DIABETES AND THE EYE: LATEST CONCEPTS AND PRACTICES

Editors:
Douglas R. Lazzaro
Samy I. McFarlane

Bentham Books

Diabetes: Current and Future Developments

(Volume 2)

(Diabetes and the Eye: Latest Concepts and Practices)

Edited by

Douglas R. Lazzaro
Department of Ophthalmology,
NYU Langone Health,
NYU Grossman School of Medicine,
USA

&

Samy I. McFarlane
Department of Medicine,
Division of Endocrinology,
State University of New York-Downstate Medical Center,
Brooklyn, New York,
USA

Diabetes: Current and Future Developments

Volume # 2

Diabetes and the Eye: Latest Concepts and Practices

Editors: Douglas R. Lazzaro and Samy I. McFarlane

ISSN (Online): 2717-5855

ISSN (Print): 2717-5847

ISBN (Online): 978-981-14-6646-5

ISBN (Print): 978-981-14-6644-1

ISBN (Paperback): 978-981-14-6645-8

need for a court order if at any point you breach any terms of this License Agreement. In no event will any delay or failure by Bentham Science Publishers in enforcing your compliance with this License Agreement constitute a waiver of any of its rights.

3. You acknowledge that you have read this License Agreement, and agree to be bound by its terms and conditions. To the extent that any other terms and conditions presented on any website of Bentham Science Publishers conflict with, or are inconsistent with, the terms and conditions set out in this License Agreement, you acknowledge that the terms and conditions set out in this License Agreement shall prevail.

Bentham Science Publishers Pte. Ltd.
80 Robinson Road #02-00
Singapore 068898
Singapore
Email: subscriptions@benthamscience.net

CONTENTS

FOREWORD i

PREFACE ii

LIST OF CONTRIBUTORS iii

CHAPTER 1 DIABETES EPIDEMIC, EPIDEMIOLOGY, STATISTICS AND TRENDS 1

Andrew M. Hendrick

INTRODUCTION 1

Epidemiology of Diabetes Mellitus 2

Epidemiology of Diabetic Retinopathy 4

Screening of Diabetic Retinopathy 7

CONCLUSION 7

CONSENT FOR PUBLICATION 8

CONFLICT OF INTEREST 8

ACKNOWLEDGEMENTS 8

REFERENCES 8

CHAPTER 2 RECENT DEVELOPMENTS IN DIABETES EVALUATION AND MANAGEMENT: IMPLICATIONS FOR THE PRACTICING CLINICIANS 13

Anna Y. Groysman, Lina Soni, Samara Skwiersky and *Samy I. McFarlane*

INTRODUCTION 13

RISK FACTORS OF DIABETES MELLITUS 15

Non-modifiable Risk Factors 15

Genetics 15

Susceptibility Loci 15

Modifiable Risk Factors 15

Lifestyle 15

Vitamins 16

Gut Bacteria 17

COMPLICATIONS OF DIABETES MELLITUS 18

Macrovascular Complications 18

Cardiovascular Diseases 18

Cancer 19

Cerebrovascular Accident 20

Peripheral Vascular Disease 20

Microvascular Complications 21

Neuropathy 21

Retinopathy 21

Diabetic Kidney Disease 21

NEW THERAPEUTIC MODALITIES FOR TREATING DIABETES MELLITUS 22

DPP-4 and SGLT2 Inhibitors: The Next Second Line Oral Agents 23

DPP-4 Inhibitors Compared to Sulfonylurea 24

The Search for Superior Insulin as Demand for Higher Doses Rises 25

Insulin Degludec 25

GPR40 Agonist 26

Lixisenatide 26

Anti-Inflammatory Treatment 27

Nitrates and Nitrites 27

Antioxidant Therapy 27

NEW TECHNOLOGIES FOR TREATMENT OF DIABETES MELLITUS 28

Glucose Monitoring 28
The Artificial Pancreas (Closed-loop Monitoring System) 29
Components of the Closed-loop Monitoring System 29
The Three-body Access Routes 30
The Efficacy of the Closed-loop System 31
Bi-hormonal Therapy and the Closed-loop System 32
Adjunctive Therapies and the Closed-loop System 32
The Outlook of the Closed-loop Monitoring System 33
Pancreas Allotransplantation 33
Islet Cell Allotransplantation 34
Becoming Insulin Free with Stem Cells 36
PREVENTION OF DIABETES MELLITUS 39
Screening 39
Lifestyle Modification 39
Pharmacological Agents 40
Motivational Interviewing 40
CONCLUSION 41
CONSENT FOR PUBLICATION 42
CONFLICT OF INTEREST 42
ACKNOWLEDGEMENTS 42
REFERENCES 42

CHAPTER 3 BLURRED VISION IN THE DIABETIC PATIENT – REVERSIBLE AND NON-REVERSIBLE CAUSES – GENERAL CLASSIFICATION OF DIABETIC EYE DISEASE 52
Rony Gelman
INTRODUCTION 52
CLASSIFICATION SYSTEM 53
REVERSIBLE AND NON-REVERSIBLE CAUSES OF VISION LOSS IN DIABETIC RETINOPATHY 54
Diabetic Macular Edema 54
Complications from Proliferative Diabetic Retinopathy 60
Vitreomacular Traction and Epiretinal Membrane 66
CONCLUSION 69
CONSENT FOR PUBLICATION 69
CONFLICT OF INTEREST 69
ACKNOWLEDGEMENTS 69
REFERENCES 69

CHAPTER 4 DIABETES AND OCULAR INFECTIONS 71
Jennifer Lopez and *Allison E. Rizzuti*
INTRODUCTION 71
RHINO-ORBITAL-CEREBRAL MUCORMYCOSIS 71
Case 1 71
PRE-SEPTAL & ORBITAL CELLULITIS 73
Case 2 73
Case 3 73
INFECTIOUS KERATITIS 75
Case 4 75
ENDOPHTHALMITIS 76
Case 5 76
CONCLUSION 77
CONSENT FOR PUBLICATION 77

CONFLICT OF INTEREST 77
ACKNOWLEDGEMENTS 78
REFERENCES 78

CHAPTER 5 NEURO-OPHTHALMIC COMPLICATIONS OF DIABETES MELLITUS 80
Julie DeBacker and *Alessandro Albano*
INTRODUCTION 80
DIABETES AND NEURO-OPHTHALMOLOGIC COMPLICATIONS 80
Cranial Nerve Palsies in Diabetes 80
Case 1: Diabetic Patient Presents with an Oculomotor Nerve Palsy 81
Cases 2 and 3: Botulinum Toxin A as a Treatment of Diplopia from Diabetic Abducens Nerve Palsy 82
Non-Arteritic Anterior Ischemic Optic Neuropathy 84
Optic Neuropathy in Young Patients with Diabetes 84
Pupils in Diabetes 85
CONCLUSION 85
CONSENT FOR PUBLICATION 85
CONFLICT OF INTEREST 85
ACKNOWLEDGEMENTS 85
REFERENCES 86

CHAPTER 6 OVERVIEW OF ANTERIOR AND POSTERIOR SEGMENT COMPLICATIONS 87
Steven Agemy, Zaki Azam and *Eric Shrier*
INTRODUCTION 87
Anterior Segment Complications 88
Ocular Surface Diseases 88
Dry Eye Syndrome (DES) 88
Diabetic Keratopathy 89
Refractive Changes 90
Cataracts 90
Ocular Movement Disorders 91
Neovascular Glaucoma 92
Posterior Segment Complications 93
Diabetic Retinopathy 93
Diabetic Papillopathy 99
CONCLUSION 100
CONSENT FOR PUBLICATION 100
CONFLICT OF INTEREST 100
ACKNOWLEDGEMENTS 100
REFERENCES 100

CHAPTER 7 DIABETES AND THE CORNEA 106
Lucy Sun and *Douglas R. Lazzaro*
CORNEAL EPITHELIUM 107
Increase in Epithelial Thickness 107
Abnormal Basement Membrane Formation 108
Impaired Epithelial Barrier Function 109
Increased Epithelial Fragility 110
Poor Healing Capacity of Epithelial Defects 110
CORNEAL INFECTIONS 110
CORNEAL STROMA 111

Altered Collagen Synthesis 111
CORNEAL ENDOTHELIUM 111
Morphological Abnormalities 112
Functional Abnormalities Leading to Increased Water Content in the Atroma and Folds in Descement's Membrane 112
CORNEAL NERVES 113
Reduced Corneal Sensation 113
Loss of the Subbasal Nerve Plexus 114
Loss of Neurotrophic Support 114
TEAR DYNAMICS AND TEARING 115
Tear Film Dysfunction 116
Decreased Reflex Tearing 116
CORNEA CONSIDERATIONS IN OCULAR SURGERY 117
Cataract Surgery 117
Refractive Surgery: PRK 118
Refractive Surgery: LASIK 118
Penetrating Keratoplasty 120
Pterygium 121
Closed Pars Plana Vitrectomy 121
CONCLUSION 122
CONSENT FOR PUBLICATION 123
CONFLICT OF INTEREST 123
ACKNOWLEDGEMENTS 123
REFERENCES 123

CHAPTER 8 DIABETES, CATARACT, AND GLAUCOMA 128
Frank Cao and *John Danias*
CATARACT 128
Anatomy 128
Risk Factors 129
Pathophysiology 130
Clinical Evaluation 131
Treatment 131
GLAUCOMA 132
Definition and Epidemiology 132
Diabetes and Glaucoma Risk 133
Diabetes and Neovascular Glaucoma 134
Clinical Examination 135
Treatment 136
CONSENT FOR PUBLICATION 139
CONFLICT OF INTEREST 140
ACKNOWLEDGEMENTS 140
REFERENCES 140

CHAPTER 9 OPTICAL COHERENCE TOMOGRAPHY AND FLUORESCEIN ANGIOGRAPHY IN DIABETIC RETINOPATHY 147
Sruthi Arepalli, Justis P. Ehlers and *Peter K. Kaiser*
OPTICAL COHERENCE TOMOGRAPHY 147
Diabetic Macular Edema 147
Morphological Patterns of Diabetic Macular Edema 148
Retinal Thickness and Individual Layer Integrity in Diabetic Macular Edema 151
Summary 156

OPTICAL COHERENCE TOMOGRAPHY ANGIOGRAPHY 156
Diabetic Macular Edema 157
Macular Ischemia 158
Increased FAZ 158
Perfusion and Vessel Density 158
Microaneurysms 160
Peripheral Ischemia 160
Proliferative Diabetic Retinopathy 160
Summary 161
FLUORESCEIN ANGIOGRAPHY 161
Diabetic Ischemia 162
Diabetic Leakage 163
WIDE FIELD FLUORESCEIN ANGIOGRAPHY 164
Summary 164
CONCLUSION 165
CONSENT FOR PUBLICATION 165
CONFLICT OF INTEREST 165
ACKNOWLEDGEMENTS 165
REFERENCES 165

CHAPTER 10 CLASSIFICATION OF PROLIFERATIVE AND NON-PROLIFERATIVE DIABETIC RETINOPATHY AND ITS IMPLICATIONS 171
Ferhina S. Ali and *Sunir J. Garg*
BACKGROUND 171
CLINICAL MANIFESTATIONS OF NONPROLIFERATIVE DIABETIC RETINOPATHY 172
NONPROLIFERATIVE DIABETIC RETINOPATHY 177
Mild Nonproliferative Diabetic Retinopathy 177
Moderate and Severe Nonproliferative Diabetic Retinopathy 177
PROLIFERATIVE DIABETIC RETINOPATHY 179
Panretinal Laser Photocoagulation 181
Anti-Vascular Endothelial Growth Factor (anti-VEGF) Therapy 182
CONCLUSION 183
CONSENT FOR PUBLICATION 183
CONFLICT OF INTEREST 183
ACKNOWLEDGEMENTS 183
REFERENCES 183

CHAPTER 11 CURRENT TREATMENT FOR DIABETIC RETINOPATHY 185
Joseph Bogaard and *Judy E. Kim*
INTRODUCTION 185
Diabetic Retinopathy 187
Treatment of Diabetic Macular Edema 188
Anti-VEGF Therapy for DME 188
Comparison of Anti-VEGF Agents for DME 189
Anti-VEGF Treatment Regimens for DME 190
Safety and Potential Side Effects of Anti-VEGF Therapy 190
Future Developments in Anti-VEGF Therapy for DME 191
Laser Photocoagulation for DME 192
Micropulse Laser Treatment for DME 193
Targeted Peripheral Laser Photocoagulation for DME 193
Corticosteroids for DME 194

Vitrectomy for DME 195
Treatment of Proliferative Diabetic Retinopathy 195
Vitrectomy for PDR 196
CONCLUSION 197
CONSENT FOR PUBLICATION 197
CONFLICT OF INTEREST 197
ACKNOWLEDGEMENTS 197
REFERENCES 197

CHAPTER 12 FUTURE DIRECTION IN DIABETIC EYE DISEASE 203
Gautam Vangipuram and *Gaurav K. Shah*
INTRODUCTION 203
Standard of Care Treatment 205
Addressing Risk Factors 205
Anti-Vascular Endothelial Growth Factor (VEGF) Therapy 206
FUTURE DIRECTIONS IN ANTI-VEGF 212
Brolucizumab 212
Faricimab 212
Conbercept 212
OPT-302 213
Port Delivery System (PDS) 213
Gene Therapy 213
Growth Factor Inhibition 214
Inflammatory Response Inhibition 215
THR-149-001 215
THR-687 215
OCS-01 215
Risuteganib 216
AKB-9778 Tie2 Mediators 216
XipereTM 217
Photobiomodulation (PBM) 217
Targeting Neurodegeneration and Other Potential Targets 217
Future Treatment Strategies for Proliferative Diabetic Retinopathy (PDR) 218
Protocol S 218
Adjuvant Anti-VEGF Usage 219
Hybrid-Gauge Surgery 219
CONCLUSION 220
CONSENT FOR PUBLICATION 220
CONFLICT OF INTEREST 220
ACKNOWLEDGEMENTS 220
REFERENCES 220

SUBJECT INDEX 225

FOREWORD

Diabetes mellitus is certainly one of the most important public health problems of the 21st century. Its protean impacts on the eye are well known to all ophthalmologists, who deal with diabetic ocular complications virtually every day. Diabetic eye disease still accounts for much preventable blindness in working age adults, despite the many advances in understanding of pathophysiology and treatment over the last three decades. It is therefore a great pleasure for me to write a foreword to this comprehensive textbook on diabetes and the eye, edited by my colleagues, Douglas R. Lazzaro, and Samy I. McFarlane. Of interest to a wide audience, this book will enhance education of trainees in ophthalmology, and will serve as a definitive resource for practicing ophthalmologists and other physicians who manage diabetes for years to come. This text not only sheds light on the current state of our understanding of ocular manifestations of diabetes, but also looks towards the future when a better understand of the risk factors for diabetic eye disease and improved treatments will reduce the burden of this disease on our society, truly a noble goal. Happy reading!

Kathryn Colby
Elisabeth J Cohen Professor and Chairman
Department of Ophthalmology
NYU Grossman School of Medicine
NYU Langone Health System
New York
USA

PREFACE

Diabetic eye disease is a heterogeneous group of disorders that affect the diabetic population and include diabetic retinopathy, cataract, macular edema, glaucoma, as well as other manifestations of the anterior and posterior segments of the eye. Among these manifestations, diabetic retinopathy and cataract are the most common cause of visual impairment and blindness. In fact people with diabetes are 25 times more likely to develop blindness compared to the general population, and diabetes is the most common cause of blindness among adults 20-74 years of age.

While diabetic retinopathy affects nearly 60% of patients with type 2 diabetes, in type 1 diabetes it is almost universal to develop diabetic retinopathy 15- 20 years after the diagnosis of diabetes is made.

With the rapid rise of obesity, diabetes has become the modern-day epidemic with its attendant complications including diabetic eye disease that leaves millions of people visually disabled, significantly decreasing the quality of life and markedly increasing the risk of injury.

In this volume on Diabetes and the Eye: Latest Concepts and Practices, we have assembled a group of renowned scholars with special expertise in diabetic eye disease, addressing a wide range of topics in a highly scientific, yet easy to read format that will benefit the generalist as well as the specialist and will appeal to the student, the graduate and the practicing physician who commonly encounter diabetic eye disorders, putting practical, yet cutting edge information at their fingertips.

Topics covered in this volume include the epidemiology and trends of the diabetes epidemic and diabetic eye disorders, the pathophysiologic mechanisms of diabetic eye disease and the various manifestations of diabetic complications in the eye. We highlight the latest research findings, the cutting edge diagnostic methods and the most recent developments in the management of retinopathy and other complications. We also discuss future directions and the latest developments in this exciting and rapidly developing field.

Douglas R. Lazzaro
Department of Ophthalmology
NYU Langone Health
NYU Grossman School of Medicine
USA

&

Samy I. McFarlane
Department of Medicine
State University of New York-Downstate Medical Center
Brooklyn, New York
USA

List of Contributors

Agemy, Steven	New York Eye and Ear Infirmary of Mount Sinai, NY, USA
Albano, Alessandro	SUNY Downstate College of Medicine, Brooklyn, NY, USA
Ali, Ferhina S.	The Retina Service of Wills Eye Hospital, Professor of Ophthalmology Thomas Jefferson University 840 Walnut Street, Suite 1020 Philadelphia, PA 19107, USA
Arepalli, Sruthi	The Cole Eye Institute, Cleveland Clinic, Cleveland, OH, USA
Azam, Zaki	SUNY-Downstate College of Medicine, Brooklyn, NY, USA
Cao, Frank	SUNY Downstate College of Medicine, SUNY Downstate Medical Center, Brooklyn, NY, USA
Danias, John	SUNY Downstate College of Medicine, SUNY Downstate Medical Center, Brooklyn, NY, USA
DeBacker, Julie	NYU School of Medicine, NYU Langone Health, NY, USA
Ehlers, Justis P.	The Cole Eye Institute, Cleveland Clinic, Cleveland, OH, USA
Garg, Sunir J.	The Retina Service of Wills Eye Hospital, Professor of Ophthalmology Thomas Jefferson University 840 Walnut Street, Suite 1020 Philadelphia, PA 19107, USA
Gelman, Rony	Department of Ophthalmology, State University of New York, Downstate Medical Center, NY, USA
Groysman, Anna Y.	Department of Medicine, Division of Endocrinology, State University of New York, Downstate-Medical Center, Brooklyn, NY, USA
Hendrick, Andrew M.	Department of Ophthalmology, Emory University, Atlanta, GA, USA
Joseph, Bogaard	Department of Ophthalmology and Visual Sciences, Medical College of Wisconsin, Milwaukee, USA
Kaiser, Peter K.	The Cole Eye Institute, Cleveland Clinic, Cleveland, OH, USA
Kim, Judy E.	Department of Ophthalmology and Visual Sciences, Medical College of Wisconsin, Milwaukee, USA
Lazzaro, Douglas R.	Department of Ophthalmology, NYU Langone Health, NY, USA
Lopez, Jennifer	Medical Center, NYU Langone, NY, USA
McFarlane, Samy I.	Department of Medicine, Division of Endocrinology, State University of New York, Downstate-Medical Center, Brooklyn, NY, USA
Rizzuti, Allison E.	Medical Center, NYU Langone, NY, USA
Shah, Gaurav K.	The Retina Institute, Saint Louis, Missouri, USA
Shrier, Eric	SUNY- Downstate College of Medicine, Brooklyn, NY, USA
Skwiersky, Samara	Department of Medicine, Division of Endocrinology, State University of New York, Downstate-Medical Center, Brooklyn, NY, USA
Soni, Lina	Department of Medicine, Division of Endocrinology, State University of New York, Downstate-Medical Center, Brooklyn, NY, USA
Sun, Lucy	SUNY Downstate Medical Center, NY, USA
Vangipuram, Gautam	The Retina Institute, Saint Louis, Missouri, USA

CHAPTER 1

Diabetes Epidemic, Epidemiology, Statistics and Trends

Andrew M. Hendrick*

Department of Ophthalmology, Emory University, Atlanta, GA, USA

Abstract: The incidence of diabetes mellitus is increasing worldwide. Over time, diabetes is associated with the development of diabetic retinopathy, a major cause of vision loss globally. Research has demonstrated factors associated with the onset and progression of the disease. Despite advancements in understanding the importance of optimizing care, the cases of vision loss due to diabetic retinopathy are also increasing. The epidemic of this systemic disease and the retinal manifestations will be discussed in detail in this chapter.

Keywords: Diabetes mellitus, Diabetic retinopathy, Epidemic, Epidemiology, Population, Type 1 Diabetes mellitus, Type 2 Diabetes mellitus.

INTRODUCTION

Diabetes mellitus (DM) is a chronic health condition defined by the presence of impaired glucose regulation leading to hyperglycemia. Normal blood sugar levels depend on the effective use of insulin, a peptide hormone responsible for triggering glucose uptake into cellular spaces (among many other critical metabolic effects). In people with diabetes mellitus, insulin is not used effectively; this is either due to underproduction as seen in type 1 diabetes mellitus (T1DM), or end-tissue resistance to the effects of insulin as seen in type 2 diabetes mellitus (T2DM). Longstanding and/or poorly controlled elevated blood sugar levels are major determinants of complications from DM such as cardiovascular disease, nerve damage, renal disease, and eye disease including retinopathy [1].

The two major subdivisions of diabetes mellitus have several distinguishing characteristics. T1DM results from an auto-immune attack of the insulin-producing pancreatic islet cells, typically during childhood. The onset of T1DM can be dramatic with diabetic ketoacidosis but can be more insidious, characterized by poor growth. T1DM requires insulin injections as the fulcrum of

* **Corresponding Author Andrew M. Hendrick:** Department of Ophthalmology, Emory University, Atlanta GA, USA; E-mail: ahendrick@emory.edu

Douglas R. Lazzaro and Samy I. McFarlane (Eds.)

therapy to normalize blood sugar levels and are required for survival. In contrast, T2DM results from dysfunction of insulin response, such that circulating glucose levels remain elevated [2]. It is often unclear when T2DM onset begins and symptoms can be poorly recognized for years in some cases. Although previous nomenclature described T2DM as adult-onset, children are increasingly affected [3]. Therapies are directed at lifestyle improvement, weight and dietary management, along with medicines taken both orally and injectable insulin [2].

Our world is in the midst of a diabetes mellitus epidemic with rising rates of people affected across the globe. Factors driving the increase include population aging, economic development, increased urbanization, sedentary lifestyle, and increased consumption of unhealthy foods [2]. Diabetes is a major driver of healthcare costs, morbidity and mortality worldwide [2]. The risk of developing complications is tied directly to the adequacy of medical management. Managing the disease and associated health-related consequences, such as blinding complications of retinopathy, is becoming increasingly important as all societies struggle with this burden. This chapter will discuss the epidemiology of diabetes mellitus, with a focus on diabetic retinopathy (DR) and the implications for vision loss.

Epidemiology of Diabetes Mellitus

T1DM accounts for nearly 10% of DM cases and the incidence has slightly increased over time, with considerable variation by region and sampling technique [3]. Data from US based studies indicate the incidence of T1DM increased from 14.8/100,000 (95% CI 14.0 – 15.6) from 1978-1988 to 23.9/100,000 (95% CI 22.2-25.6) from 2002-2004 and was noted to increase in both Hispanic and non-Hispanic youth [4]. The prevalence of T1DM for adults in the US is estimated to be 0.55% (95% CI 0.46-0.66) [5].

90% of all people with DM have T2DM, also known as adult-onset diabetes. As a result, global estimates of diabetes are predominantly reflective of change due to T2DM. T2DM is increasingly more common - likely due to the strong association with obesity, population aging, inactive lifestyle and poor dietary habits [6]. Fig. (**1**) demonstrates a graphical estimate of worldwide numbers of people with diabetes over since 2000. These estimates represent a compilation of best-available data sources, but high-quality data are not universally available. In 2015, the International Diabetes Federation estimated that the worldwide burden of diabetes mellitus (DM) affected 415 million people and would increase to 642 million globally by the year 2040 [2]. Current estimates demonstrate a global prevalence of ~9% of all adults with only half of individuals being formally diagnosed with DM [2]. The International Diabetes Federation predicts that low-

and middle-income countries will be disproportionately affected by this epidemic and are expected to have the greatest increase in prevalence [2]. This is critical because of the magnitude of impact: Approximately 75% of all individuals with T2DM live in low- and middle-income countries [2].

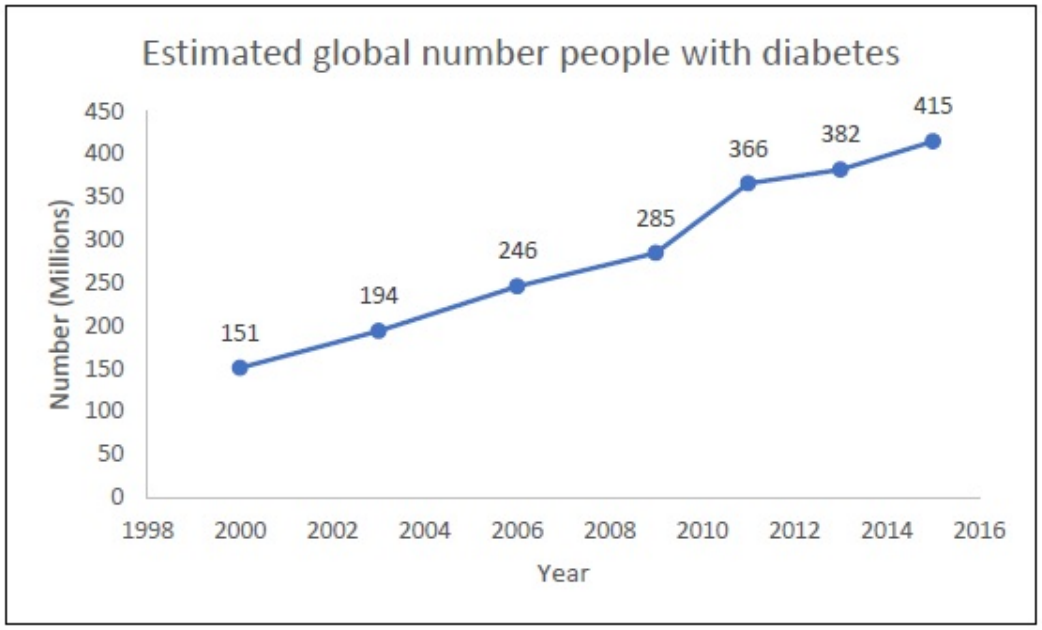


Fig. (1). Estimated number of people with diabetes over time worldwide (in millions) [2].

The fallout from chronic hyperglycemia on the human body is accumulative over time. Morbidity and disability that arises from serious complications of diabetes include cardiovascular disease, kidney disease, neuropathy, limb amputation, and retinopathy. These complications, in turn, lead to an increased demand for medical care, reduce the quality of life, and place stress on families including financial burden. Altogether, diabetes-related care incurs an estimated $673 billion (12%) of global healthcare expenditure and 8% of all-cause mortality [7]. The presence of T2DM increases the risk of heart attack comparable to the risk attributable to having had a prior heart attack [8]. Actual risk varies by study, but the prevalence of coronary heart disease in T2DM is around 21% (ranges between 12-32%) [8]. Similarly, stroke risk is also increased nearly three-fold in people with diabetes compared to those without [8]. Interestingly, the presence of diabetic retinopathy serves as an independent risk factor predicting a higher likelihood of systemic comorbidities such as both stroke and heart disease [9 - 11]. Furthermore, T2DM is a leading cause of renal failure and lower limb amputation [12, 13]. It is estimated that T2DM accounts for estimated up to 21-

CHAPTER 2

Recent Developments in Diabetes Evaluation and Management: Implications for the Practicing Clinicians

Anna Y. Groysman, Lina Soni, Samara Skwiersky and **Samy I. McFarlane**[*]

Department of Medicine, Division of Endocrinology, State University of New York, Downstate-Medical Center, Brooklyn, NY, USA

Abstract: Diabetes is a major public health problem affecting millions of people around the globe. In the United States alone, over 7.5 million have type 2 diabetes and an alarming 78 million adults have prediabetes and remain largely undiagnosed. This epidemic was ushered in by the ongoing epidemic of obesity and is caused in-part by sedentary life style and aging population. In this chapter we discuss the diabetes epidemic highlighting the major risk factor of diabetes, particularly type 2. We also discuss the complications of diabetes including microvascular complications as well as macrovascular disease including coronary heart disease and stroke, the major cause of morbidity and mortality in the diabetic population. Finally, we present the major therapeutic advances in diabetes including modern pharmacologic agents and their potential effects on cardiovascular risk. We also outline the recent technological advances in diabetes management including closed loop systems, artificial pancreas, stem cell therapy among other ongoing research bound to prevent and/or alleviate the effects of this ongoing epidemic.

Keywords: Complications, Diabetes, Glucose monitoring technology, Modern therapy, Risk factors.

INTRODUCTION

Diabetes mellitus is a progressively debilitating condition resulting in vascular complications, including cardiovascular, cerebrovascular, and peripheral vascular disease. This disease, together with microvascular diseases, including retinopathy, nephropathy, and peripheral neuropathy, lead to devastating complications and increased mortality. Although adults are generally afflicted with this condition, rising numbers of children, teenagers, and adolescents are also affected [1].

[*] **Corresponding Author Samy I. McFarlane:** Department of Medicine, Division of Endocrinology, State University of New York, Downstate-Medical Center, Brooklyn, NY, USA; Tel: 718-270- 3711; Fax: 718-270- 6358; E-mail: smcfarlane@downstate.edu

Driven mainly by a continuous rise in type 2 diabetes, the global epidemic of diabetes, according to data from the World Health Organization, reached over 422 million adults worldwide in 2014, exceeding the previous forecast of 439 million worldwide by 2030 [2].

Diabetes does not affect the population homogeneously and significant disparities exist that are worth noting. Diabetes disproportionally affects racial and ethnic minority groups. African Americans (13.2%), American Indians/Alaska Natives (15.9%), Asian Americans and Pacific Islanders (9.0%), and Latinos (12.8%) are about twice as likely to have been diagnosed with diabetes as non-Hispanic, white (7.6%) adults [6]. Diabetes has also been shown to disproportionally affect people living in rural *versus* urban areas. Individual factors, such as health literacy, communication barriers, and cultural differences, have been associated with diabetes disparities [7]

The observed disparities have been explained by numerous analyses. A fully adjusted study found that both the prevalence of diabetes and the likelihood of forgoing medical care among people diagnosed with diabetes were higher for those with lower incomes, racial/ethnic minority groups, lower incomes, and living in the South of the U.S [8]. Additionally, "food insecurity" is the inability to regularly obtain nutritious food without resorting to socially unusual practices. Unfortunately, one in seven people in America is "food insecure". This rate is higher among racial/ethnic minorities and in low-income households. The reason being that people are faced with the difficult choice of buying nutritious but more expensive food *versus* less expensive, high calorie, and low nutrient containing foods [9].

Many resources have been focused on developing modalities to achieve euglycemia in patients and to reduce the prevalence of macro-and microvascular complications. Unfortunately, the primary cause of mortality in patients with diabetes is cardiovascular disease. Within the next thirty years, the number of people living with diabetes is predicted to double and with it, the prevalence of incapacitating complications [3]. The incidence of diabetes increases with age and as the number of older adults in the United States is growing, so is the prevalence of the disease. The advent of insulin therapy has prolonged the lives of patients with type 1 diabetes (T1D), but every year of life comes with an increased risk of complications. As the prevalence of obesity rises in the United States, T2D occurs at an earlier age. This is because overweight and obese people tend to have an earlier onset of insulin resistance. Such factors are increasing the number of people who need medical care and require interventions to prevent the complications or progression of diabetes complications [4].

The risk of diabetes is increased with non-modifiable factors, such as age, a positive family history, and genetics. However, the list of modifiable risk factors is much longer. Overweight and obesity is rampant in the United States and is the leading cause of diabetes onset. Lack of physical exercise and poor dietary choices or options are significant contributors [2]. Less well-known risk factors include vitamin deficiencies and compositions of gut bacteria [5], which are now being identified and will be further discussed in this chapter.

This chapter aims to elucidate what is known about diabetes, as well as where we are headed. The novel risk factors of diabetes will be explained as well as the pervasive complications. The focus of the chapter will be a discussion of the many medical and technological treatment approaches that have been developed to improve glycemic control or hold a promise to finding a cure. Finally, evidence of diabetes prevention will be discussed as it is as vital as disease treatment in managing this pandemic.

RISK FACTORS OF DIABETES MELLITUS

Non-modifiable Risk Factors (Table 1)

Genetics

The pathophysiology of T2DM has not yet been fully delineated; however, studies find that there is a significant genetic component. This is supported by a high concordance rate in monozygotic twins (96%) to develop T2D. Even 40% of first degree relatives of T2D patients develop diabetes as compared to only 6% observed in the general population [10].

Susceptibility Loci

Since 2007, Genome-Wide Association Studies have identified linkage signals at the same or different chromosomes with T2DM. Seventy-five susceptibility loci that are related to T2DM have been identified. For example, IGF2BP2 is involved in pancreas development and stimulation of insulin action. Unsorted loci for T2DM pathogenesis still remain but may serve to be useful in understanding the condition to eventually find a cure [11, 12].

Modifiable Risk Factors (Table 1)

Lifestyle

Numerous environmental and lifestyle factors have been found to contribute to the development of T2DM. Obesity, which may contribute to the development of

CHAPTER 3

Blurred Vision in the Diabetic Patient – Reversible and Non-reversible Causes – General Classification of Diabetic Eye Disease

Rony Gelman*

Department of Ophthalmology, State University of New York, Downstate Medical Center, NY, USA

Abstract: In this chapter, we review the established classification system of diabetic retinopathy and diabetic macular edema. Reversible and non-reversible causes of vision loss in diabetic patients are discussed with illustrative clinical examples.

Keywords: Diabetic retinopathy, Epiretinal membrane, Macular edema, Macular ischemia, Neovascular glaucoma, Tractional retinal detachment, Vitreomacular traction.

INTRODUCTION

Diabetic eye disease may be characterized by the location of involvement within the eye, specifically the anterior or posterior segment. Anterior segment changes may involve the cornea, aqueous fluid drainage angle, or the natural crystalline lens, resulting in poor corneal epithelial wound healing, neovascular glaucoma (NVG), or cataract formation, respectively.

Certain causes of vision loss due to anterior segment changes may be reversible, assuming no concomitant irreversible posterior segment damage. Cataract secondary to diabetes mellitus (DM), for example, maybe successfully treated with surgery. On the other hand, certain anterior segment changes may result in irreversible vision loss. NVG, for example, is due to occlusion of the trabecular meshwork from angle neovascularization and may lead to irreversible optic neuropathy and vision loss despite treatment with glaucoma filtration surgery [1].

Diabetic eye disease involving the anterior segment is fully discussed in chapters 5 (“Diabetes and the Cornea”) and 6 (“Diabetes, Cataract, and Glaucoma”). In this

* **Corresponding author Rony Gelman:** Department of Ophthalmology, State University of New York, Downstate Medical Center, NY, USA; E-mail: rony.gelman@downstate.edu

chapter, we review the classification system of diabetic retinopathy and focus on reversible and non-reversible causes of vision loss secondary to involvement of the posterior segment.

CLASSIFICATION SYSTEM

Diabetic eye disease involving the posterior segment may be classified based on structural changes observed on clinical examination, fluorescein angiography, and optical coherence tomography (OCT). A well-established classification system divides diabetic retinopathy into non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR) [2].

NPDR is characterized by vascular changes confined to the intraretinal space: microaneurysms, dilation of retinal venules, intraretinal hemorrhages, and cotton-wool spots, which are vascular infarctions at the level of the retinal nerve fiber layer. A severity scale subdivides NPDR into mild, moderate, and severe forms. Mild NPDR includes microaneurysms only, while moderate NPDR is characterized by more than solely microaneurysms but less severe changes than seen in severe NPDR. Severe NPDR is classically described as following the "4-2-1" rule, where presence of any of the following indicates severe NPDR: severe intraretinal hemorrhages and microaneurysms in each of the four quadrants of the retina, beading of the retinal venous blood vessels in two or more quadrants, or a prominent intraretinal microvascular abnormality (IRMA) in one or more quadrant. If two or more characteristics of severe NPDR are present, then it is characterized as very severe NPDR.

Progression of diabetic retinopathy from NPDR leads to PDR. Neovascularization is the hallmark of PDR and may occur at the optic disc (neovascularization of the disc [NVD]) or elsewhere on the retinal surface (neovascularization elsewhere [NVE]). A severity scale subdivides PDR into an early non-high risk and a high-risk form. Early PDR is defined by the presence of neovascularization that does not meet high-risk PDR criteria.

Criteria for high-risk PDR include any of the following: neovascularization on or within one disc diameter of the optic disc measuring about one-quarter to one-third of the disc area with preretinal or vitreous hemorrhage, any NVD with preretinal or vitreous hemorrhage, or NVE at least one-quarter of disc area with preretinal or vitreous hemorrhage.

Lastly, diabetic retinopathy at any stage may lead to increased vascular permeability, resulting in retinal edema and intra-retinal deposition of lipids in the form of hard exudates (HE). A classification system of diabetic macular edema (DME) based on the location of edema and HE deposits subdivides macular

edema into clinically significant macular edema (CSME) and non-CSME [2]. CSME is defined as presence of any of the following detected by biomicroscopic examination or stereoscopic fundus photography: thickening of the retina within 500 microns of the macular center, deposition of HE at or within 500 microns of the macular center with associated thickening of the adjacent retina, or retinal thickening measuring at least one disc area in size that is at least partly within one disc diameter of the macular center.

Spectral-domain OCT (SD-OCT) is a novel imaging modality that has supplemented clinical examination for the detection and monitoring of macular edema [3]. The use of OCT to study diabetic eye disease is fully discussed in chapter 7 ("OCT and fluorescein findings in the diabetic patient"). OCT enables the accurate detection of and quantitative measurements of center-involving DME (ci-DME) and its progression, which has been critical in anti-VEGF treatment strategies, established by several pivotal randomized clinical trials [4 - 6]. These are discussed further in chapters 8 and 10.

REVERSIBLE AND NON-REVERSIBLE CAUSES OF VISION LOSS IN DIABETIC RETINOPATHY

Reversible posterior segment causes of vision loss include DME, non-clearing vitreous hemorrhage (NCVH), vitreomacular traction (VMT) and epiretinal membrane (ERM), and tractional retinal detachment (TRD) without macular detachment. Non-reversible causes of vision loss include chronic DME, DME complicated by subfoveal HE or fibrosis, advanced TRD with the detachment of the macula, TRD complicated by rhegmatogenous retinal detachment (RRD), macular ischemia, and NVG. We discuss these etiologies with illustrative examples in the sections to follow.

Diabetic Macular Edema

DME is a spectrum of disease and clinically may present in mild, moderate or severe forms [2]. OCT enables precise quantitative metrics to assess the degree of DME.

Mild DME may present as mild thickening or cystic changes that maybe only appreciated by OCT with minimal to no effect on vision. Fig. (**1**) shows a patient with mild cystic changes on OCT and no visual complaints with 20/30 vision. Mild DME in such cases may cause minimal to no vision loss and may resolve after improvement of glycemic control.

CHAPTER 4

Diabetes and Ocular Infections

Jennifer Lopez and **Allison E. Rizzuti***

Medical Center, NYU Langone, NY, United States

Abstract: This chapter will review some of the infections that can be seen in and around the eye in diabetic patients. Specifically, six cases of infection will be highlighted and discussed.

Keywords: Cerebral, Cellulitis, Cornea, Endophthalmitis, Infection, Mucor, Preseptal, Ulcer, Vitritis.

INTRODUCTION

Infection is a well-known complication of diabetes, and most commonly involves the skin, lower respiratory tract and genitourinary tract. Patients with diabetes are also prone to ocular infection, and studies have found that diabetics are at an increased risk of conjunctivitis [1, 2] However, there is limited research examining the association between diabetes and other ocular infections, such as keratitis, endophthalmitis and orbital cellulitis. It is well established that diabetics are particularly susceptible to infections involving staphylococcus, pneumococcus, mycobacteria and candida; organisms which can cause devastating consequences in the eye. Not only can these infections be vision threatening, but because of the eye's close proximity to the cavernous sinus and brain, they can be life threatening as well. In this chapter, we will examine the topic of ocular infection in diabetes with a series of case reports.

RHINO-ORBITAL-CEREBRAL MUCORMYCOSIS

Case 1

A 27-year-old man with a history of poorly controlled diabetes presented with 5 days of left eyelid swelling and vision loss. He had a mildly elevated temperature at 38.4°C, but otherwise stable vital signs. His physical examination on presentation was remarkable for eyelid edema resulting in the inability to open his

* **Corresponding author Allison Rizzuti:** Medical Center, NYU Langone, NY, United States;
E-mail: Allison.Rizzuti@nyumc.org

Douglas R. Lazzaro and Samy I. McFarlane (Eds.)

left eye and loss of his left light pupillary reflex. His labs were significant for a white blood cell count of 21,100 cells/μL with a left shift and decreased hemoglobin of 10.9g/dL. He had a blood glucose level of 22.4mmol/L and hemoglobin A1c of 15.7%. The patient was admitted to the hospital with diabetic ketoacidosis and treated with intravenous insulin and fluids. One day after the presentation, his eyelid and facial edema worsened, his left eye became ophthalmoplegic and his left pupil was noted to be mid-dilated. Funduscopic examination revealed a pale optic disc, a cherry-red spot in his macula, and narrow retinal arteries consistent with a retinal artery occlusion (Fig. **1**). He was also noted to have areas of necrosis and purulent discharge within his nasal cavity which rapidly destroyed his nasal architecture. Cultures from the purulent discharge revealed mucormycosis and he was treated with intravenous amphotericin B.

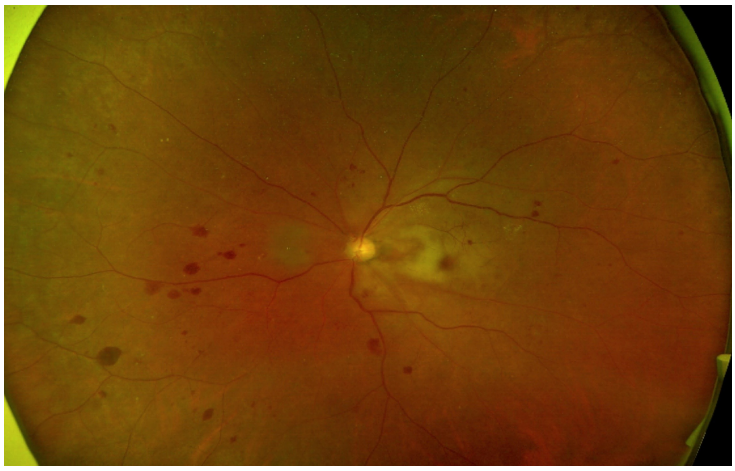


Fig. (1). Left fundus showing a pale optic disc and cherry-red spot on macula consistent with retinal artery occlusion.

Diabetic patients are at an increased risk of developing rhino-orbito-cerebral mucormycosis, an infection caused by a fungal pathogen that causes rapid tissue necrosis. Patients with uncontrolled hyperglycemia are most susceptible, particularly patients with diabetic ketoacidosis due to the resulting acidosis which creates a favorable environment for the growth of *Rhizopus* [4]. The infection occurs after the inhalation of spores into the paranasal sinuses and the orbit may become involved when the infection spreads laterally. Irreversible vision loss can occur due to the compressive effect on the optic nerve and the central retinal artery. If not treated promptly, the infection can spread to the brain *via* the cavernous sinus and can ultimately result in death. Patients typically present with signs and symptoms of orbital cellulitis and so the suspicion of mucormycosis

must be high in order to institute the appropriate management. Mucormycosis is initially treated with surgical debridement and intravenous amphotericin B as well as treating the underlying predisposing factor such as hyperglycemia.

PRE-SEPTAL & ORBITAL CELLULITIS

Case 2

A 58-year-old male with uncontrolled diabetes presented with one week of redness and swelling of the left eye (Fig. **2**). Physical examination of his left eye was significant for periorbital edema and erythema with a round and reactive pupil and full extraocular muscle movements. On presentation, his best corrected visual acuity was 20/30 in the left eye. Slit lamp examination of his left eye was significant for 1+ injection with decreased tear film and superficial punctate epithelial erosions. His glucose on admission was 210mg/dL and labs revealed a hemoglobin A1C of 11.9%. He received intravenous Vancomycin and Unasyn that was transitioned to oral Augmentin along with erythromycin ointment. Cultures eventually grew *streptococcus anginosus.* At the time of discharge, his visual acuity improved to 20/20 -1 bilaterally.

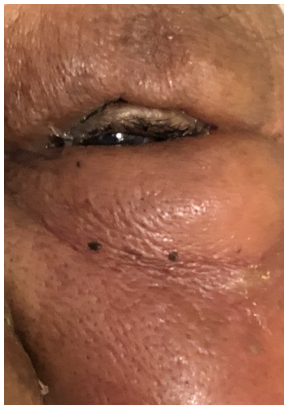


Fig. (2). Pre-septal cellulitis.

Case 3

A 46 year old man with no known past medical history presented with pain and swelling of his right eye for three days. On presentation, he was found to be febrile with an exam remarkable for right periorbital erythema, edema and discharge. Physical examination of his right eye revealed decreased visual acuity, chemosis, and evidence of severe non-proliferative diabetic retinopathy. He was diagnosed with Type 2 Diabetes after his labs revealed a glucose level of 277mg/dL and a hemoglobinA1c of 9.8%. CT scan of the orbit showed post septal

CHAPTER 5

Neuro-Ophthalmic Complications of Diabetes Mellitus

Julie DeBacker[1,*] and **Alessandro Albano**[2]

[1] *NYU School of Medicine, NYU Langone Health, NY, USA*

[2] *SUNY Downstate College of Medicine, Brooklyn, NY, USA*

Abstract: Eye disease attributed to Diabetes can have devastating effects on all aspects of vision as all parts of the eyes are subject to damage including the optic nerve and cranial nerves. In this chapter, we will discuss the most common neuro-ophthalmic problems seen in diabetic patients.

Keywords: Cataract, Cranial Nerve, Diplopia, Neuro-Ophthalmology, Neuropathy, Optic, Pupil.

INTRODUCTION

DIABETES AND NEURO-OPHTHALMOLOGIC COMPLICATIONS

Cranial Nerve Palsies in Diabetes

Double vision greatly limits a person's daily activities, and diabetes mellitus is one of the known culprits affecting cranial nerves innervating eye muscles leading to symptomatic ocular misalignment and thus binocular diplopia. Nerves are damaged by microvascular injury of small blood vessels that supply nerves, a common serious complication of diabetes. Endothelial cells lining blood vessels are not insulin-dependent and therefore take in greater than normal amounts of glucose when glucose levels are high in diabetes. The excess glucose causes abnormal thickening and weakening of the blood vessel basement membranes, leading to bleeding and slowing of blood flow. This poor blood flow to nerves and neurons causes neuronal ischemia, leading to loss of function [1].

Diabetes most commonly affects the third cranial nerve (III) followed by the sixth cranial nerve (VI), which control eye muscles affecting ocular movements. Crani-

[*] **Corresponding author Julie DeBacker:** NYU School of Medicine, NYU Langone Health, NY, USA; E-mail: julie.debacker@nyumc.org

al nerve four (IV), also involved in eye movement, is much less commonly affected. Isolated palsies of CN III and CN VI secondary to diabetes occur significantly more frequently than palsies of multiple nerves at the same time [2]. And, the nerve palsies typically occur unilaterally. Ischemic injury of two nerves simultaneously is very rare, and bilateral ischemic injury of the same ocular motor nerve is even rarer [3]. Multiple cranial nerve involvement and/or bilateral cranial nerve involvement warrants further workup for an alternative cause.

The oculomotor nerve (CN III) innervates the medial rectus which adducts the eye, the superior rectus which elevates the eye while in the abducted position, the inferior oblique which elevates the eye while in the adducted position, and the inferior rectus which depresses the eye. It also innervates the levator palpebrae superioris muscle, which elevates the superior eyelid. CN III also carries parasympathetic nerve fibers to the ciliary body for accommodation and to the pupillary constrictor muscle to constrict the pupil [3]. The abducens nerve (CN VI) controls only the lateral rectus muscle, which abducts the eye [4]. Both cranial nerve palsies may cause significant binocular diplopia, and again, this can be quite debilitating and have negative impacts on the lives of affected patients. Diabetic cranial nerve palsies are significantly linked to poor glycemic control and are shown to recover with the improvement of hyperglycemia [4, 5]. Three patient cases are presented here to discuss common clinical presentations of oculomotor and abducens nerve palsies caused by diabetes along with a treatment option to shorten the recovery time from an abducens nerve palsy.

Case 1: Diabetic Patient Presents with an Oculomotor Nerve Palsy

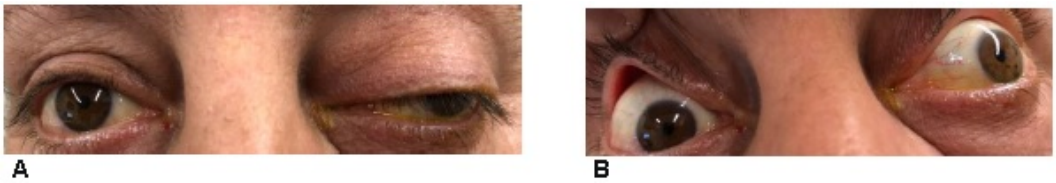


Fig. (1). Patient showing exotropic strabismus with a downward and outward position of the left eye (A and B) with left ptosis (A).

A 65-year-old male patient of the NYU Medical Center's Department of Ophthalmology with a past medical history of diabetes mellitus type 2 presented with a left partial pupil-sparing CN III palsy with which progressed to include ptosis within one week. The patient displayed limitations of left adduction, elevation and depression of the eye, and left ptosis (Figs. **1**, **2**, and **3**).

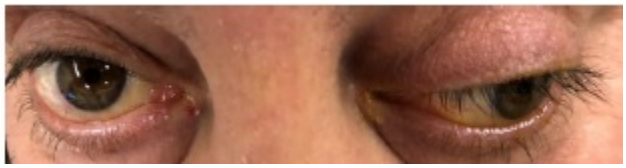


Fig. (2). Patient showing limited adduction and elevation of the left eye.

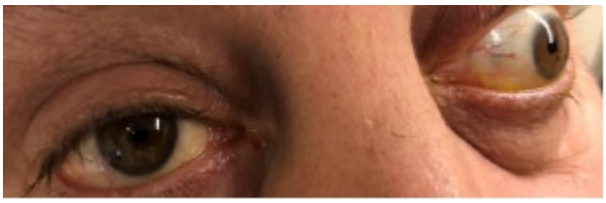


Fig. (3). Patient showing limited elevation of the left eyelid.

In diabetes, a CN III palsy is pupil-sparing, whereas a complete, isolated oculomotor nerve palsy results in ophthalmoplegia, ptosis, and mydriasis. The oculomotor nerve has a branched structure, with the parasympathetic fibers controlling pupil constriction running superficial to the nerve [5]. Partial oculomotor nerve palsies may have varied presentations based on the muscles affected downstream of the nerve damage. Typically, the eye movement abnormalities cause exotropic strabismus (diverging crossed eyes) leading to binocular diplopia. The affected eye will be displaced inferiorly and laterally ("down and out"). An isolated CN III palsy leaves the action of the other two cranial nerves, CN IV and VI, unopposed: The lateral rectus pulls the eye laterally without opposition from the medial rectus, and the superior oblique muscle (innervated by CN IV—the trochlear nerve) pushes the eye downward without opposition from the superior rectus and inferior oblique muscles. With control of a diabetic patient's hyperglycemia, the oculomotor nerve function is expected to return with symptoms self-resolving over three to six months but may take up to or over one year.

Less common but more serious causes of oculomotor nerve palsies should always be considered and ruled out with neuroimaging, especially compression of CN III by an aneurysm of the posterior communicating artery or the posterior cerebral artery in the brain.[7] Of note, oculomotor nerve palsy due to compression by an aneurysmal lesion typically presents with pupil dilation, which is a distinguishing feature from oculomotor nerve palsy caused by diabetes [6].

Cases 2 and 3: Botulinum Toxin A as a Treatment of Diplopia from Diabetic Abducens Nerve Palsy

A 52-year-old female patient with a 15-year history of diabetes mellitus type 2

CHAPTER 6

Overview of Anterior and Posterior Segment Complications

Steven Agemy[1], Zaki Azam[2] and **Eric Shrier[2,*]**

[1] *New York Eye and Ear Infirmary of Mount Sinai, NY, USA*

[2] *SUNY- Downstate College of Medicine, Brooklyn, NY, USA*

Abstract: Diabetic eye disease is a potential vision-threatening condition. The most well-known complication of uncontrolled diabetes is diabetic retinopathy, but diabetes can affect various structures of the globe other than the retina. Anterior segment complications include ocular surface disease, which includes Dry Eye Syndrome and diabetic keratopathy, cataracts, refractive changes, extraocular movement disorders, and neovascular glaucoma. Posterior segment complications include diabetic papillopathy and retinopathy. Diabetic retinopathy causes vision loss in multiple ways including macular edema and ischemia, vitreous hemorrhage, and retinal detachment. Tight glucose control can help to prevent these complications from occurring.

Keywords: Cataract, Dry Eye Syndrome, Diabetic keratopathy, Diabetic papillopathy, Diabetic retinopathy, Diabetic macular edema, Non-proliferative diabetic retinopathy, Neovascular glaucoma, Ocular surface disease, Proliferative diabetic retinopathy, Tractional retinal detachment.

INTRODUCTION

Diabetic eye disease is becoming an increasing problem, in part due to longer life expectancy and the change in diet and exercise habits in developed countries [1, 2]. The most well known ocular complication, diabetic retinopathy, is one of the leading causes of blindness worldwide [3]. In the eye, manifestations are found in almost every segment including the orbit and lids and the anterior and posterior segments of the globe [4]. As these complications can lead to permanent vision loss, it is imperative that they are promptly identified so that proper treatment can be initiated. The onset of these complications can vary depending on how well the blood glucose is controlled and the time since the development of diabetes. The following chapter will give a general overview of the diabetic ocular complications associated with the anterior and posterior segment of the globe.

* **Corresponding author Eric M. Shrier:** DO - State University of New York - SUNY - Downstate College of Medicine, NY, 11203, USA; E-mail: eric.shrier@downstate.edu

Anterior Segment Complications

Ocular Surface Diseases

Ocular Surface Diseases (OSD) can damage the interpalpebral ocular surface, including the conjunctiva and cornea. Mechanisms related to diabetic OSD include decreased tear production, reduced corneal sensitivity, and impaired corneal re-epithelialization [5 - 7]. This process can lead to signs and symptoms of damage to ocular surface structures, including noticeable irritation from corneal epitheliopathy, decline of visual function, and even chronic tissue disruption. Dry eye syndrome (DES) and diabetic keratopathy are two forms of OSD for which diabetes is a risk factor [8].

Dry Eye Syndrome (DES)

DM is a known risk factor for DES. The prevalence of DES in diabetes has been reported to be as high as 54.3% [9]. That number increases with aging and is 50% more common among women than men. The incidence has a positive correlation with the level of glycated hemoglobin [8]. 20% of dry eye syndrome may occur in individuals with Type 2 diabetes aged between 43 and 86 years [10]. Additionally, there is a significant correlation between DES and the duration of diabetes [8].

The connection between diabetes mellitus and dry eye syndrome is complex and multifactorial. Sustained hyperglycemia triggers an inflammatory cascade leading to corneal epithelial dysfunction, lacrimal gland dysfunction, decreased mucin production, and diabetic keratopathy. These issues lead to decreased tear formation and tear film instability causing the dry eye syndrome [11 - 14].

Diabetic patients with dry eye syndrome typically have the same symptoms as non-diabetics with DES. The common presenting symptoms include foreign body sensation, burning, itching, excessive tearing, discharge, redness, light-sensitivity, and intermittent blurring of vision [15]. On slit lamp examination, various stains can be used to visualize damaged or absent conjunctival/corneal epithelium. In more severe cases, slit lamp examination may identify corneal filaments, neovascularization, and scarring [16]. Additional diagnostic testing includes tear break up time (TBUT), Schirmer's test, matrix metalloproteinase-9 (MMP-9) testing, tear osmolarity, and tear film interferometry [17].

The early diagnosis and treatment of dry eye are pivotal to prevent complications. Other than strict glycemic control, the current treatments for diabetic and non-diabetic dry eye patients are largely the same. The mainstay of mild to moderate disease is supplemental lubrication using artificial tears and longer-acting agents

such as artificial tear ointments. Tear conserving interventions such as punctual plugs are also helpful. Concomitant lid disease must also be treated using warm compresses and eyelash scrubs. For more severe disease, prescribing anti-inflammatory agents such as cyclosporine and lifitegrast may enhance the production of the aqueous component of the tear layer and decrease inflammatory mediators [18 - 20]. Diet supplementation with oral flaxseed oil or fish oil has also been found to be useful in alleviating symptoms [21, 22].

Diabetic Keratopathy

Keratopathy is a well-known ocular manifestation of DM, presenting in more than 70% of the DM patients [23]. Abnormalities of the corneal epithelium and diminished corneal sensitivity increase the risk of developing corneal erosions, persistent epithelial defects, and/or corneal ulcers [23, 24]. Not only do diabetics have a higher incidence of these conditions, but they also tend to have more severe disease that may recur and be unresponsive to standard treatment options [25, 26].

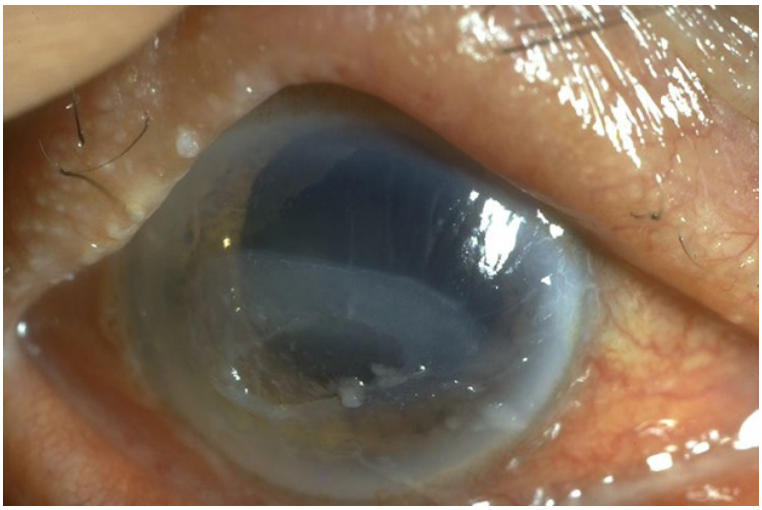


Fig. (1). Neurotrophic ulcer in a poorly controlled diabetic patient. An epithelial defect is noted centrally with surrounding whitening indicating stromal infiltrate. © 2017 American Academy of Ophthalmology.

Similar to dry eye syndrome in diabetics, the cause of diabetic keratopathy is multifactorial. The corneas of patients with diabetic keratopathy show pathologic changes including abnormally thickened basement membranes, abnormal adhesion between the stroma and basement membrane, and a reduction in hemidesmosomes, contributing to weak adhesions between the epithelium and underlying stroma [27 - 29]. In addition to structural changes, the loss of corneal sensation leads to numerous problems including delayed epithelial healing,

CHAPTER 7

Diabetes and the Cornea

Lucy Sun[1] and **Douglas R. Lazzaro**[2,*]

[1] *SUNY Downstate Medical Center, NY, USA*

[2] *Department of Ophthalmology, NYU Langone Health, NY, USA*

Abstract: Diabetes affects the eye in many ways. We most commonly think of posterior segment complications as the main problem causing loss of vision in diabetes which is certainly the most common way people suffer ocular damage. However, the anterior segment is not immune to diabetic complications, and the cornea can be affected in a variety of ways. The manifestations of the corneal disease will be discussed in detail in this chapter.

Keywords: Cornea, Cataract, Epithelial, Infection, Keratitis, Postoperative, Refractive, Ulcer.

The adult cornea is located in the outermost layer of the eye and functions to protect the eye from damage while also focusing on the entry of light. It contributes to approximately two-thirds of the eye's total focusing power, and is the most sensitive tissue of the body with the highest density of pain receptors. Therefore, damage to the cornea can lead to loss of vision, altered corneal sensation, and increased risk of infection. Structurally, the cornea is composed of 5 tissue layers organized into a transparent tissue containing immature resident immune cells and sensory nerve fibers. The 5 layers, from anterior to posterior are: corneal epithelium, bowman's layer, corneal stroma, Descemet's membrane, and corneal endothelium (Fig. **1**).

The cornea topography can be easily imaged by various methods and helps to determine normal *versus* abnormal layering of both anterior and posterior surfaces (Fig. **2**). Due to its transparent nature, the cornea is avascular and receives oxygen and nourishment *via* diffusion from the tear fluid of the outer surface, from the aqueous humor of the inner surface, and from the neurotrophins of the nerve fibers.

* **Corresponding author Douglas R. Lazzaro:** Department of Ophthalmology, NYU Langone Medical Center, USA; Email: Douglas.Lazzaro@nyulangone.org

Diabetes mellitus is a major systemic disease that can have marked effects and complications on all layers of the cornea. Corneal abnormalities as a result of diabetes have been termed diabetic keratopathy. This chapter reviews the pathophysiological, morphological, and clinical features of corneal changes secondary to diabetes.

CORNEAL EPITHELIUM

The corneal epithelium is an exceedingly active, self-renewing multicellular tissue layer composed of 5 to 7 layers of cells, with the outermost layer shedding constantly and the basal layer regenerating continuously to support the same thickness profile to maintain corneal power. It is extremely thin, measuring approximately 53um in thickness, with no statistically significant difference between the left and right eyes with respect to age, spherical equivalent refraction, or keratometry [1].

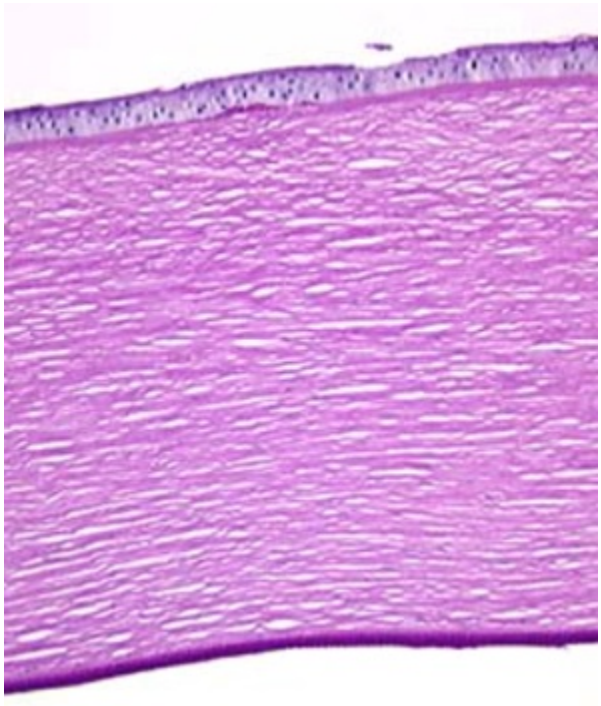


Fig. (1). -Cornea cross section-epithelium on top and endothelium on bottom.

Increase in Epithelial Thickness

In diabetic patients, an increase in central corneal epithelial thickness has been

observed and may be one of the earliest detectable clinical changes in the diabetic eye [2]. The average corneal basement membrane (BM) thickness in non-diabetic patients is 54um, compared to 57um in diabetic patients [3]. The thickening is uniform along the length of the epithelial BM in the central cornea. No clear association has been found between central corneal thickness and age or sex. Data regarding the correlation between central corneal thickness and the duration of diabetes are inconsistent. Busted *et al*. [2] found no correlation while Lee *et al*. [4] showed a significant correlation between central corneal thickness and diabetes duration of over or under 10 years. Although the occurrence of multilaminar BM was more common in the diabetic eye than in the non-diabetic eye, the odds ratio was not statistically significant. The multilamination of BM, however, correlated more closely with the presence of the BM thickness than with the presence or absence of diabetes [5].

Abnormal Basement Membrane Formation

The corneas of diabetic patients are exposed to elevated glucose concentrations, and through the mechanism of non-enzymatic glycation, advanced glycation end products (AGEs) form and accumulate in the BM of the corneal epithelium. More specifically, the N-carboxymethyl lysine protein (CML), which is located in the laminin of epithelial BM, is the main AGEs antigen target.

In a study by Kaji *et al*., age-matched diabetic and non-diabetic corneas were examined, and CML immunoreactivity was present in the epithelial BMs of most diabetic corneas, and absent in the corresponding areas of most non-diabetic corneas [6]. The presence of AGEs in the epithelial BM decreases adhesion and spread of the corneal epithelial cells. *In vitro* studies with glucose-6-phosphate (G-6-P) on glycation of laminin-coated matrix showed that glycation of laminin significantly diminished the number of attached corneal epithelial cells. When aminoguanidine, which inhibits CML formation with G-6-P, was added into the incubation mixture during glycation, both the number and the surface area of adherent corneal epithelial cells increased in a dose-dependent manner.

In addition to the presence of AGEs, another alteration that is specific to the diabetic cornea was the significant decrease in immunostaining of several major BM components and their binding epithelial integrins. The underlying mechanism is likely due to an increase in the degradation of these components by extracellular proteinases. Saghizadeh *et al*. studied various proteinases and noticed an increase in gene expression of matrix metalloproteinases (MMPs), which are a group of zinc enzymes responsible for degrading BM components [7]. This results in the weakening of the epithelial anchoring system, making the diabetic cornea more vulnerable to mechanical injuries and recurrent erosions.

CHAPTER 8

Diabetes, Cataract, and Glaucoma

Frank Cao and **John Danias***

SUNY Downstate College of Medicine, SUNY Downstate Medical Center, Brooklyn, NY, USA

Abstract: Diabetes Mellitus (DM) affects many parts of the eye. While we traditionally associate vision loss from DM with diabetic retinopathy, it can affect various structures of the eye other than the retina. In this chapter, we will focus on the disease's effects on the lens, and on the drainage apparatus of the eye. Specifically, we will look at cataract and glaucoma incidence in DM and its etiologic role, and then discuss treatment strategies.

Keywords: Cataract, Glaucoma, Glaucoma Implant, Intraocular pressure, Lens, Neovascular, Photocoagulation, Trabeculectomy, VEGF.

CATARACT

Anatomy

The crystalline lens occupies the space behind the iris anterior to the vitreous humor (Fig. **1**). It is formed in embryogenesis from surface ectoderm and serves to provide refractive power to help focus images on the retina, especially during accommodation. The lens sits within the capsular bag, which is held in place by zonules that attach to the ciliary body.

The crystalline lens is normally transparent. However, with age, or as a result of other causes, opacities to the lens often develop, which are collectively called cataracts. Anterior subcapsular cataracts are located just posterior to the anterior capsule, while posterior subcapsular cataracts are located anterior to the posterior capsule (Fig. **1**). The lens is anatomically categorized into an inner nucleus that occupies the center of the structure and is formed during embryogenesis, the surrounding cortex, and epi-nucleus that is the outermost layer. Nuclear sclerosis is defined by the opacification of the center(nucleus) of the lens (Fig. **2**), while cortical cataracts are characterized by the opacification of the cortical layer of the lens and may appear as spoking (Fig. **3**).

* **Corresponding author John Danias:** SUNY Downstate College of Medicine, SUNY Downstate Health Sciences University, Brooklyn, NY, USA; E-mail: John.Danias@downstate.edu

Douglas R. Lazzaro and Samy I. McFarlane (Eds.)

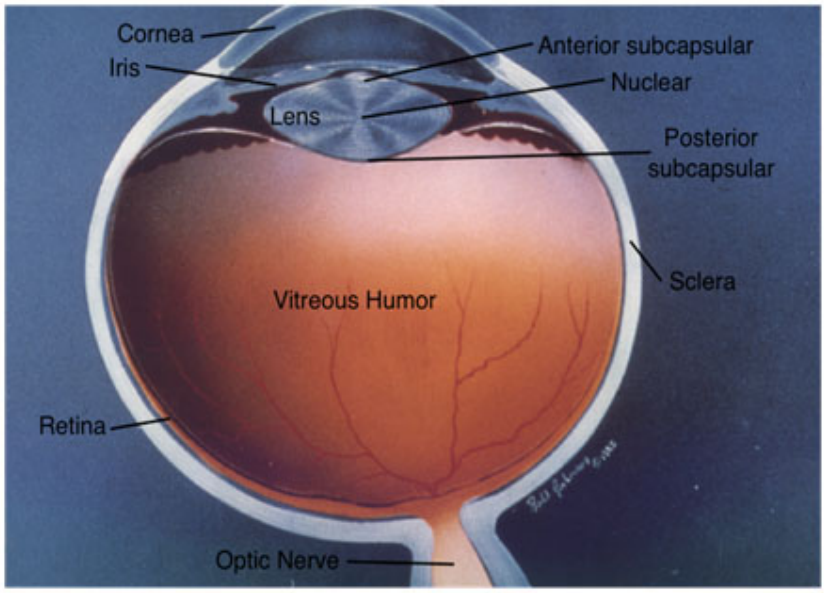


Fig. (1). Diagram of the eye and internal structures including lens. Based on "Normally Developing Eye". *National Eye Institute, National Institutes of Health*. https://www.flickr.com/photos/nationaleyeinstitute/7544655788/in/album-72157646829197286/. Accessed 4/10/2017.

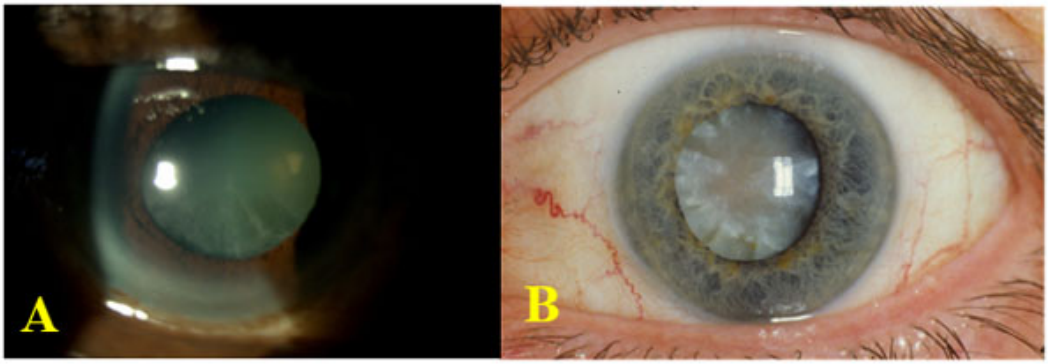


Fig. (2). Nuclear sclerotic cataracts. A. Moderate B. Severe. Image B is available at *National Eye Institute, National Institutes of Health*. https://www.flickr.com/photos/nationaleyeinstitute/7544344000/in/album-72157651546570359/. Accessed 6/8/2020.

Risk Factors

Cataract development is a multifactorial process that may involve ultraviolet light, smoking, medications, trauma, ocular inflammation, or a host of other factors. Cataracts have been shown to have associations with Diabetes Mellitus (DM). In individuals with diabetes, cataract develops at a younger age [1], and they have a 2-5 times higher risk of developing cataract than non-diabetic individuals [2, 3].

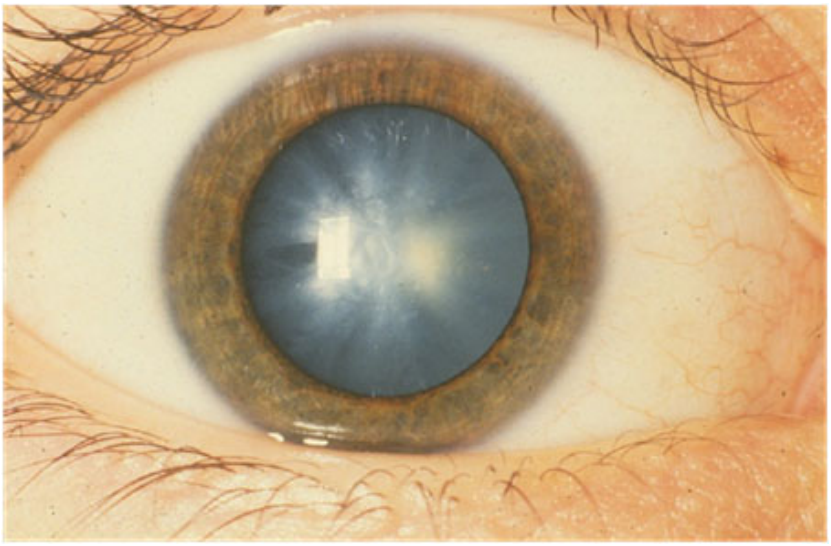


Fig. (3). Combined Cortical and Nuclear sclerotic cataract. Notice the "spoke" patterns of lens opacities. Image is available at *National Eye Institute, National Institutes of Health*. https://www.flickr.com/photos/ Accessed nationaleyeinstitute/7544344214/in/album-72157651546570359/_6/8/2020.

The most common form of cataract among diabetic patients is a mixed cataract with a combination of posterior subcapsular and cortical cataract [4]. Among the non-mixed types, cortical cataract is reported as the most common [4], followed by the nuclear type [5]. The term *snowflake cataract* is used to describe bilateral, acute, widespread subcapsular lens changes, typically seen in younger patients. These cataracts are characterized by many gray-white subcapsular opacities with a snowflake appearance beginning in the lens cortex.

Pathophysiology

There have been multiple proposed mechanisms for the increased cataract formation in patients with DM. These include increased osmotic stress from activation of the polyol sorbitol-aldolase reductase pathway, increased oxidative stress, and non-enzymatic glycation of lens proteins [6 - 15]. The polyol pathway normally converts excess blood glucose to sorbitol. Sorbitol accumulates inside the lens because it can not easily cross cell membranes. Accumulation of sorbitol in the crystalline lens creates an osmotic gradient that causes fluid to accumulate inside the lens. High sorbitol concentrations also cause collapse and liquefaction of the lens fibers, resulting in loss of transparency and development of cataract [16, 17]. The increased osmotic stress also causes apoptosis of lens epithelial cells which contributes to cataract formation [16, 17].

CHAPTER 9

Optical Coherence Tomography and Fluorescein Angiography in Diabetic Retinopathy

Sruthi Arepalli, Justis P. Ehlers and **Peter K. Kaiser***

The Cole Eye Institute, Cleveland Clinic, Cleveland, OH, USA

Abstract: The assessment and monitoring of diabetic retinopathy are aided by multiple imaging techniques, including optical coherence tomography, optical coherence tomography angiography, and fluorescein angiography. We will discuss each modality in this chapter.

Keywords: Fluorescein angiography (FA), Optical coherence tomography (OCT), Optical coherence angiography (OCTA).

OPTICAL COHERENCE TOMOGRAPHY

Optical coherence tomography (OCT) has become an indispensable imaging technique in diabetic retinopathy and choroidopathy. OCT offers cross-sectional, detailed images of retinal tissue with high resolution on the level of microns [1 - 3]. This accuracy allows for the monitoring of disease progression and analysis of various characteristics associated with diabetic retinopathy.

Diabetic Macular Edema

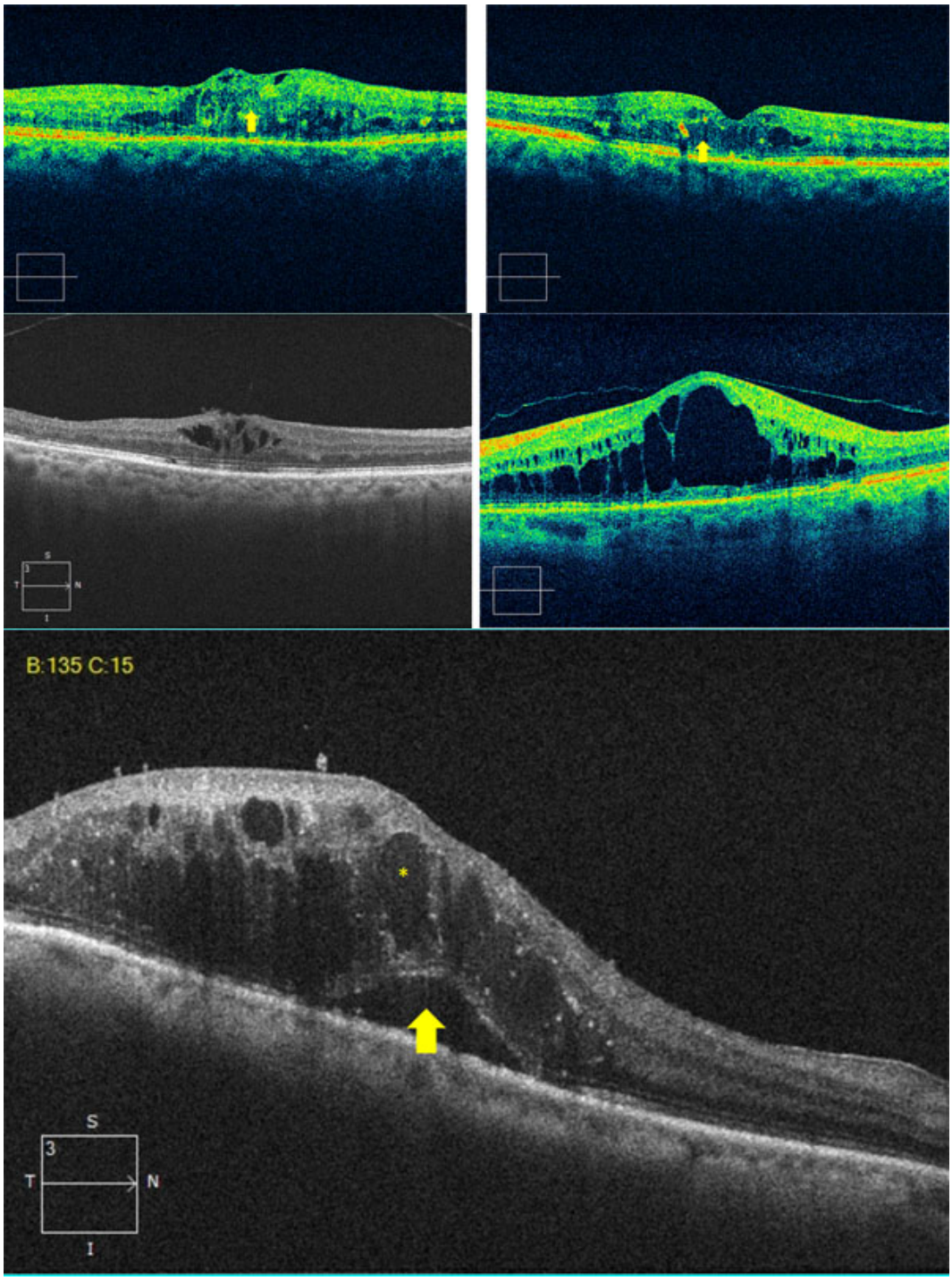
Diabetic macular edema (DME), a major sequela of diabetes, presents at any stage of diabetic retinopathy and often results in a significant visual decline among working-aged individuals [4, 5]. In an epidemiological study reviewing the 10-year outcomes of patients with diabetes, DME occurred in 20.1% of the young-onset group and 25.4% in the older onset group taking insulin. This study estimates that DME will develop in over 800,000 patients, with clinically significant macular edema developing in over 550,000 people [6]. Therefore, the assessment and review of diabetic macular edema are integral to patient management and care.

* **Corresponding author Peter K. Kaiser:** From the Cole Eye Institute, Cleveland Clinic, Cleveland, OH; E-mail: PKaiser@aol.com

The pathogenesis behind DME involves the alteration of endothelial cells and pericytes to create a hyperpermeable blood-retinal barrier, leading to the accumulation of plasma and lipid products in the macula [7]. This often leads to a detectable retinal elevation on fundoscopic examination. While the clinical examination was initially the standard for diagnosing macular edema, OCT can detect even minute amounts of edema invisible to the examiner [8]. This detailed view allows for the serial analysis and classification of various metrics in diabetes, including morphological retina edema patterns, evaluation of the vitreoretinal interface, measurement of retinal thickness and assessment of individual layers, and choroidal thickness [9]. This fact has also made the finding of clinically significant macular edema (CSME) as described in the Early Treatment Diabetic Retinopathy Study (ETDRS) replaced by the center-involved diabetic macular edema (CI-DME) based on OCT evaluation and not the clinical exam.

Morphological Patterns of Diabetic Macular Edema

Several morphological patterns of DME have been described in the literature [10 - 12]. The main classification system, set forth by Kim *et al.*, contains 5 categories: sponge-like, diffuse retinal thickening (DRT, defined as thickening greater than 200 *u*m), cystoid macular edema (CME), serous retinal detachment (SRD), posterior hyaloid traction (PHT), and tractional retinal detachment (TRD) with PHT (Fig. **1**). These patterns of edema are not mutually exclusive and can present in conjunction with each other [10]. In this particular study, diffuse retinal thickening (present in 97% of scans) and cystoid macular edema (55% of scans) were the most common findings [10]. These results were compatible with previously published studies [11, 12]. DRT was the most commonly found sole presentation in eyes (39.5%), and DRT and CME were the most common combination (29% of scans) [10]. The same paper found that both CME and PHT without TRD were significantly associated with decreased vision. Additionally, cystic changes had the highest predisposition to decreased vision [10]. Kaiser *et al.* also described the unique form of DME associated with PHT, an entity that may be missed on clinical biomicroscopy alone. The recognition of this pattern is important as these patients may be more resistant to therapy and require surgical intervention earlier, although the exact mechanism of visual recovery is unknown [13].



(Fig. 1) contd.....

CHAPTER 10

Classification of Proliferative and Non-Proliferative Diabetic Retinopathy and its Implications

Ferhina S. Ali and **Sunir J. Garg***

The Retina Service of Wills Eye Hospital, Professor of Ophthalmology Thomas Jefferson University 840 Walnut Street, Suite 1020 Philadelphia, PA 19107, USA

Abstract: An understanding of the classification scheme of nonproliferative and proliferative diabetic retinopathy is essential for the proper management of diabetic eye disease. The level of retinopathy is based on clinical findings seen on fundus examination.

Keywords: Anti-VEGF, Diabetic Retinopathy Study (DRS), Diabetic retinopathy, Early Treatment of Diabetic Retinopathy Study, Mild, Moderate, Nonproliferative, Neovascularization, Proliferative, Severe.

BACKGROUND

The global prevalence of diabetes has been increasing rapidly, with a projected estimate of over 360 million people worldwide affected by the year 2030. As such, the need to identify and to treat diabetic retinopathy is critical to prevent vision loss. Central to this is an understanding of the classification and severity stages of diabetic retinopathy [1].

In 1968, an expert panel developed the Airlie House classification scheme for diabetic retinopathy that was subsequently modified and used in the landmark Diabetic Retinopathy Study (DRS) and the Early Treatment Diabetic Retinopathy Study (ETDRS) [2, 3]. The classification is based on grading seven-field 30-degree standard stereo-photographs [4]. While this has been the gold standard for clinical trials, it remains challenging to use in daily clinical practice. Simplification of this classification occurred through the International Clinical

* **Corresponding authors Sunir J. Garg:** The Retina Service of Wills Eye Hospital Professor of Ophthalmology Thomas Jefferson University 840 Walnut Street, Suite 1020 Philadelphia, PA 19107, USA; Tel: (800) 331-6634; Fax: (610) 667-1328; E-mail: SunirGarg@yahoo.com

Douglas R. Lazzaro and Samy I. McFarlane (Eds.)

Disease Severity Scale for Diabetic Retinopathy that consists of five scales with increasing degrees of retinopathy observed on dilated ophthalmoscopy (Table **1**) [2].

Table 1. International Clinical Diabetic Retinopathy Disease Severity Scale (adapted from the American Academy of Ophthalmology Diabetic Retinopathy Preferred Practice Patterns 2019).

Proposed Disease Severity Level	Findings Observable upon Dilated Ophthalmoscopy
No Apparent Retinopathy	No abnormalities
Mild Non-Proliferative Diabetic Retinopathy	Microaneurysms only
Moderate Non-Proliferative Diabetic Retinopathy	More than just microaneurysms but less than Severe NPDR
Severe Non-Proliferative Diabetic Retinopathy	Any of the following: More than 20 intraretinal hemorrhages in each of 4 quadrants Definite venous beading in 2+ quadrants Prominent IRMA in 1+ quadrant and no signs of proliferative retinopathy
Proliferative Diabetic Retinopathy	One or more of the following: Neovascularization Vitreous/preretinal hemorrhage

CLINICAL MANIFESTATIONS OF NONPROLIFERATIVE DIABETIC RETINOPATHY

Diabetic retinopathy is a microvascular disease that has a characteristic clinical appearance that results from damage to the retinal capillaries and smaller retinal vessels. A brief description of the common clinical findings follows below.

Intraretinal hemorrhages have a diverse appearance in diabetic retinopathy. Eyes can develop focal, round, well-defined hemorrhages called dot-blot hemorrhages (Fig. **1**, arrow). These occur in the outer retina and/or inner plexiform layers, which are vertically oriented. This results in the round focal appearance of these hemorrhages. Flame-shaped hemorrhages are larger with less distinct margins with morphology that corresponds to the orientation of the retinal nerve fiber layer (Fig. **1**, asterisk). As a result, they are horizontal and linear. In contrast to microaneurysms, intraretinal hemorrhages are hypofluorescent on fluorescein angiography because blood blocks the normal choroidal fluorescence (Fig. **2**, asterisk).

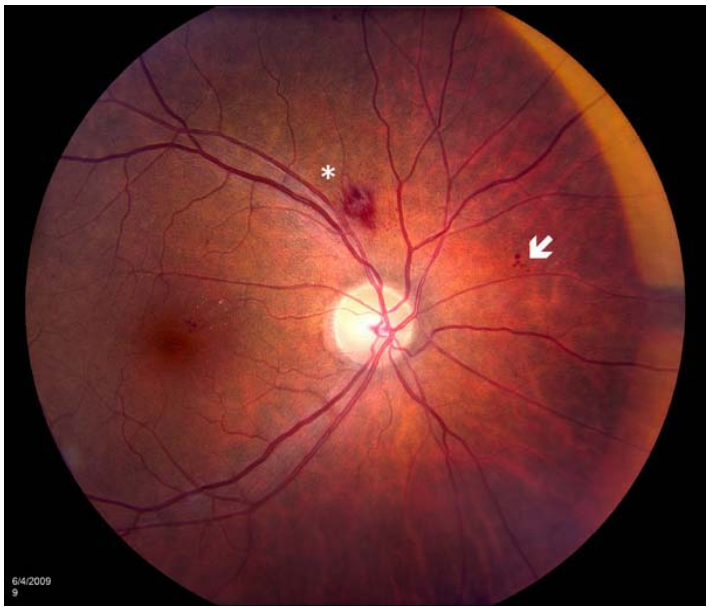


Fig. (1). Dot blot hemorrhage (arrow) and flame hemorrhage (asterisk).

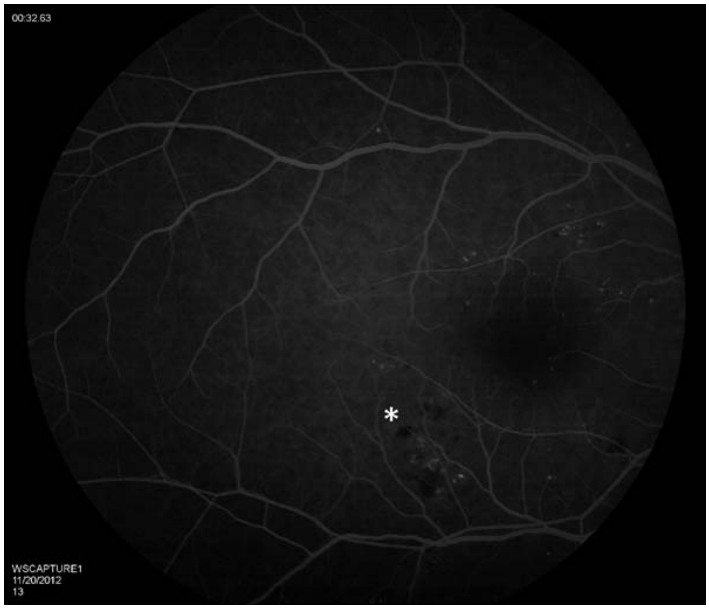


Fig. (2). Hypofluorescence of retinal hemorrhage (asterisk).

Hard exudates are discrete yellow-white deposits in the retina, usually at the border of edematous and nonedematous retina. These occur from incompetent vessels that allow fluid exudation. Over time, the associated edema may get

CHAPTER 11

Current Treatment for Diabetic Retinopathy

Joseph Bogaard and **Judy E. Kim***

Department of Ophthalmology and Visual Sciences, Medical College of Wisconsin, Milwaukee, USA

Abstract: This chapter will review most common therapies currently used for diabetic retinopathy. Specifically, the treatments being used for diabetic macular edema (DME) and proliferative diabetic retinopathy will be discussed.

Keywords: Anti-VEGF, Diabetes, DME, Edema, Laser, Laser, Macula, Retinopathy, Steroids, Treatment, Vitrectomy.

INTRODUCTION

Diabetic retinopathy is the most common microvascular complication of diabetes. Ten percent of people with diabetes have vision-threatening diabetic retinopathy (DR). It is also a major public health threat and is the leading cause of blindness in working-aged individuals in industrialized nations [1]. Diabetic macular edema (DME) accounts for the majority of diabetic retinopathy-related vision loss, followed by complications resulting from proliferative diabetic retinopathy (PDR). Tremendous advances have been made in the treatment of DME and PDR in recent years, particularly with the discovery of the role that vascular endothelial growth factor (VEGF) plays in diabetic retinopathy and the advent of intravitreal anti-vascular endothelial growth factor (anti-VEGF) therapy.

The VEGF family is the master regulator of angiogenesis, vasculogenesis and lymphangiogenesis. It consists of six members VEGF-A, VEGF-B, VEGF-C, VEGF-D, viral VEGF-E, and placental growth factor (PIGF). Of these, VEGF-A is the most important member and is what most of our anti-VEGF therapies currently target. VEGF is an anti-parallel homodimeric peptide with numerous cysteine residues that form intramolecular disulphide bonds, making it a member of the "cys-loop" superfamily of proteins.

* **Corresponding author Judy E. Kim**: Department of Ophthalmology and Visual Sciences, Medical College of Wisconsin, Milwaukee, Milwaukee, USA; E-mail:jekim@mcw.edu

The human VEGF-A gene located on chromosome 6 consists of 8 exons with alternate splice sites in exons 6, 7 and 8 leading to 16 currently known different isoforms of the VEGF-A protein, each with different biological properties and activities. These isoforms are most commonly from six transcripts: $VEGF_{111}$, $VEGF_{121}$, $VEGF_{145}$, $VEGF_{165,}$ $VEGF_{189}$, and $VEGF_{206}$. Exon 8 contains a major site of alternative splicing resulting in either the prototypical $VEGF_{xxxa}$ form or the "anti-angiogenic" $VEGF_{xxxb}$ isoform. The shorter isoforms $VEGF_{111}$ and $VEGF_{121}$ are freely diffusible due to their excluded exons 6 and 7 which contain heparin and Neuropilin-1 binding sites. Longer isoforms $VEGF_{145}$, $VEGF_{189}$, and $VEGF_{206}$ have high affinity binding to heparin sulfate glycoproteins which tightly tether them to the extracellular matrix. Finally, $VEGF_{165}$ represents an intermediate between freely diffusible and tightly bound isoforms [2, 3].

VEGF plays an important role in the development of both PDR and DME. VEGF production is induced in response to ischemia or hypoxia through a DNA binding protein called hypoxia-inducible factor 1 (HIF-1) which leads to increased transcription of VEGF mRNA [4]. VEGF molecules bind to tyrosine kinase receptors on the endothelial cell surface causing them to dimerize and activate *via* transphosphorylation. This transphosphorylation induces a cascade of intracellular signaling pathways shown in Fig. (**1**). This complex signal cascade causes an increase in vascular permeability, cell proliferation, cell migration, and cell survival. This cascade also causes the release of matrix metalloproteinases and urokinase-type plasminogen resulting in the destruction of basement membranes allowing for migration, proliferation, and creation of new basement membranes [5].

Anti-VEGF agents currently Food and Drug Administration (FDA) approved for the treatment of DME include aflibercept (Eylea, Regeneron, Eastview, New York, United States) and ranibizumab (Lucentis, Genentech, South San Francisco, California, United States). Bevacizumab (Avastin, Genentech, South San Francisco, California, United States) is also used off-label. These anti-VEGF agents have been shown to prevent progression of PDR, reverse diabetic retinopathy severity scores, and improve visual acuity (VA) and retinal thickness in eyes with center-involved DME. Despite these advances, many challenges remain in the treatment of diabetic retinopathy, including patient access to health care services, early screening, and increasing costs related to drug therapy. Future therapeutic agents may help by decreasing the socioeconomic treatment burden and durability of treatment effect.

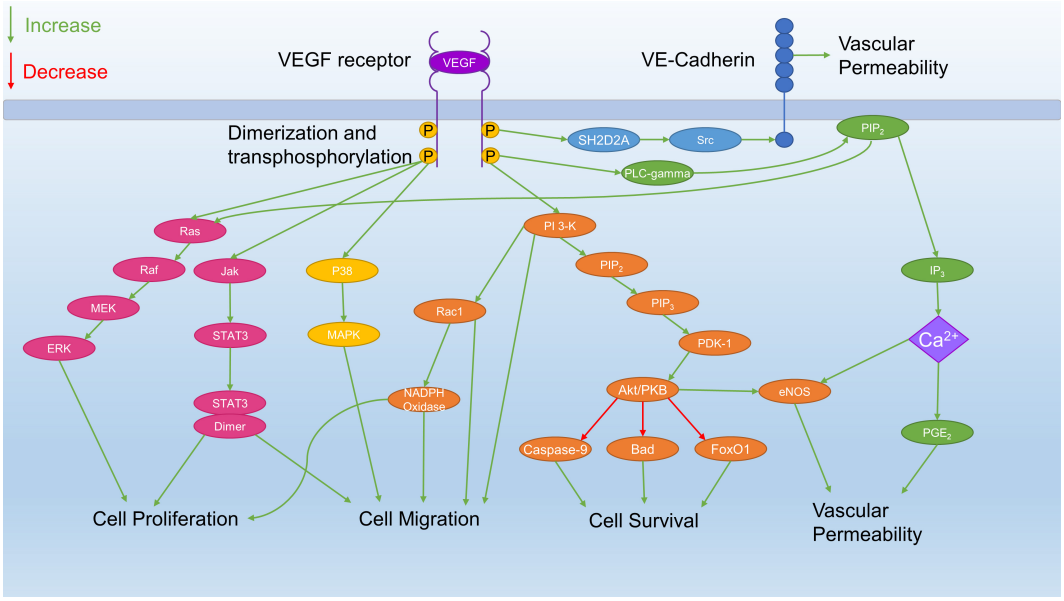


Fig. (1). MEK – Mitogen-activated protein kinase kinases ERK – Extracellular signal-regulated kinases Jak – Janus kinases STAT3 – Signal transducer and activator of transcription 3 MAPK- Mitogen-activated protein kinases Rac1 – Ras-related C3 botulinum toxin substrate 1 NADPH Oxidase - Nicotinamide adenine dinucleotide phosphate oxidase PI 3-K – Phosphoinositide 3-kinases PIP_2 – Phosphatidylinositol 4,5-bisphosphate PIP_3 – Phosphatidylinositol (3,4,5)-trisphosphate PDK-1 – Pyruvate dehydrogenase lipoamide kinase isozyme 1 AKT/PKB – Protein Kinase B BAD – B cell lymphoma 2 associated death promoter FoxO1 – Forkhead box protein O1 eNOS – Endothelial nitric oxide synthase SH2D2A – SH2 domain-containing protein 2A PLC-gamma – Phospholipase C gamma IP_3 – inositol 1,4,5-trisphosphate Ca^{2+} – Ionic Calcium 2+ PGE2 – Prostaglandin E2.

Diabetic Retinopathy

Management of DR requires timely diagnosis and and access to treatments when needed. Perhaps the most effective form of treatment for DR is prevention and early diagnosis. This is often a collaborative effort with primary care providers and endocrinologists and involves appropriate diabetes screening and blood sugar control, followed by routine eye examinations to detect DR in the earliest stages. Despite well-established screening guidelines [6 - 8] and education programs directed at both physicians and patients [9], only 50% of patients with diabetes undergo screening eye examinations within a given year, and only 16% receive exams in two consecutive years [10]. Non-adherence to screening guidelines has been attributed to socioeconomic, cultural, and geographic reasons [11]. In developing countries, screening examinations may be limited by an insufficient number of physicians [12]. Telemedicine may help ease the burden of screening exams by allowing patients to be examined in locations that are more convenient or accessible to them. The fundus images obtained from a camera can be sent through an established telemedicine program to an ophthalmologist's office or a

CHAPTER 12

Future Direction in Diabetic Eye Disease

Gautam Vangipuram* and **Gaurav K. Shah**

The Retina Institute, Saint Louis, Missouri, USA

Abstract: Diabetic retinopathy is one of the leading causes of vision loss worldwide and its incidence is only projected to increase. Much effort has been dedicated to investigating new therapies and drug delivery approach in treating its complications, diabetic macular edema (DME) and proliferative diabetic retinopathy (PDR). Although anti-vascular endothelial growth factor (VEGF) has gained popularity in treatment for DR, patients who respond poorly to intravitreal injections have prompted the search for additional pathogenic pathways and thus therapeutic targets that may better control disease activity. These novel therapies, including various anti-angiogenic agents, growth factor inhibitors, integrin inhibitors, sustained delivery platforms, gene therapy, chemokine and other inflammatory inhibitors, and neuroprotective agents, are currently being evaluated for the management of DR. Optimal treatment paradigms in the management of PDR are also under investigation.

Keywords: Anti-VEGF, Angiogenic, Cytokine, Complications, DME, Diabetes, Integrin, Implant, Laser, Neovascularization, Proliferative, Retinopathy, Steroid, Target, Therapeutic.

INTRODUCTION

Diabetic retinopathy (DR) remains the leading cause of blindness among working-age individuals in developed countries. Unfortunately, given current demographic trends in population and obesity, the disease shows no sign of remission . As of 2013, the estimated incidence of diabetic macular edema (DME) disease worldwide has affected 26 million individuals and is expected to increase to 40 million by 2035 [1]. With DR being the most common complication of diabetes, vision-threatening conditions such as DME and proliferative diabetic retinopathy (PDR) have become a large portion of retinal subspecialty care [2]. The underlying pathogenesis of DR is still under investigation with vascular basement membrane thickening and pericyte loss leading to vascular permeability and capillary loss often cited as casual. However, multiple mechanisms to this disease have been postulated and are currently the target of novel treatment agents

* **Corresponding author Gautam Vangipuram:** The Retina Institute, Saint Louis, Missouri, USA; Tel: (314) 367-1181; Fax: (314) 968-5117; E-mail: gautam.vangipuram@gmail.com

Douglas R. Lazzaro and Samy I. McFarlane (Eds.)

(Fig. **1**). Therapies targeting alternative pathways responsible for promoting inflammation, including Ang2 and integrin, have shown early promise. Eventually with progressive non-perfusion, proliferative disease develops as a result of the release of Vascular Endothelial Growth Factor (VEGF) which leads to the development of neovascularization.

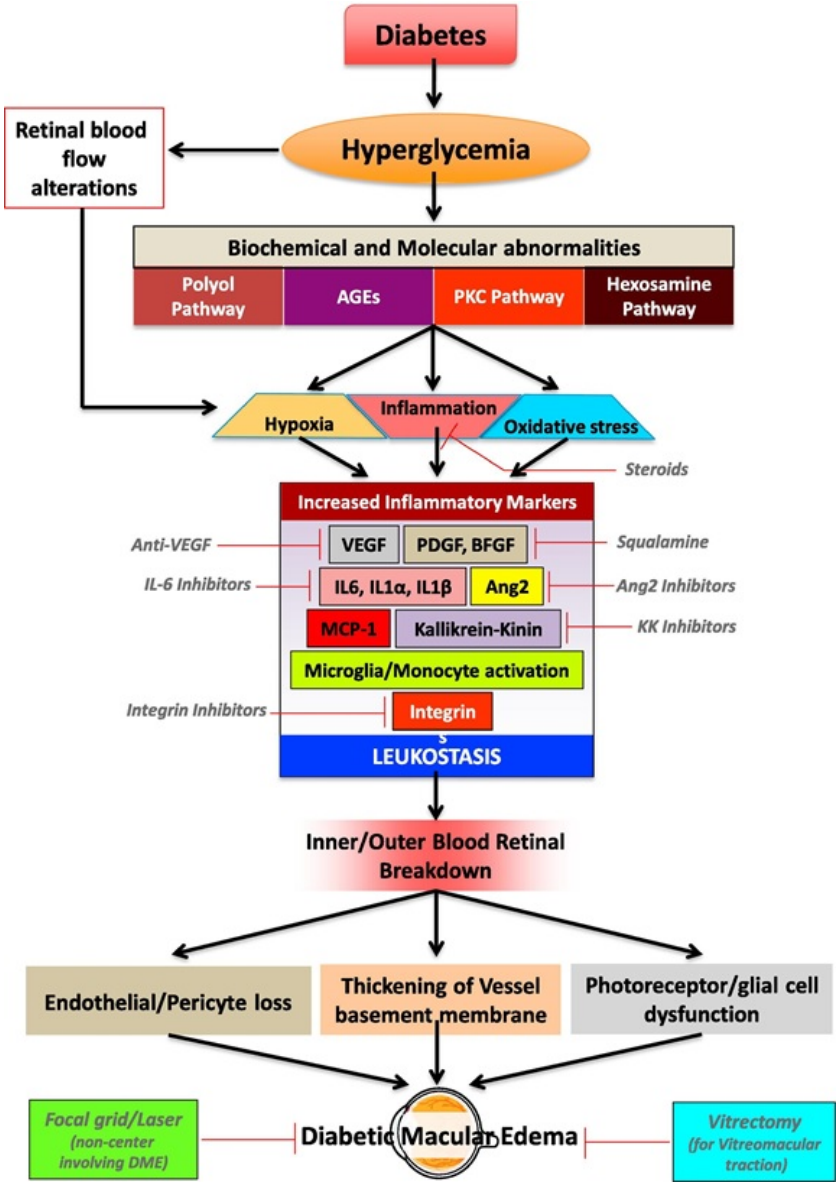


Fig. (1). Schematic pathway of pro-inflammatory cytokines and neovascular factors involved in the development of DME.[44] (Adapted from Urias EA *et al*.).

Current treatment for DR involves risk factor modification and working with a patient's primary care physician or endocrinologist to help manage blood sugar control and concomitant hypertension if present. In the treatment of DR, laser photocoagulation had been the mainstay of treatment for decades in managing both proliferative diabetic disease and diabetic macular edema (DME). With the advent of anti-VEGF agents, however, several randomized controlled studies have proven these medications as efficacious in some regards to the standard of care laser. Furthermore, exploration of the inflammatory mechanisms, combination therapy, and drug delivery platforms remains ongoing. The goal of this chapter is to briefly review current therapies and treatment modalities in diabetic retinopathy and discuss future directions in management.

Standard of Care Treatment

Addressing Risk Factors

Duration of diabetic disease is the main risk factor for developing DR along with poor glycemic control and hypertension, as several studies have investigated the effects of tight control over these parameters. Recently, there is increasing evidence to suggest diabetic complications may be linked by a series of faulty metabolic regulatory systems including oxidative stress, non-enzymatic glycosylation of proteins, epigenetic changes, and chronic inflammation producing a new "metabolic memory" [3, 47, 48]. Proponents of this theory, therefore, suggest aggressive early intervention once diabetes is diagnosed to restore the body's natural homeostasis.

In the United Kingdom Prospective Diabetes Study (UKPDS), intensive glycemic management in type 2 diabetes resulted in a 39% reduction in the risk for laser photocoagulation when compared with conventional glycemic control standards [3]. Similarly, the Diabetes Control and Complications Trial (DCCT) showed that tight glycemic control with insulin in type 1 diabetics reduced the risk of new retinopathy by 76% and decreased the progression of the existing disease by 54% [4]. It was recently reported that HbA1c maintenance below 7.6% may prevent PDR in type 1 diabetes for up to 20 years [5].

With regard to hypertension, the UKPDS study demonstrated a benefit in slowing DR progression by controlling blood pressure (systolic blood pressure <150 *vs*. <180 mmHg *vs*. standard control) using angiotensin-converting enzyme inhibitors or β-adrenergic blockers in type 2 diabetics [6]. In contrast, the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) and Action to Control Cardiovascular Risk in Diabetes (ACCORD) trials showed equivocal results for retinopathy with intensive management of blood pressure [7, 8]. Importantly, the UKPDS study required a baseline

SUBJECT INDEX

A

Abducens nerve palsies 81, 84
  acquired unilateral 84
  isolated 84
Accumulation 19, 27, 109, 130, 131, 148, 150
  subretinal fluid 150
  visceral fat 27
Activity 112, 131, 186, 208
  antioxidant enzyme 131
Acute leukemia 35
Adenomas 19
  advanced 19
Adenomatous polyps 19
Adiponectin 6
Advances in laser technology 193
Aflibercept monotherapy 217
Aflibercept protein 214
Agents 22, 23, 38, 89, 137, 138, 139, 186, 189, 190, 203, 206, 208, 220
  alkylating 138
  anti-angiogenic 203
  anticholinergic 138
  anti-inflammatory 89
  chronic immunosuppressive 38
  cycloplegic 139
  neuroprotective 203
  therapeutic 186
Aldose reductase 6, 90, 116
  inhibitors 116
  pathway 6
Altered collagen synthesis 111
American diabetes association (ADA) 22, 34, 39, 40
AMP-activated protein kinase 22
Amphotericin 72, 73, 74
  intravenous 72, 73
Analysis, retrospective pooled 219
Ang-2 inhibitor drug 212
Angiogenesis 179, 185, 215
Angiogenic 134, 179
  growth factors 134
  stimulus 179
Angiography 161
Angle 52, 133, 134, 135, 137
  aqueous fluid drainage 52
  neovascularization 52, 134, 135, 137
  iridocorneal 133, 134, 135
Anti-inflammatory treatment 27
Antioxidant therapy 27
Anti-VEGF 182, 185, 191, 193, 195, 196, 203, 206, 207, 212, 214, 219, 220
  adjunctive 220
  adjuvant 219
Anti-VEGF agents 137, 138, 186, 188, 189, 191, 193, 194, 196, 205, 206, 207, 215, 217, 219
Anti-VEGF injections 183, 196, 207, 216, 218, 219
  serial intravitreal 183
Anti-VEGF intravitreal 93, 98
  injections 93
  treatment 98
Anti-VEGF therapy 139, 182, 185, 189, 190, 191, 192, 193, 194, 195, 196, 218
  adjunctive 139
  monthly 189, 195
Anti-VEGF treatment 91, 196
  post-operative 91
Apoptosis 19, 36, 130, 134
  cardiomyocyte 19
Aseptic technique 188
Atheroembolic disease 21
Atherosclerosis, accelerated 19, 20
ATPase 111, 112
  activity 112
  enzyme 112
Autoreactive, inhibiting 36
Autosomal recessive syndrome 85

B

Bi-hormonal 32
  systems 32

therapy 32
Biomicroscopy 153
Blindness 4, 65, 87, 132, 133, 185, 203
non-reversible 132
prevention efforts 133
Blood glucose 24, 28, 29, 41, 87, 130, 131
excess 130
concentrations 24
fluctuates 28
fasting 41
variability 29
Blood pressure 27, 41, 94, 191, 205
decreasing 27
elevated 191
systolic 205

C

Cancer 18, 19, 22
colorectal 19
Cardiomyocytes 19
Cardiomyopathy 18, 19
diabetic 18, 19
Cardiovascular diseases 1, 3, 14, 17, 18
Carotid artery disease 20
Cascade 186
complex signal 186
Cataract development 129, 130
Cavernous sinus thrombosis 75
Cell apoptosis 21, 27, 217
endothelial 21
retinal ganglion 217
Cellulitis 21, 71
Choriocapillaris 156, 157, 159, 161
Choroidoscleral interface 155
Chronic renal insufficiency 93
Cinnamic acids 28
Clinically significant macular edema (CSME) 54, 55, 58, 59, 69, 147, 148
CML immunoreactivity 108
Collagen 19, 20, 95, 111
deposition 20
fibers 111
vascular diseases 95
Compensatory vascular anomalies 95
Concomitant 52, 64, 67, 89, 205
hypertension 205
lid disease 89
Conjunctiva 88, 116
Continuous glucose monitoring system (CGMS) 28, 29
Contraction 97, 135, 180, 219
fibrovascular 219
rapid membrane 219
Cornea 108, 109, 114, 117, 121
diabetic 108, 109, 117, 121
healthy 114
non-diabetic 108, 117
Corneal 76, 88, 106, 108, 110, 111, 112, 114, 116, 117, 118, 121, 122, 139
adherent 108
contact lenses 122
decompensation 139
disease 106
endothelium 106, 111, 112, 118, 122
epitheliopathy 88
stimulate 114
Corneal epithelium 75, 76, 106, 107, 108, 110, 113, 114, 115, 118, 122
paracentral 114
Corneal infections 76, 109, 110
developing 76
Corneal nerve fibers 113, 114
release neurotransmitters 114
Corneal thickness 108, 111, 112
central 108, 112
increased 112
Cornea topography 106
Coronary artery disease 18, 19, 93
Cortical cataracts, focal 91
Corticosteroid(s) 193, 194, 195, 207, 217
comparing sustained-release 195
triamcinolone acetonide 217
Cranial 4, 81, 85, 91
nerve ischemia 91
nerve mononeuropathies 91
nerve palsies 4, 81, 85, 91
Cyclocryotherapy 139
Cyclooxygenase 208
Cyclophotocoagulation 138, 139

Cystoid macular edema (CME) 148, 160, 163, 218
Cytokines 27, 28, 203, 204, 216
  inflammatory 28
  pro-inflammatory 27, 204

D

Damage 4, 52, 58, 59, 76, 80, 88, 95, 99, 106, 113, 116, 117, 135
  increased corneal 117
  irreversible posterior segment 52
  permanent visual 99
  protein 95
Deep capillary plexus (DCP) 157, 158, 159, 160, 161
Degradation 23, 108, 109, 111
  proteolytic 109
  thermal 111
Densities 111, 112, 113, 114
  basal epithelial cell 114
  endothelial cell 111, 112
Destruction 37, 152, 186
  autoimmune 37
Destructive immunity 38
Diabetes 2, 6, 14, 21, 205
  adult-onset 2
  control and complications trial (DCCT) 6, 205
  damages 21
  disparities 14
Diabetes mellitus 2, 7
  epidemiology of 2
  managing 7
Diabetic disease 92, 205
  proliferative 92, 205
Diabetic 5, 54, 55, 87, 88, 89, 90, 94, 99, 107, 110, 119, 120, 131, 147, 148, 151, 155, 157, 162, 163, 185, 189, 190, 192, 193, 194, 195, 196, 203, 207, 212, 216
  edema eyes 155
  ischemia 162
  keratopathy 87, 88, 89, 90, 107, 110, 119, 120
  leakage 163
  macular edema (DME) 5, 54, 55, 94, 147, 148, 151, 157, 185, 189, 190, 192, 193, 194, 195, 196, 203, 207, 212, 216
  papillopathy (DP) 87, 99
  retinal diseases 131
Diabetic retinopathy 4, 7, 73, 94, 174, 177, 179, 185, 197, 220
  epidemiology of 4, 7
  progression 4
  severe nonproliferative 174, 177, 179
  severe non-proliferative 73
  sight-threatening 94
  treatment 197
  vision-threatening 185
  vitrectomy study (DRVS) 220
Disease 1, 2, 5, 7, 8, 13, 14, 18, 22, 25, 75, 116, 134, 135, 172, 203, 205, 218, 220
  cerebrovascular 18
  epithelial 116
  orbital 75
  severity scale for diabetic retinopathy 172
Disorders 87, 91
  extraocular movement 87
  ocular movement 91
DME therapy 188, 190
DNA 19, 186
  binding protein 186
  damage 19
Drug 22, 23
  appropriate glucose-lowering 22
  oral glucose-lowering 23
Dry eye 88, 100, 117, 119
  chronic 117
  discomfort 119
  treating 117

Dry eye syndrome 87, 88, 89
  and diabetic keratopathy 87
Dysfunction 2, 19, 21, 28, 88, 95, 114
  contractile 19
  endothelial 28
  lacrimal gland 88
  microcirculatory 21
  ventricular 19
Dyslipidemia 17

E

Early treatment of diabetic retinopathy study (ETDRS) 98, 148, 171, 179, 182, 188, 206
Edema 21, 53, 54, 71, 72, 73, 74, 77, 148, 155, 182, 185, 206
  diabetic 155
  diffuse 206
  eyelid 71, 74, 77
  facial 72
Embryogenesis 128
Endocrinologists 187, 205
Endophthalmitis 71, 76, 77, 91, 191, 192
  developing post-operative 77
  endogenous 76, 77
Endothelial cell(s) 80, 118
  density post cataract phacoemulsification 118
  lining blood vessels 80
Endothelial homogenate 112
Epidermal growth factor receptor 36
Epiretinal membrane 52, 54, 66, 97
Epithelial 73, 119, 122
  erosions 73, 119
  healing problems 122
  stem cell homeostasis 115
Epithelium 88, 89, 109, 133, 134, 135, 139, 113, 121
  absent conjunctival/corneal 88
  iris pigment 135
  non-pigmented ciliary 133, 139
  pigmented 134
  retinal pigment 95, 193
Erythema 73, 74, 75
  right periorbital 73
Erythromycin ointment 73
Erythropoietin 179
Esotropic strabismus 83
Evidence for superiority of anti-VEGF therapy 189
Eyecare specialist 94
Eye disease 1, 80, 94, 119, 214
  pre-existing dry 119
  severe 94
  thyroid 214
Eye 77, 116
  fatigue 116
  infections 77
Eyes 60, 61, 71, 77, 81, 82, 84, 106, 108, 114, 128, 131,133, 134, 135, 138, 139, 154, 156, 182, 190, 192, 193, 194, 195, 196
  contralateral 84
  diabetic 108, 114, 131
  non-diabetic 108
  pseudophakic 194
  treatment-naïve 193
  vitrectomized 138

F

Factors 2, 4, 21, 29, 34, 35, 38, 60, 64, 73, 92, 93, 113, 114, 129, 134, 186, 204, 217
  angiogenesis 92
  angiogenic 134
  anti-angiogenesis 93
  anti-fibrotic 38
  cell-derived neurotrophic 114
  cytoprotective 217
  down-regulated neuroprotective 217
  hypoxia-inducible 186
  neovascular 204
  nuclear-transcriptional 21
  proangiogenesis 93
Fibrosis 19, 21, 54, 58
  interstitial 21
  myocardial 19
Fibrous capsule 138
Fibrovascular membranes 62, 93, 135, 139, 219
  delicate 219
Fluorescein angiogram 56, 59, 62, 63, 162, 163
  field optos 62, 63
  of macular ischemia 162
Fluorescein angiography 98, 178
  intravenous 98

of microaneurysms 178
Food 14, 17, 39, 40, 41, 186
healthy 40, 41
high-fat 39
nutritious 14
Food and drug administration (FDA) 119, 186, 188, 207, 208, 210, 214, 215
Function 22, 24, 92, 109, 111, 113, 118, 137, 217
cognitive 24
endothelial barrier 118, 137
epithelial barrier 109
extraocular muscle 92
insulin secretory 22
optical 111
photopic b-wave 217
sensory 113

G

Gastric emptying effect 27
Gastrointestinal tolerability 27
Genitourinary tract 71
Gestational diabetes 17
Glaucoma 133, 138, 139
drainage devices (GDDs) 138, 139
Risk 133
Glucagon 22, 23, 26, 32
like peptide (GLP) 22, 26, 32
secretion 23, 26, 32
Glucose levels 24, 29, 30, 32, 33, 72, 73, 75, 80, 90
abnormal blood 90
blood 24, 29, 72, 75, 90
fasting 134
postprandial plasma 26
track blood 29
Glucose-lowering 22, 23
drug (GLDs) 22, 23
Glucose monitoring technology 13
Glycation 27, 108, 130, 131
non-enzymatic 108, 130, 131
Glycemic 36, 94
control, long term insulin-free 36
Growth 22, 72, 92, 114, 115, 134, 160, 197
epithelial cell 114
inhibiting cell 22
Growth factors 99, 113, 116, 134, 163, 179, 182, 185, 203, 206, 209
anti-vascular endothelial 99, 163, 182, 185, 203, 206, 209
binding placental 190
epithelial 116
fibroblast 113
placental 185
proangiogenic 182
transforming 134
tumor 179
Gut 17
microbes 17
microflora 17

H

Healing 119, 122
delayed 119
Heart diseases 3, 18
coronary 3, 13, 18
Heart failure 18
congestive 18
Hematopoietic stem cells (HSCs) 37, 38
Heparin sulfate glycoproteins 186
Hyperglycemia 3, 19, 21, 27, 34, 35, 37, 42, 90, 95, 111, 112, 114, 117, 131
chronic 3, 21, 117, 131
prolonged 114
Hypoglycemia 18, 22, 23, 24, 25, 26, 31, 32, 34, 42, 90
hyperinsulinemic 24
risk of 23, 26, 32
Hypoglycemic states 29

I

Immunomodulatory drug regimens 38
Inflammation 19, 27, 74, 75, 77, 95, 113, 118, 194, 204, 205, 207, 215, 217
chronic 205

hyperglycemia-induced 113
systemic 27
Inflammatory 137, 210, 215
extravasation 137
Response Inhibition 210, 215
Infusion 35, 122, 214, 219
cord blood cell 35
intravenous 214
pressure 219
stream 122
Injury 114, 117, 122
epithelial 122
stress-related 117
Innate immunity 35
Insulin 1, 14, 16, 19, 22, 23, 24, 25, 26, 28, 29, 30, 31, 32, 36, 37, 38, 40
absorption 31
release 29
resistance 14, 16, 28
Insulin secretion 23, 24, 26, 27
acute glucose-dependent 26
glucose-dependent 26
Insulin therapy 14, 22, 33, 34
exogenous 33
International transplant registry (IPTR) 33
Interventions 14, 41, 195
explored home telemedicine 41
novel therapeutic 20
Intraocular surgery 197
Iris 91, 92, 93, 128, 131, 134, 135, 136, 137, 138, 180
ischemia 131
neovascularization 91, 136
Ischemia 65, 80, 84, 87, 95, 131, 134, 159, 160, 161, 162, 165
neuronal 80
Ischemic 81, 135
injury 81
retinal diseases 135
syndrome 135

K

Keratitis 71, 75, 106, 109, 110, 114
infectious 75, 109
microbial 110
neurotrophic 114
Keratopathy 76, 89, 113, 120
diabetic neurotrophic 76
Ketoacidosis 1, 18, 34, 72
diabetic 1, 72
Kidney disease 3, 21
diabetic 21

L

Laser 61, 64, 97, 137, 189, 192, 193, 194, 197, 205, 206, 218
monotherapy 189
panretinal photocoagulation 97
photocoagulation 192, 193, 197, 205, 206, 218
technology 193
therapy 218
treatment 61, 64, 137, 194
LASIK-induced 119, 120
neuropathy 119
neurotropic epitheliopathy 120
LASIK-induced neutrotrophic 119
epitheliopathy 119
Lens 85, 90, 128, 129, 130, 131, 155
cloudy 131
Lensectomy 122
Leukostasis 215
Linoleic acid 16
Lipogenesis 17
Lymphangiogenesis 185

M

Macrovascular disease 13, 33
Macular edema 52, 54, 55, 59, 96, 100, 131, 132, 156, 163, 165, 182, 183
Macular ischemia 52, 54, 62, 63, 64, 65, 66, 67, 68, 156, 158, 159, 162
diabetic 159
extensive 162
severe 65, 66, 68

Mechanisms 17, 19, 20, 21, 24, 37, 42, 92, 108, 113, 116, 130, 137, 205, 217
  inflammatory 205
  neurodegenerative 217
  secondary closed-angle 92
Meibomian glands 116
Metabolic 18, 29
  complications 18
  glucose processing 29
Metamorphopsia 67, 68
Microaneurysmal saccular changes 95
Microvascular diseases 13, 172
Model predictive controller (MPC) 30
Mucormycosis 72
Mucormycosis 73

N

Natural homeostasis 205
Necrosis 72
  rapid tissue 72
Neovascular glaucoma 52, 87, 92, 93, 134
Neovascularization 53, 96, 97, 98, 135, 136, 137, 161, 162, 163, 164, 165, 180, 181, 195, 196, 218
  regressing 218
  regression 137
Neovascularized fibrovascular tissue 96
Nephropathy 13, 18, 21, 27, 33
  diabetic 18, 21
  ischemic 21
Nerve fibers 81, 95, 106, 113, 174
  bundle 114
  integrity 113
  layer infarcts 95, 174
  parasympathetic 81
  sensory 106
Neurodegeneration 134, 211
Neurodegenerative process 154
Non-clearing vitreous hemorrhage (NCVH) 54, 60, 64, 66, 67, 68, 137, 218
Nonproliferative diabetic retinopathy 95, 172, 177
Novel imaging techniques 154
Nuclear 91, 128, 129, 130
  sclerosis 128
  sclerotic cataract 91, 129, 130

O

Obstructive sleep apnea (OSA) 16, 17
OCT 155, 156, 163
  edema morphology 163
  imaging 163
  technology 155, 156
Ocular
  complications 4, 7, 87
  hypertension 98, 191
  misalignment, symptomatic 80
Ocular surface 87, 88, 115, 122
  diseases (OSD) 87, 88
  disorders 100
  health 115
  issues 122
  structures 88
Ocular surgery 117
Oil 89, 132, 138
  fish 89
  oral flaxseed 89
  silicone 132, 138
Ophthalmoparesis 92
Optical coherence tomography angiography (OCTA) 147, 156, 157, 158, 159, 160, 161, 162, 163, 165
Optic neuropathy 52, 65, 84, 85, 97, 174
  anterior ischemic 84
  diabetic 174
  irreversible 52
  ischemic 84, 174
  posterior ischemic 84
Osmotic stress 90
Osteomyelitis 21
Oxidative stress 19, 21, 28, 95, 113, 205, 216

P

Pancreas 33, 34
  allotransplantation 33

kidney transplantation 34
Pan-retinal photocoagulation (PRP) 60, 61, 62, 63, 97, 98, 136, 137, 181, 182, 183, 195, 196, 217, 218
Pars-plana vitrectomy (PPV) 96, 97, 137, 196, 197
Pathways 28, 130, 204, 206, 215, 220
hexosamine 28
polyol sorbitol-aldolase reductase 130
targeting alternative 204
Peripheral 20, 40, 136, 181
arterial disease (PAD) 20
glucose uptake 40
ischemic retina 136, 181
Plasma 115, 122, 148, 160, 191
serum 115
Plasma glucose 17, 26
fasting 26
Platelet-derived growth factor (PDGF) 95, 209
Poly ADP ribose polymerase (PARP) 19
Polymegathism 112
Port delivery system (PDS) 192, 209, 213, 214
Posterior 91, 148
capsular cataract 91
hyaloid traction (PHT) 148
Primary open angle glaucoma (POAG) 133
Progression 4, 14, 20, 21, 53, 54, 91, 98, 131, 132, 151, 179, 205, 211
diabetic 151
preventing retinopathy 4
Progressive optic nerve atrophy 85
Proliferation 37, 61, 63, 64, 68, 92, 97, 111, 114, 186, 219
fibrovascular 63, 64, 68, 97, 219
fibrovascular membrane 61
tractional membrane 61
Proliferative diabetic retinopathy (PDR) 5, 53, 60, 63, 64, 65, 66, 68, 94, 97, 98, 135, 160, 179, 180, 185, 195, 196, 203, 218
Properties 28, 36, 39, 111
antioxidant 28
immunomodulatory 36, 39
Proportional-integral-derivative (PID) 30
Proteinases 108, 110
Protein(s) 22, 26, 27, 28, 137, 185, 186, 187, 189, 192, 205, 212, 214
coupled free fatty acid receptor 26
engineered fusion 212
glycosylation 28
inhibitor 214
kinase 28, 187
recombinant fusion 189
Proteoglycans 111

R

Reactive oxygen species (ROS) 19, 28
Refillable port delivery system 214
Renin-angiotensin-aldosterone system (RAAS) 21
Retina 193, 196
neurosensory 193
surgeons 196
Retinal 53, 93, 94, 95, 134, 135, 137, 155, 159, 161, 173, 179, 191, 193
causative 135
damage 93, 193
disease 94
edema 53
hemorrhage 173
microcirculation 134
neovascularization 137, 161, 179
nerve fiber layer thinning 191
pigment epithelium (RPE) 95, 193
Retinal detachment 54, 67, 87, 93, 97, 138
rhegmatogenous 54, 93, 97
Retinal ischemia 60, 61, 62, 65, 92, 95, 120, 135, 136, 138, 160, 161, 164, 179, 193
extensive peripheral 61
peripheral 60, 62, 164
severe peripheral 65
transient 120
treating 138
Retinopathy 1, 2, 3, 4, 18, 21, 93, 94, 117, 118, 171, 172, 180, 183, 205, 206, 217
advanced 118
early DR 217
postoperative progression of 117

preoperative 117
progression of 118, 180
threatening 94, 118
Rhegmatogenous retinal detachment (RRD) 54, 64, 93, 97
Rhino-orbital-cerebral mucormycosis 71
Risk 2, 3, 13, 15, 16, 18, 19, 22, 23, 40, 60, 76, 97, 179, 191, 205
cardiovascular 13
hypoglycemic 22

S

SAP therapy 31
Serous retinal detachment (SRD) 148, 152
Serum LDL cholesterol concentrations 22
Spectral-domain optical coherence tomography (SDOCT) 96, 195
SPK transplantation 34, 35
Stabilized PDR disease 62
Stem cell(s) 36, 37, 38, 39, 42, 115
epithelial 115
hematopoietic 37
human embryonic 37
transplantations 42
Steroid-mediated inhibition 215
Stress 3, 112, 118
chronic metabolic 112
mechanical 118
Subfoveal choroidal thickness 155, 156
Subretinal fibrosis 193
Superficial capillary plexus (SCP) 157, 159, 160
Surgery 52, 67, 68, 97, 99, 118, 121, 131, 137, 196, 197, 218, 219
glaucoma filtration 52
membrane peeling 67
vitreoretinal 97
Surgical management in PDR 220
System 7, 21, 25, 29, 31, 32, 33, 108, 188, 193, 205
cardiovascular 25
faulty metabolic regulatory 205
gradable fundus imaging 188
micropulse laser 193
renin-angiotensin-aldosterone 21

T

Tear break up time (TBUT) 88
Tenosynovitis 76, 77
Therapy 20, 25, 34, 58, 84, 137, 138, 206, 207
anti-inflammatory 206, 207
definitive 137
effective 84
insulin-based 34
intravenous tissue plasminogen activator 20
medical glaucoma 138
optimal diabetes 25
pharmacologic 58
Tissue 106
sensitive 106
transparent 106
Tractional retinal detachment (TRD) 52, 54, 61, 63, 64, 67, 68, 96, 97, 148, 219
Transplant, renal 34
Transplantation 33, 34, 35, 36, 37, 38
islet cell 34, 35
kidney 34
solid organ 38
Treatment 28, 188, 218
of diabetes mellitus 28
of diabetic macular edema 188
strategies for proliferative diabetic retinopathy 218

U

Ulcers 71, 76, 106, 110
United Kingdom prospective diabetes study (UKPDS) 205

V

Vascular disease 13, 18, 20, 28, 135, 137, 205
peripheral 13, 18, 20
systemic 20

Vascular endothelial growth factor (VEGF) 6, 92, 95, 96, 98, 99, 134, 179, 185, 203, 204, 206, 209, 215, 216
  upregulation 95
  vasculogenesis 185
Vessels 20, 96, 135, 136, 155, 157, 161, 173
  dilated iris 135
  fragile 96
  medium choroidal 155
  renal 20
  small caliber 161
Vision 54, 55, 60, 61, 63, 64, 66, 67, 68, 71, 76, 88, 91, 106, 132, 139, 152
  blurry 76, 119
  color 134
  compromised 132
  decreasing 152
Vision loss 1, 2, 7, 52, 53, 54, 64, 65, 66, 67, 92, 93, 94, 182, 185, 188, 189, 195, 196
  developing severe 7
  diabetic retinopathy-related 185
  preventing severe 182
  risk of severe 195
Visually threatening diabetic retinopathy (VTDR) 5
Visual 64, 66, 94, 99, 117
  prognosis 64, 94, 99, 117
  symptoms 66
Vitreo-macular traction syndrome (VMTS) 96, 97

W

Wide-field fluorescein angiography 164
Wisconsin epidemiologic study of diabetic retinopathy (WESDR) 4, 5, 6, 179
Wolfram syndrome 85
Wound healing 38, 114, 115

DOUGLAS R. LAZZARO

Dr. Douglas R. Lazzaro is Professor and Vice Chairman of Operations, Clinical Affairs, and Business Development at NYU Langone Health. Prior to joining NYU, he served as the Troutman Distinguished Professor and Chairman of the Department of Ophthalmology at SUNY Downstate Medical Center for 12 years. Dr. Lazzaro has co-edited a textbook on ocular trauma, published many book chapters, has lectured nationally and internationally, and has published over 50 peer reviewed articles in leading eye journals. He is a practicing ophthalmologist with over 25 years of experience, and manages thousands of diabetic patients with eye diseases. He is a national expert for continuing medical education for ophthalmologists, and serves on the medical advisory board for the Eyebank for Sight Restoration, and is a journal reviewer for a number of medical journals.

SAMY I. MCFARLANE

Dr. Samy I. McFarlane has extensive experience in clinical and translational research in the area of prevention of diabetes and its complications. He served as the chief of the Division of Endocrinology, Diabetes, and Metabolism and as medical director of Clinical Research at SUNY-Downstate-Health Science University. Dr. McFarlane is the editor of several books and has authored over 300 publications on diabetes, cardiovascular disease, and related disorders. His work has attracted over 250,000 reads and over 10,000 citations at major medical journals. He is the founding editor-in-chief of the International Journal of Clinical Research and Trials. served as a 3 -term member and as a chair of the NIH-NIDDK committee, and has also served as the Brooklyn district president for the American College of Physicians. Dr. McFarlane has also received a ertificate of Special Congressional Recognition from the US House of Representatives. He is a well-recognized mentor with trainees in leadership positions at the NIH and other major institutions.