://doi.org/10.1016/S1056-8727(03)00073-4

Oniscu, G. C., Brown, H., & Forsythe, J. L. R. (2005). Impact of cadaveric renal transplantation on survival in patients listed for transplantation. *Journal of the American Society of Nephrology*, *16*(6), 1859–1865. https://doi.org/10.1681/ASN.2004121092

Ostri, C., Lund-Andersen, H., Sander, B., Hvidt-Nielsen, D., & Larsen, M. (2010). Bilateral diabetic papillopathy and metabolic control. *Ophthalmology*, *117*(11), 2214–2217. https://doi.org/10.1016/J.OPHTHA.2010.03.006

Otani, T., & Kishi, S. (2001). Tomographic findings of foveal hard exudates in diabetic macular edema. *American Journal of Ophthalmology*, *131*(1), 50–54. https://doi.org/10.1016/S0002-9394(00)00661-9

Parikh, R. N., Traband, A., Kolomeyer, A. M., VanderBeek, B. L., Kim, B. J., Maguire, A. M., & Brucker, A. J. (2017). Intravitreal bevacizumab for the treatment of vitreous hemorrhage due to proliferative diabetic retinopathy. *American Journal of Ophthalmology*, *176*, 194–202. https://doi.org/10.1016/J.AJO.2017.01.010

Park, Y. J., Ahn, J., Kim, T. W., Park, S. J., Joo, K., Park, K. H., & Shin, J. Y. (2021). Efficacy of bevacizumab for vitreous haemorrhage in proliferative diabetic retinopathy with prior complete panretinal photocoagulation. *Eye (London, England)*, *35*(11), 3056–3063. https://doi.org/10.1038/S41433-020-01384-Y

Parviainen, A., But, A., Siljander, H., Knip, M., & Finnish Pediatric Diabetes Register. (2020). Decreased incidence of type 1 diabetes in young finnish children. *Diabetes Care*, *43*(12), 2953–2958. https://doi.org/10.2337/dc20-0604

Pendergast, S. D., Hassan, T. S., Williams, G. A., Cox, M. S., Margherio, R. R., Ferrone, P. J., Garretson, B. R., & Trese, M. T. (2000). Vitrectomy for diffuse diabetic macular edema associated with a taut premacular posterior hyaloid. *American Journal of Ophthalmology*, *130*(2), 178–186. https://doi.org/10.1016/S0002-9394(00)00472-4

Perk, J., de Backer, G., Gohlke, H., Graham, I., Reiner, Ž., Verschuren, M., Albus, C., Benlian, P., Boysen, G., Cifkova, R., Deaton, C., Ebrahim, S., Fisher, M., Germano, G., Hobbs, R., Hoes, A., Karadeniz, S., Mezzani, A., Prescott, E., … Wolpert, C. (2012). European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). *European Heart Journal*, *33*(13), 1635–1701. https://doi.org/10.1093/EURHEARTJ/EHS092

Pietropaolo, M., & Eisenbarth, G. S. (2001). Autoantibodies in human diabetes. *Current Directions in Autoimmunity*, *4*, 252–282. https://doi.org/10.1159/000060541

Pirart, J. (1978). Diabetes mellitus and its degenerative complications: a prospective study of 4,400 patients observed between 1947 and 1973. *Diabetes Care*, *1*(4), 252–263. https://doi.org/10.2337/diacare.1.4.252

Porta, M., Sjoelie, A. K., Chaturvedi, N., Stevens, L., Rottiers, R., Veglio, M., & Fuller, J. H. (2001). Risk factors for progression to proliferative diabetic retinopathy in the EURODIAB Prospective Complications Study. *Diabetologia*, *44*(12), 2203–2209. https://doi.org/10.1007/S001250100030

Pournaras, C. J., Rungger-Brändle, E., Riva, C. E., Hardarson, S. H., & Stefansson, E. (2008). Regulation of retinal blood flow in health and disease. *Progress in Retinal and Eye Research*, *27*(3), 284–330. https://doi.org/10.1016/J.PRETEYERES.2008.02.002

Powell, E. D. U., & Field, R. A. (1964). Diabetic retinopathy and rheumatoid arthritis. *The Lancet*, *284*(7349), 17–18. https://doi.org/10.1016/S0140-6736(64)90008-X

Powers, A. C., & Eisenbarth, G. S. (1985). Autoimmunity to islet cells in diabetes mellitus. *Annual Review of Medicine*, *36*, 533–544. https://doi.org/10.1146/ANNUREV.ME.36.020185.002533

Praidou, A., Harris, M., Niakas, D., & Labiris, G. (2017). Physical activity and its correlation to diabetic retinopathy. *Journal of Diabetes and Its Complications*, *31*(2), 456–461. https://doi.org/10.1016/J.JDIACOMP.2016.06.027

Price, L. D., Au, S., & Chong, N. V. (2015). Optomap ultrawide field imaging identifies additional retinal abnormalities in patients with diabetic retinopathy. *Clinical Ophthalmology (Auckland, N.Z.)*, *9*, 527. https://doi.org/10.2147/OPTH.S79448

Prigge, R., Wild, S. H., & Jackson, C. A. (2022). Depression, diabetes, comorbid depression and diabetes and risk of all-cause and cause-specific mortality: a prospective cohort study. *Diabetologia*, *65*(9). https://doi.org/10.1007/S00125-022-05723-4

Purola, P. K. M., Ojamo, M. U. I., Gissler, M., & Uusitalo, H. M. T. (2022). changes in visual impairment due to diabetic retinopathy during 1980–2019 based on nationwide register data. *Diabetes Care*. https://doi.org/10.2337/DC21-2369

Pyykkönen, A. J., Räikkönen, K., Tuomi, T., Eriksson, J. G., Groop, L., & Isomaa, B. (2011). Depressive symptoms, antidepressant medication use, and insulin resistance: the PPP-Botnia Study. *Diabetes Care*, *34*(12), 2545–2547. https://doi.org/10.2337/DC11-0107

Quinn, L. M., Wong, F. S., & Narendran, P. (2021). Environmental determinants of type 1 diabetes: from association to proving causality. *Frontiers in Immunology*, *12*. https://doi.org/10.3389/FIMMU.2021.737964

Rabinowitz, R., Yagev, R., Shoham, A., & Lifshitz, T. (2004). Comparison between clinical and ultrasound findings in patients with vitreous hemorrhage. *Eye*, *18*(3), 253–256. https://doi.org/10.1038/sj.eye.6700632

Rajendram, R., Fraser-Bell, S., Kaines, A., Michaelides, M., Hamilton, R. D., Esposti, S. D., Peto, T., Egan, C., Bunce, C., Leslie, R. D., & Hykin, P. G. (2012). A 2-year prospective randomized controlled trial of intravitreal bevacizumab or laser therapy (BOLT) in the management of diabetic macular edema: 24-month data: report 3. *Archives of Ophthalmology (Chicago, Ill. : 1960)*, *130*(8), 972–979. https://doi.org/10.1001/ARCHOPHTHALMOL.2012.393

Rawshani, A., Rawshani, A., Franzén, S., Sattar, N., Eliasson, B., Svensson, A.-M., Zethelius, B., Miftaraj, M., McGuire, D. K., Rosengren, A., & Gudbjörnsdottir, S. (2018). Risk factors, mortality, and cardiovascular outcomes in patients with type 2 diabetes. *New England Journal of Medicine*, *379*(7), 633–644. https://doi.org/10.1056/NEJMOA1800256/SUPPL_FILE/NEJMOA1800256_DISCLOSURES.PDF

Recchia, F. M., Ruby, A. J., & Carvalho Recchia, C. A. (2005). Pars plana vitrectomy with removal of the internal limiting membrane in the treatment of persistent diabetic macular edema. *American Journal of Ophthalmology*, *139*(3), 447–454. https://doi.org/10.1016/J.AJO.2004.09.076

Redondo, M. J., Jeffrey, J., Fain, P. R., Eisenbarth, G. S., & Orban, T. (2008). Concordance for Islet Autoimmunity among Monozygotic Twins. *359*(26), 2849–2850. https://doi.org/10.1056/NEJMC0805398

Regillo, C. D., Brown, G. C., Savino, P. J., Byrnes, G. A., Benson, W. E., Tasman, W. S., & Sergott, R. C. (1995). Diabetic Papillopathy: Patient Characteristics and Fundus Findings. *Archives of Ophthalmology*, *113*(7), 889–895. https://doi.org/10.1001/ARCHOPHT.1995.01100070063026

Rogell, G. D. (1980). Corneal Hypesthesia and Retinopathy in Diabetes Mellitus. *Ophthalmology*, *87*(3), 229–233. https://doi.org/10.1016/S0161-6420(80)35257-3

Romero-Aroca, P., Fernández-Balart, J., Baget-Bernaldiz, M., Martinez-Salcedo, I., Méndez-Marín, I., Salvat-Serra, M., & Buil-Calvo, J. A. (2009). Changes in the diabetic retinopathy epidemiology after 14 years in a population of Type 1 and 2 diabetic patients after the new diabetes mellitus diagnosis criteria and a more strict control of the patients. *Journal of Diabetes and Its Complications*, *23*(4), 229–238. https://doi.org/10.1016/J.JDIACOMP.2008.02.012

Rosenfeld, P. J., Moshfeghi, A. A., & Puliafito, C. A. (2005). Optical coherence tomography findings after an intravitreal injection of bevacizumab (Avastin®) for neovascular age-related macular degeneration. *Ophthalmic Surgery Lasers and Imaging*, *36*(4), 331–335. https://doi.org/10.3928/1542-8877-20050701-14

Roy, S., Amin, S., & Roy, S. (2016). Retinal fibrosis in diabetic retinopathy. *Experimental Eye Research*, *142*, 71–75. https://doi.org/10.1016/J.EXER.2015.04.004

Ryan, C. M., Geckle, M. O., & Orchard, T. J. (2003). Cognitive efficiency declines over time in adults with Type 1 diabetes: effects of micro- and macrovascular complications. *Diabetologia*, *46*(7), 940–948. https://doi.org/10.1007/S00125-003-1128-2

Saeedi, P., Petersohn, I., Salpea, P., Malanda, B., Karuranga, S., Unwin, N., Colagiuri, S., Guariguata, L., Motala, A. A., Ogurtsova, K., Shaw, J. E., Bright, D., Williams, R., Saeedi, P., Almutairi, R., Montoya, P. A., Basit, A., Phane Besanç, S., Bommer, C., … Zhang, P. (2019). Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9th edition. *Diabetes Research and Clinical Practice*, *157*. https://doi.org/10.1016/J.DIABRES.2019.107843

Sameen, M., Khan, M. S., Mukhtar, A., Yaqub, M. A., & Ishaq, M. (2017). Efficacy of intravitreal bevacizumab combined with pan retinal photocoagulation versus panretinal photocoagulation alone in treatment of proliferative diabetic retinopathy. *Pakistan Journal of Medical Sciences*, *33*(1), 142–145. https://doi.org/10.12669/PJMS.331.11497

Sanders, S. K., Kawasaki, A., & Purvin, V. A. (2002). Long-term prognosis in patients with vasculopathic sixth nerve palsy. *American Journal of Ophthalmology*, *134*(1), 81–84. https://doi.org/10.1016/S0002-9394(02)01439-3

Savolainen, E. A., & Lee, Q. P. (1982). Diabetic retinopathy - need and demand for photocoagulation and its cost-effectiveness: evaluation based on services in the United Kingdom. *Diabetologia*, *23*(2), 138–140. https://doi.org/10.1007/BF01271176

Schanner, C., Falck, A., Keskitalo, A., & Hautala, N. (2016). Health-related quality of life of Finnish patients with diabetes. *Scandinavian Journal of Public Health*, *44*(8), 765–771. https://doi.org/10.1177/1403494816666732

Schmidt-Erfurth, U., Garcia-Arumi, J., Bandello, F., Berg, K., Chakravarthy, U., Gerendas, B. S., Jonas, J., Larsen, M., Tadayoni, R., & Loewenstein, A. (2017). Guidelines for the management of diabetic macular edema by the European society of retina specialists (EURETINA). *Ophthalmologica. Journal International d'ophtalmologie. International Journal of Ophthalmology. Zeitschrift Fur Augenheilkunde*, *237*(4), 185–222. https://doi.org/10.1159/000458539

Schultz, R. O., van Horn, D. L., Peters, M. A., Klewin, K. M., & Schutten, W. H. (1981). Diabetic keratopathy. *Transactions of the American Ophthalmological Society*, *79*, 180. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1312182/

Selenius, J. S., Wasenius, N. S., Kautiainen, H., Salonen, M., von Bonsdorff, M., & Eriksson, J. G. (2020). Impaired glucose regulation, depressive symptoms, and health-related quality of life. *BMJ Open Diabetes Research & Care*, *8*(1). https://doi.org/10.1136/BMJDRC-2020-001568

Semba, R. D., Huang, H., Lutty, G. A., van Eyk, J. E., & Hart, G. W. (2014). The Role of O-GlcNAc Signaling in the Pathogenesis of Diabetic Retinopathy. *Proteomics. Clinical Applications*, *8*(0), 218. https://doi.org/10.1002/PRCA.201300076

Sharma, S., Oliver-Fernandez, A., Liu, W., Buchholz, P., & Walt, J. (2005). The impact of diabetic retinopathy on health-related quality of life. *Current Opinion in Ophthalmology*, *16*(3), 155–159. https://doi.org/10.1097/01.ICU.0000161227.21797.3D

Shiba, T., Inoguchi, T., Sportsman, J. R., Heath, W. F., Bursell, S., & King, G. L. (1993). Correlation of diacylglycerol level and protein kinase C activity in rat retina to retinal circulation. *Https://Doi.Org/10.1152/Ajpendo.1993.265.5.E783*, *265*(5 28-5). https://doi.org/10.1152/AJPENDO.1993.265.5.E783

Shimouchi, A., Ishibazawa, A., Ishiko, S., Omae, T., Ro-Mase, T., Yanagi, Y., & Yoshida, A. (2020). A proposed classification of intraretinal microvascular abnormalities in diabetic retinopathy following panretinal photocoagulation. *Investigative Ophthalmology & Visual Science*, *61*(3), 34–34. https://doi.org/10.1167/IOVS.61.3.34

Simó, R., Stitt, A. W., & Gardner, T. W. (2018). Neurodegeneration in diabetic retinopathy: does it really matter? *Diabetologia*, *61*(9), 1902–1912. https://doi.org/10.1007/S00125-018-4692-1

Simunovic, M. P., & Maberley, D. A. L. (2015). Anti-vascular endothelial growth factor therapy for proliferative diabetic retinopathy. *Retina*, *35*(10), 1931–1942. https://doi.org/10.1097/IAE.0000000000000723

Sivak-Callcott, J. A., O'Day, D. M., Gass, J. D. M., & Tsai, J. C. (2001). Evidence-based recommendations for the diagnosis and treatment of neovascular glaucoma. *Ophthalmology*, *108*(10), 1767–1776. https://doi.org/10.1016/S0161-6420(01)00775-8

Sivaprasad, S., Hykin, P., Prevost, A. T., Vasconcelos, J., Riddell, A., Ramu, J., Murphy, C., Kelly, J., Edwards, R. T., Yeo, S. T., Bainbridge, J., Hopkins, D., & White-Alao, B. (2018). Intravitreal aflibercept compared with panretinal photocoagulation for proliferative diabetic retinopathy: the CLARITY non-inferiority RCT. *Efficacy and Mechanism Evaluation*, *5*(5), 1–112. https://doi.org/10.3310/EME05050

Sivaprasad, S., Prevost, A. T., Vasconcelos, J. C., Riddell, A., Murphy, C., Kelly, J., Bainbridge, J., Tudor-Edwards, R., Hopkins, D., Hykin, P., Bhatnagar, A., Burton, B., Chakravarthy, U., Eleftheriadis, H., Empeslidis, T., Gale, R., George, S., Habib, M., Kelly, S., … Karia, N. (2017). Clinical efficacy of intravitreal aflibercept versus panretinal photocoagulation for best corrected visual acuity in patients with proliferative diabetic retinopathy at 52 weeks (CLARITY): a multicentre, single-blinded, randomised, controlled, phase 2b, non-inferiority trial. *Lancet (London, England)*, *389*(10085), 2193–2203. https://doi.org/10.1016/S0140-6736(17)31193-5

Spaide, R. F., Fujimoto, J. G., & Waheed, N. K. (2015). Image artifacts in optical coherence tomography angiography. *Retina (Philadelphia, Pa.)*, *35*(11), 2163–2180. https://doi.org/10.1097/IAE.0000000000000765

Spaide, R. F., Klancnik, J. M., & Cooney, M. J. (2015). Retinal vascular layers imaged by fluorescein angiography and optical coherence tomography angiography. *JAMA Ophthalmology*, *133*(1), 45–50. https://doi.org/10.1001/JAMAOPHTHALMOL.2014.3616

Spencer, B. G., Estevez, J. J., Liu, E., Craig, J. E., & Finnie, J. W. (2020). Pericytes, inflammation, and diabetic retinopathy. *Inflammopharmacology*, *28*(3), 697–709. https://doi.org/10.1007/S10787-019-00647-9

Srinivasan, S., Raman, R., Swaminathan, G., Ganesan, S., Kulothungan, V., & Sharma, T. (2017). Incidence, progression, and risk factors for cataract in type 2 diabetes. *Investigative Ophthalmology & Visual Science*, *58*(13), 5921–5929. https://doi.org/10.1167/IOVS.17-22264

Stanik, J., Dusatkova, P., Cinek, O., Valentinova, L., Huckova, M., Skopkova, M., Dusatkova, L., Stanikova, D., Pura, M., Klimes, I., Lebl, J., Gasperikova, D., & Pruhova, S. (2014). De novo mutations of GCK , HNF1A and HNF4A may be more frequent in MODY than previously assumed. *Diabetologia*, *57*(3), 480–484. https://doi.org/10.1007/s00125-013-3119-2

Steffes, M. W., Sibley, S., Jackson, M., & Thomas, W. (2003). Beta-cell function and the development of diabetes-related complications in the diabetes control and complications trial. *Diabetes Care*, *26*(3), 832–836. https://doi.org/10.2337/DIACARE.26.3.832

Steiner, S. (2016). Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *Zeitschrift Fur Gefassmedizin*, *13*(1), 17–18. https://doi.org/10.1056/NEJMOA1504720/SUPPL_FILE/NEJMOA1504720_DISCLOSURES.PDF

Steinmetz, P. R., Balko, C., & Gabbay, K. H. (1973). The sorbitol pathway and the complications of diabetes. *The New England Journal of Medicine*, *288*(16), 831–836. https://doi.org/10.1056/NEJM197304192881609

Sullivan, P. W., Morrato, E. H., Ghushchyan, V., Wyatt, H. R., & Hill, J. O. (2005). Obesity, inactivity, and the prevalence of diabetes and diabetes-related cardiovascular comorbidities in the U.S., 2000-2002. *Diabetes Care*, *28*(7), 1599–1603. https://doi.org/10.2337/DIACARE.28.7.1599

Sun, H., Saeedi, P., Karuranga, S., Pinkepank, M., Ogurtsova, K., Duncan, B. B., Stein, C., Basit, A., Chan, J. C. N., Mbanya, J. C., Pavkov, M. E., Ramachandaran, A., Wild, S. H., James, S., Herman, W. H., Zhang, P., Bommer, C., Kuo, S., Boyko, E. J., & Magliano, D. J. (2022). IDF Diabetes Atlas: Global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. *Diabetes Research and Clinical Practice*, *183*. https://doi.org/10.1016/J.DIABRES.2021.109119

Talcott, K. E., Valentim, C. C. S., Hill, L., Stoilov, I., & Singh, R. P. (2023). Baseline diabetic retinopathy severity and time to diabetic macular edema resolution with ranibizumab treatment: a meta-analysis. *Ophthalmology. Retina*. https://doi.org/10.1016/J.ORET.2023.02.003

Tang, J., & Kern, T. S. (2011). Inflammation in diabetic retinopathy. *Progress in Retinal and Eye Research*, *30*(5), 343–358. https://doi.org/10.1016/J.PRETEYERES.2011.05.002

Tasman, W., Magargal, L. E., & Augsburger, J. J. (1980). Effects of argon laser photocoagulation on rubeosis iridis and angle neovascularization. *Ophthalmology*, *87*(5), 400–402. https://doi.org/10.1016/S0161-6420(80)35225-1

Teo, Z. L., Tham, Y. C., Yu, M., Chee, M. L., Rim, T. H., Cheung, N., Bikbov, M. M., Wang, Y. X., Tang, Y., Lu, Y., Wong, I. Y., Ting, D. S. W., Tan, G. S. W., Jonas, J. B., Sabanayagam, C., Wong, T. Y., & Cheng, C. Y. (2021). Global prevalence of diabetic retinopathy and projection of burden through 2045: systematic review and meta-analysis. *Ophthalmology*, *128*(11), 1580–1591. https://doi.org/10.1016/J.OPHTHA.2021.04.027

Tesfaye, S., Chaturvedi, N., Eaton, S. E. M., Ward, J. D., Manes, C., Ionescu-Tirgoviste, C., Witte, D. R., & Fuller, J. H. (2005). Vascular risk factors and diabetic neuropathy, *352*(4), 341–350. https://doi.org/10.1056/NEJMOA032782

The Diabetes Control and Complications Trial Research Group. (1993). The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *329*(14), 977–986. https://doi.org/10.1056/NEJM199309303291401

The Diabetes Control and Complications Trial Research Group. (1998). The effect of intensive diabetes therapy on measures of autonomic nervous system function in the Diabetes Control and Complications Trial (DCCT). *Diabetologia*, *41*(4), 416–423. https://doi.org/10.1007/S001250050924

Thomas, D., Bunce, C., Moorman, C., & Laidlaw, D. A. H. (2005). A randomised controlled feasibility trial of vitrectomy versus laser for diabetic macular oedema. *The British Journal of Ophthalmology*, *89*(1), 81–86. https://doi.org/10.1136/BJO.2004.044966

Tobon-Velasco, J., Cuevas, E., & Torres-Ramos, M. (2014). Receptor for AGEs (RAGE) as mediator of NF-kB pathway activation in neuroinflammation and oxidative stress. *CNS & Neurological Disorders Drug Targets*, *13*(9), 1615–1626. https://doi.org/10.2174/1871527313666140806144831

Tsalamandris, S., Antonopoulos, A. S., Oikonomou, E., Papamikroulis, G. A., Vogiatzi, G., Papaioannou, S., Deftereos, S., & Tousoulis, D. (2019). The role of inflammation in diabetes: Current concepts and future perspectives. *European Cardiology Review* , *14*(1), 50–59. https://doi.org/10.15420/ECR.2018.33.1

Tuomi, T., Santoro, N., Caprio, S., Cai, M., Weng, J., & Groop, L. (2014). The many faces of diabetes: a disease with increasing heterogeneity. *Lancet (London, England)*, *383*(9922), 1084–1094. https://doi.org/10.1016/S0140-6736(13)62219-9

Tuomilehto, J., Lindström, J., Eriksson, J. G., Valle, T. T., Hämäläinen, H., Ilanne-Parikka, P., Keinänen-Kiukaanniemi, S., Laakso, M., Louheranta, A., Rastas, M., Salminen, V., Aunola, S., Cepaitis, Z., Moltchanov, V., Hakumäki, M., Mannelin, M., Martikkala, V., Sundvall, J., & Uusitupa, M. (2001). Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *The New England Journal of Medicine*, *344*(18), 1343–1350. https://doi.org/10.1056/NEJM200105033441801

Turner, G. S., Inglesby, D. v., Sharriff, B., & Kohner, E. M. (1985). Natural history of peripheral neovascularisation in diabetic retinopathy. *The British Journal of Ophthalmology*, *69*(6), 420–424. https://doi.org/10.1136/BJO.69.6.420

UKPDS Group. (1998a). Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. *Lancet (London, England)*, *352*(9131), 854–865. https://doi.org/10.1016/S0140-6736(98)07037-8

UKPDS Group. (1998b). Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *The Lancet*, *352*(9131), 837–853. https://doi.org/10.1016/S0140-6736(98)07019-6

Umpierrez, G., & Korytkowski, M. (2016). Diabetic emergencies - ketoacidosis, hyperglycaemic hyperosmolar state and hypoglycaemia. *Nature Reviews. Endocrinology*, *12*(4), 222–232. https://doi.org/10.1038/NRENDO.2016.15

Vader, M. J. C., Schauwvlieghe, A. S. M. E., Verbraak, F. D., Dijkman, G., Hooymans, J. M. M., Los, L. I., Zwinderman, A. H., Peto, T., Hoyng, C. B., van Leeuwen, R., Vingerling, J. R., Moll, A. C., van Lith-Verhoeven, J. J. C., Dijkgraaf, M. G. W., & Schlingemann, R. O. (2020). Comparing the efficacy of bevacizumab and ranibizumab in patients with diabetic macular edema (BRDME): The BRDME Study, a Randomized Trial. *Ophthalmology Retina*, *4*(8), 777–788. https://doi.org/10.1016/j.oret.2020.02.008

Vallon, V., & Komers, R. (2011). Pathophysiology of the Diabetic Kidney. *Comprehensive Physiology*, *1*(3), 1175–1232. https://doi.org/10.1002/CPHY.C100049

van Dijk, H. W., Kok, P. H. B., Garvin, M., Sonka, M., Hans Devries, J., Michels, R. P. J., van Velthoven, M. E. J., Schlingemann, R. O., Verbraak, F. D., & Abràmoff, M. D. (2009). Selective loss of inner retinal layer thickness in type 1 diabetic patients with minimal diabetic retinopathy. *Investigative Ophthalmology & Visual Science*, *50*(7), 3404. https://doi.org/10.1167/IOVS.08-3143

van Dijk, H. W., Verbraak, F. D., Kok, P. H. B., Stehouwer, M., Garvin, M. K., Sonka, M., Hans Devries, J., Schlingemann, R. O., & Abràmoff, M. D. (2012). Early neurodegeneration in the retina of type 2 diabetic patients. *Investigative Ophthalmology & Visual Science*, *53*(6), 2715–2719. https://doi.org/10.1167/IOVS.11-8997

van Leiden, H. A., Dekker, J. M., Moll, A. C., Nijpels, G., Heine, R. J., Bouter, L. M., Stehouwer, C. D. A., & Polak, B. C. P. (2003). Risk factors for incident retinopathy in a diabetic and nondiabetic population: The Hoorn Study. *Archives of Ophthalmology*, *121*(2), 245–251. https://doi.org/10.1001/ARCHOPHT.121.2.245

Virgili, G., Menchini, F., Casazza, G., Hogg, R., Das, R. R., Wang, X., & Michelessi, M. (2015). Optical coherence tomography (OCT) for detection of macular oedema in patients with diabetic retinopathy. *The Cochrane Database of Systematic Reviews*, *1*(1). https://doi.org/10.1002/14651858.CD008081.PUB3

Virgili, G., Parravano, M., Evans, J. R., Gordon, I., & Lucenteforte, E. (2018). Anti-vascular endothelial growth factor for diabetic macular oedema: a network meta-analysis. *The Cochrane Database of Systematic Reviews*, *10*(10). https://doi.org/10.1002/14651858.CD007419.PUB6

Wakabayashi, T., Oshima, Y., Sakaguchi, H., Ikuno, Y., Miki, A., Gomi, F., Otori, Y., Kamei, M., Kusaka, S., & Tano, Y. (2008). Intravitreal bevacizumab to treat iris neovascularization and neovascular glaucoma secondary to ischemic retinal diseases in 41 consecutive cases. *Ophthalmology*, *115*(9). https://doi.org/10.1016/J.OPHTHA.2008.02.026

Wang, C.-Y., Cheang, W.-M., Hwang, D.-K., & Lin, C.-H. (2017). Vitreous haemorrhage: a population-based study of the incidence and risk factors in Taiwan. *International Journal of Ophthalmology*, *10*(3), 461–466. https://doi.org/10.18240/ijo.2017.03.21

Warwick, A. N., Brooks, A. P., Osmond, C., & Krishnan, R. (2017). Prevalence of referable, sight-threatening retinopathy in type 1 diabetes and its relationship to diabetes duration and systemic risk factors. *Eye (London, England)*, *31*(2), 334–340. https://doi.org/10.1038/EYE.2016.294

Watanabe, K., Hagura, R., Akanuma, Y., Takasu, T., Kajinuma, H., Kuzuya, N., & Irie, M. (1990). Characteristics of cranial nerve palsies in diabetic patients. *Diabetes Research and Clinical Practice*, *10*(1), 19–27. https://doi.org/10.1016/0168-8227(90)90077-7

Way, K. J., Katai, N., & King, G. L. (2001). Protein kinase C and the development of diabetic vascular complications. *Diabetic Medicine*, *18*(12), 945–959. https://doi.org/10.1046/J.0742-3071.2001.00638.X

Weires, M. B., Tausch, B., Haug, P. J., Edwards, C. Q., Wetter, T., & Cannon-Albright, L. A. (2007). Familiality of diabetes mellitus. *Experimental and Clinical Endocrinology & Diabetes : Official Journal, German Society of Endocrinology [and] German Diabetes Association*, *115*(10), 634–640. https://doi.org/10.1055/S-2007-984443

Wells, J. A., Glassman, A. R., Ayala, A. R., Jampol, L. M., Bressler, N. M., Bressler, S. B., Brucker, A. J., Ferris, F. L., Hampton, G. R., Jhaveri, C., Melia, M., & Beck, R. W. (2016). Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema: two-year results from a comparative effectiveness randomized clinical trial. *Ophthalmology*, *123*(6), 1351–1359. https://doi.org/10.1016/J.OPHTHA.2016.02.022

Wessels, A. M., Rombouts, S. A. R. B., Remijnse, P. L., Boom, Y., Scheltens, P., Barkhof, F., Heine, R. J., & Snoek, F. J. (2007). Cognitive performance in type 1 diabetes patients is associated with cerebral white matter volume. *Diabetologia*, *50*(8), 1763–1769. https://doi.org/10.1007/S00125-007-0714-0

Whicher, C. A., O'neill, S., & Holt, R. I. G. (2020). Diabetes UK Position Statements Diabetes in the UK: 2019. *Diabetic Medicine : A Journal of the British Diabetic Association*, *37*(2), 242–247. https://doi.org/10.1111/dme.14225

WHO (2015). *World report on Ageing And Health*. www.who.int

Wilker, S. C., Rucker, J. C., Newman, N. J., Biousse, V., & Tomsak, R. L. (2009). Pain in ischaemic ocular motor cranial nerve palsies. *The British Journal of Ophthalmology*, *93*(12), 1657–1659. https://doi.org/10.1136/BJO.2008.155150

Wilkinson, C. P., Ferris, F. L., Klein, R. E., Lee, P. P., Agardh, C. D., Davis, M., Dills, D., Kampik, A., Pararajasegaram, R., Verdaguer, J. T., & Lum, F. (2003a). Proposed international clinical diabetic retinopathy and diabetic macular edema disease severity scales. *Ophthalmology*, *110*(9), 1677–1682. https://doi.org/10.1016/S0161-6420(03)00475-5

Wilkinson, C. P., Ferris, F. L., Klein, R. E., Lee, P. P., Agardh, C. D., Davis, M., Dills, D., Kampik, A., Pararajasegaram, R., Verdaguer, J. T., & Lum, F. (2003b). Proposed international clinical diabetic retinopathy and diabetic macular edema disease severity scales. *Ophthalmology*, *110*(9), 1677–1682. https://doi.org/10.1016/S0161-6420(03)00475-5

Willi, C., Bodenmann, P., Ghali, W. A., Faris, P. D., & Cornuz, J. (2007). Active smoking and the risk of type 2 diabetes: a systematic review and meta-analysis. *JAMA*, *298*(22), 2654–2664. https://doi.org/10.1001/JAMA.298.22.2654

Willis, J. R., Doan, Q. v., Gleeson, M., Haskova, Z., Ramulu, P., Morse, L., & Cantrell, R. A. (2017). Vision-related functional burden of diabetic retinopathy across severity levels in the United States. *JAMA Ophthalmology*, *135*(9), 926–932. https://doi.org/10.1001/JAMAOPHTHALMOL.2017.2553

Wong, T. Y., Sun, J., Kawasaki, R., Ruamviboonsuk, P., Gupta, N., Lansingh, V. C., Maia, M., Mathenge, W., Moreker, S., Muqit, M. M. K., Resnikoff, S., Verdaguer, J., Zhao, P., Ferris, F., Aiello, L. P., & Taylor, H. R. (2018). Guidelines on diabetic eye care: the international council of ophthalmology recommendations for screening, follow-up, referral, and treatment based on resource settings. *Ophthalmology*, *125*(10), 1608–1622. https://doi.org/10.1016/J.OPHTHA.2018.04.007

World Health Organization. (2011). *Use of Glycated Haemoglobin (HbA1c) in the Diagnosis of Diabetes Mellitus Abbreviated Report of a WHO Consultation*.

World Health Organization. (2019). *Classification of diabetes mellitus*. http://apps.who.int/bookorders.

Wu, M., Mei, F., Hu, K., Feng, L., Wang, Z., Gao, Q., Chen, F., Zhao, L., Li, X., & Ma, B. (2022). Diabetic retinopathy and cognitive dysfunction: a systematic review and meta-analysis. *Acta Diabetologica*, *59*(4), 443–459. https://doi.org/10.1007/S00592-021-01829-0

Wubben, T. J., Johnson, M. W., Sohn, E. H., Peairs, J. J., Kay, C. N., Kim, S. J., Gardner, T. W., Paulus, Y. M., Zacks, D. N., Steinle, N. C., Avery, R. L., & Berrocal, M. H. (2019). Anti-vascular endothelial growth factor therapy for diabetic retinopathy: consequences of inadvertent treatment interruptions. *American Journal of Ophthalmology*, *204*, 13–18. https://doi.org/10.1016/J.AJO.2019.03.005

Yamagishi, S. I., Matsui, T., Nakamura, K., Inoue, H., Takeuchi, M., Ueda, S., Okuda, S., & Imaizumi, T. (2008). Olmesartan blocks inflammatory reactions in endothelial cells evoked by advanced glycation end products by suppressing generation of reactive oxygen species. *Ophthalmic Research*, *40*(1), 10–15. https://doi.org/10.1159/000111152

Yannuzzi, L. A., Rohrer, K. T., Tindel, L. J., Sobel, R. S., Costanza, M. A., Shields, W., & Zang, E. (1986). Fluorescein angiography complication survey. *Ophthalmology*, *93*(5), 611–617. https://doi.org/10.1016/S0161-6420(86)33697-2

Yapanis, M., James, S., Craig, M. E., O'Neal, D., & Ekinci, E. I. (2022). Complications of Diabetes and Metrics of Glycemic Management Derived From Continuous Glucose Monitoring. *The Journal of Clinical Endocrinology and Metabolism*, *107*(6), E2221–E2236. https://doi.org/10.1210/CLINEM/DGAC034

Yates, W. B., Mammo, Z., & Simunovic, M. P. (2021). Intravitreal anti-vascular endothelial growth factor versus panretinal LASER photocoagulation for proliferative diabetic retinopathy: a systematic review and meta-analysis. *Canadian Journal of Ophthalmology. Journal Canadien d'ophtalmologie*, *56*(6), 355–363. https://doi.org/10.1016/J.JCJO.2021.01.017

Yau, J. W. Y., Rogers, S. L., Kawasaki, R., Lamoureux, E. L., Kowalski, J. W., Bek, T., Chen, S. J., Dekker, J. M., Fletcher, A., Grauslund, J., Haffner, S., Hamman, R. F., Ikram, M. K., Kayama, T., Klein, B. E. K., Klein, R., Krishnaiah, S., Mayurasakorn, K., O'Hare, J. P., Wong , T. Y. (2012). Global prevalence and major risk factors of diabetic retinopathy. *Diabetes Care*, *35*(3), 556–564. https://doi.org/10.2337/DC11-1909

Yeung, A., & Dwarakanathan, S. (2021). Diabetic keratopathy. *Disease-a-Month*, *67*(5), 101135. https://doi.org/10.1016/J.DISAMONTH.2021.101135

Young, M. J., Boulton, A. J. M., Macleod, A. F., Williams, D. R. R., & Sonksen, P. H. (1993). A multicentre study of the prevalence of diabetic peripheral neuropathy in the United Kingdom hospital clinic population. *Diabetologia*, *36*(2), 150–154. https://doi.org/10.1007/BF00400697

Yu, F. shin X., Lee, P. S. Y., Yang, L., Gao, N., Zhang, Y., Ljubimov, A. v., Yang, E., Zhou, Q., & Xie, L. (2022). The impact of sensory neuropathy and inflammation on epithelial wound healing in diabetic corneas. *Progress in Retinal and Eye Research*, *89*, 101039. https://doi.org/10.1016/J.PRETEYERES.2021.101039

Yuen, L., Saeedi, P., Riaz, M., Karuranga, S., Divakar, H., Levitt, N., Yang, X., & Simmons, D. (2019). Projections of the prevalence of hyperglycaemia in pregnancy in 2019 and beyond: Results from the International Diabetes Federation Diabetes Atlas, 9th edition. *Diabetes Research and Clinical Practice*, *157*. https://doi.org/10.1016/J.DIABRES.2019.107841

Zeiner, J., Loukovaara, S., Losenkova, K., Zuccarini, M., Korhonen, A. M., Lehti, K., Kauppinen, A., Kaarniranta, K., Müller, C. E., Jalkanen, S., & Yegutkin, G. G. (2019). Soluble and membrane-bound adenylate kinase and nucleotidases augment ATP-mediated inflammation in diabetic retinopathy eyes with vitreous hemorrhage. *Journal of Molecular Medicine (Berlin, Germany)*, *97*(3), 341–354. https://doi.org/10.1007/S00109-018-01734-0

Zelniker, T. A., Wiviott, S. D., Raz, I., Im, K., Goodrich, E. L., Bonaca, M. P., Mosenzon, O., Kato, E. T., Cahn, A., Furtado, R. H. M., Bhatt, D. L., Leiter, L. A., McGuire, D. K., Wilding, J. P. H., & Sabatine, M. S. (2019). SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *The Lancet*, *393*(10166), 31–39. https://doi.org/10.1016/S0140-6736(18)32590-X

Zhang, J., Zhang, J., Zhang, C., Zhang, J., Gu, L., Luo, D., & Qiu, Q. (2022). Diabetic Macular Edema: Current Understanding, molecular mechanisms and therapeutic implications. *Cells*, *11*(21). https://doi.org/10.3390/CELLS11213362

Zhang, L., Krzentowski, G., Albert, A., & Lefebvre, P. J. (2001). Risk of developing retinopathy in Diabetes Control and Complications Trial type 1 diabetic patients with good or poor metabolic control. *Diabetes Care*, *24*(7), 1275–1279. https://doi.org/10.2337/DIACARE.24.7.1275

Zhang, X., Saaddine, J. B., Chou, C. F., Cotch, M. F., Cheng, Y. J., Geiss, L. S., Gregg, E. W., Albright, A. L., Klein, B. E. K., & Klein, R. (2010). Prevalence of diabetic retinopathy in the United States, 2005-2008. *JAMA*, *304*(6), 649–656. https://doi.org/10.1001/JAMA.2010.1111

Ziemianski, M. C., McMeel, J. W., & Franks, E. P. (1980). Natural history of vitreous hemorrhage in diabetic retinopathy. *Ophthalmology*, *87*(4), 306–312. https://doi.org/10.1016/S0161-6420(80)35232-9

Original publications

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II Wirkkala, J., Kubin, A. M., Ohtonen, P., Falck, A., & Hautala, N. (2023). Outcomes of 35-year duration of type 1 diabetes and proliferative diabetic retinopathy on functional vision and quality of life: Benefits of good glycemic control. Journal of diabetes and its complications, 37(2), 108408. Advance online publication. https://doi.org/10.1016/j.jdiacomp.2023.108408

III Wirkkala, J., Kubin, A. M., Ohtonen, P., Yliselä, J., Siik, T., & Hautala, N. (2022). Visual outcomes of observation, macular laser and anti-VEGF in diabetic macular edema in type 1 diabetes: a real-world study. BMC ophthalmology, 22(1), 258. https://doi.org/10.1186/s12886-022-02482-z

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