Diabetic Complications

Subjects: Biochemistry & Molecular Biology

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Diabetes is the cause of several macrovascular and microvascular complications. Macrovascular complications associated with diabetes include atherosclerosis and stroke; and microvascular complications include diabetic retinopathy, nephropathy, and neuropathy. Due to the progressive nature of diabetes, diabetes vascular complications causes the majority of the burden of diabetes with intense consequences on the anatomy, structure, and function of several cells, tissues, and organs, and consequently on the patient's well-being.

diabetic complications | phytochemicals | polyphenols | oxidative stress | diabetic retinopathy | diabetic nephropathy | diabetic neuropathy | diabetes | atherosclerosis | diabetic cardiomyopathy

1. Diabetic Retinopathy (DR)

DR is the most common microvascular complication of diabetes that can affect the retinal metabolism, physiology, and microvasculature of the eyes, it is also determined recently as the prominent cause of blindness in the working population [1]. The impact of DR on normal vision varies broadly depending on the stage of DR and the earliest stage of DR may be asymptomatic [2][3][4][5]. General symptoms of DR which usually develop gradually could include temporarily blurred vision, floaters, and flashes of light or blind spots in the field of vision, and gradual or sudden loss of vision [6][7].

Generally, DR is classically categorized into two major classes: non-proliferative DR (NPDR) and proliferative DR (PDR). NPDR symptoms are defects of the retinal vasculature including hemorrhages such as dot hemorrhages and blot hemorrhages [8][9], hard exudation [9][10], cotton wool spots [8][9][10][11], microaneurysms [8][9][10], and vascular leakage [10][11]. The major PDR hallmarks are related to pathological retinal angiogenesis which involves the growth of new abnormal blood vessels from the pre-existing vascular network, and pathological retinal neovascularization which encompasses the development of new blood vessels by de novo formation (vasculogenesis) and angiogenesis [9][12][13][14][15][16]. The progression from NPDR to PDR is characterized by ischemia, hypoxia, and the increased expression of proangiogenic growth factors including vascular endothelial growth factor (VEGF), fibroblast growth factor-2 (FGF-2), platelet-derived growth factor (PDGF), and angiopoietin-2 (Ang-2) which activate the growth of aberrant retina blood vessels which can protrude into the preretinal space [13][14][17].

Apart from the clinical features already discussed, other hallmark pathological changes in DR include pericyte loss, microglial activation, modifications to macroglial functions (Müller cells and astrocytes), thickening of the basement membrane, retinal leukocyte adhesion, blood–retinal barrier (BRB) breakdown, leukostasis, capillary nonperfusion, and capillary endothelial cell injury and death [8][9][10]; and degeneration of retinal neurons [18][19].

Prevailing recommended treatments for DR are laser pan-retinal photocoagulation (PRP) [20][21], vitreoretinal surgery [10], and anti-VEGF intravitreal injections [22][23]. Although the aforesaid treatments may slow down the progression of DR towards blindness, they are not effective in tackling every instance of the disease and have significant side effects [21][24][25][26][27][28]; therefore, it becomes imperative to find exigent alternatives or adjuvant therapeutic options to prevent DR or slow down its progression towards blindness.

2. Diabetic Peripheral Neuropathy (DPN)

DPN is a microvascular diabetic complication that is characterized by peripheral nerve dysfunction. DPN is a significant cause of morbidity in diabetic patients and about half of all diabetic individuals suffer from this complication [29]. In the clinic, the manifestations of DPN include painful neuropathic sensations and insensitivity, the latter significantly increases the risk of unintentional injuries, burns, and foot ulcers, which potentially leads to non-traumatic amputation and a significant reduction in the health status of patients [30][31]. Once DPN initiates, it would be irreversible, but progression can be slowed down [32].

The Toronto Diabetic Neuropathy Expert group categorized DPN into three major classes: (I) possible DPN, wherein any of the following signs or symptoms may be present: symptoms–decreased sensation, positive neuropathic sensory symptoms (e.g., “asleep numbness”, prickling or stabbing, burning or aching pain) that predominantly occur in the toes, feet, or legs, signs—a symmetric decrease in distal sensation or unequivocally decreased or absent ankle reflexes; (II) probable DPN, wherein two or more of the following signs and symptoms of neuropathy are present: neuropathic symptoms, decreased distal sensation, or unequivocally decreased or absent ankle reflexes; and (III) confirmed DPN, wherein nerve conduction is anomalous and a sign or symptom of neuropathy is present [30].

DPN is currently managed by tight glycemic control focusing on reducing HbA1c, however, for many patients, it is challenging to accomplish glycemic control [31]. The pain symptoms of DPN are managed with pharmacological agents including anticonvulsants (e.g., pregabalin and gabapentin) as the first-line pain therapy, serotonin–norepinephrine reuptake inhibitors (e.g., duloxetine and venlafaxine), secondary amine tricyclic antidepressants (e.g., nortriptyline and desipramine) and opioid agonists (e.g., oxycodone and methadone) [31][32].

3. Diabetic Nephropathy (DN)

DN is another microvascular diabetic complication that is the global leading cause of end-stage renal disease (ESRD) and dialysis, constituting about 40% of total patients who need renal replacement therapy [33][34]. The mortality rate is about 30 times higher in DN patients compared with other diabetic patients without DN [35].

Glomerular basement membrane (GBM) thickening, mesangial matrix expansion, proteinuria (classically manifested as albuminuria), the development of characteristic Kimmelstiel–Wilson nodules, and progressive regression in glomerular filtration rate (GFR) are characteristic features of DN [36][37].

DN is classically categorized into five stages based on urinary albumin excretion (UAE), GFR, and blood pressure (BP) [35][37]: (1) glomerular hyperfiltration wherein, GFR is normal ">90 mL/min/1.73 m^2" or increased, UAE value is <30 mg/day and blood pressure (BP) is normotensive; (2) silent stage, wherein, GFR is normal. UAE rate is <30 mg/day and BP is ±hypertensive along with thickened basement membrane; (3) incipient nephropathy with GFR of <60 mL/min/1.73 m^2, microalbuminuria (UAE of 30–300 mg/day; the earliest clinically detectable sign), and BP of ±hypertensive; (4) overt nephropathy, wherein, GFR is <30 mL/min/1.73 m^2, macroalbuminuria (UAE of >300 mg/day) and hypertensive BP are present; and ultimately, (5) ESRD, wherein, GFR value is <15 mL/min/1.73 m^2, with conditions of hypertensive BP and macroalbuminuria in which usually dialysis or transplantation is required [37].

Currently, tight glycemic and BP control, and the inhibition of the renin–angiotensin-aldosterone system (RAAS) via angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers are the central approaches of DN therapy [35][37]. However, these management approaches have limitations in preventing DN progression towards ESRD, hence, effective therapies are urgently needed [37].

4. Diabetes-Induced Cardiovascular and Cerebrovascular Diseases

Diabetics are at a greater risk of both cardiovascular and cerebrovascular diseases including atherosclerosis, cardiomyopathy, and stroke, which significantly increase morbidity and mortality in these patients [38][39][40][41].

Atherosclerosis is a macrovascular disease that is the primary cause of various heart diseases and stroke; diabetes-induced atherosclerosis is a significant cause of morbidity amongst diabetics [39][42]. It manifests as intimal thickening, inflammation, and narrowing of arteries by the build-up of plaques [42]. The Insulin Resistance Atherosclerosis (IRAS) study [39] has shown that compared with non-diabetics, diabetics have an increased rate of progression of carotid atherosclerosis, with diabetics having twice the mean progression of intimal-medial thickness in both the common carotid artery and the internal carotid artery.

Diabetic cardiomyopathy is the diabetes-induced functional and structural change of the myocardium in the absence of other risk factors including hypertension, coronary artery disease, and significant valvular disease [38]. The lack of specific standardized guidelines governing both the diagnosis and treatment of diabetic cardiomyopathy makes a definitive diagnosis, and treatment problematic [43]. Clinical pathological changes include cardiac remodeling, diastolic dysfunction, myocardial fibrosis, cardiac stiffness, impaired calcium handling, increased atrial filling, enlargement, and increased left ventricular end-diastolic pressure [38][44].

Stroke (or cerebrovascular accident) emerges due to the combination of extracranial carotid artery disease and intracranial vessel diseases [45]. The risk of stroke is increased by 36% in diabetics compared with non-diabetics [46] and one-third of all stroke patients are diabetics [47]. There are two main forms of stroke that may feature in diabetes, ischemic and hemorrhagic stroke, with both having the potential of significantly increasing morbidity and mortality amongst diabetics [48]; and in the clinic, stroke is manifested as asymptomatic carotid artery occlusion or cerebral small vessel disease to transitory ischemic attack [45].

Strict glycemic and lipid control as well as management of hypertension are essential for managing both diabetes-induced cardiovascular and cerebrovascular diseases; furthermore, pharmacological interventions for diabetes-induced cardiovascular diseases including glucagon-like peptide 1 (GLP-1) receptor agonists, agonists of peroxisome proliferator-activated receptor gamma-γ (PPAR-γ) (e.g., pioglitazone), and the pharmacological inhibition of sodium-glucose cotransporter type 2 (SGLT2) and RAAS (e.g., by an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin-receptor blocker) have shown clinical benefits [43][49][50][51]. Pharmacological interventions that can prevent stroke in diabetics include pioglitazone and anti-platelet drugs, such as, clopidogrel and aspirin; however, to reduce the combined risk of ischemic stroke, myocardial infarction or vascular death, clopidogrel may be more effective than aspirin [51][52][53]. Although these pharmacological interventions are available, they are inadequate for most diabetics and novel alternative adjuvant treatment options are needed.

References

1. Cheung, N.; Mitchell, P.; Wong, T.Y. Diabetic Retinopathy. Lancet 2010, 376, 124–136.
2. Biallosterski, C.; van Velthoven, M.E.J.; Michels, R.P.J.; Schlingemann, R.O.; DeVries, J.H.; Verbraak, F.D. Decreased Optical Coherence Tomography-Measured Pericentral Retinal Thickness in Patients with Diabetes Mellitus Type 1 with Minimal Diabetic Retinopathy. Br. J. Ophthalmol. 2007, 91, 1135–1138.
3. Lamoureux, E.L.; Tai, E.S.; Thumboo, J.; Kawasaki, R.; Saw, S.-M.; Mitchell, P.; Wong, T.Y. Impact of Diabetic Retinopathy on Vision-Specific Function. Ophthalmology 2010, 117, 757–765.
4. Fenwick, E.K.; Pesudovs, K.; Rees, G.; Dirani, M.; Kawasaki, R.; Wong, T.Y.; Lamoureux, E.L. The Impact of Diabetic Retinopathy: Understanding the Patient's Perspective. Br. J. Ophthalmol. 2011, 95, 774–782.
5. Shi, R.; Chen, L.; Wang, W.; Deng, Y.; Liu, Y.; Zhou, H.; Lin, R. Plasma MiR-26a-5p Is a Biomarker for Retinal Neurodegeneration of Early Diabetic Retinopathy. Eye 2021, 35, 1587–1599.
6. Coyne, K.S.; Margolis, M.K.; Kennedy-Martin, T.; Baker, T.M.; Klein, R.; Paul, M.D.; Revicki, D.A. The Impact of Diabetic Retinopathy: Perspectives from Patient Focus Groups. Fam. Pract. 2004, 21, 447–453.

7. Watkinson, S.; Seewoodhary, R. Ocular Complications Associated with Diabetes Mellitus. Nurs. Stand. 2008, 22, 51–57, quiz 58, 60.
8. Stitt, A.W.; Lois, N.; Medina, R.J.; Adamson, P.; Curtis, T.M. Advances in Our Understanding of Diabetic Retinopathy. Clin. Sci. 2013, 125, 1–17.
9. Duh, E.J.; Sun, J.K.; Stitt, A.W. Diabetic Retinopathy: Current Understanding, Mechanisms, and Treatment Strategies. JCI Insight 2017, 2, e93751.
10. Stitt, A.W.; Curtis, T.M.; Chen, M.; Medina, R.J.; McKay, G.J.; Jenkins, A.; Gardiner, T.A.; Lyons, T.J.; Hammes, H.-P.; Simó, R. The Progress in Understanding and Treatment of Diabetic Retinopathy. Prog. Retin. Eye Res. 2016, 51, 156–186.
11. Meyerle, C.B.; Chew, E.Y.; Ferris, F.L. Nonproliferative Diabetic Retinopathy. In Diabetic Retinopathy; Duh, E.J., Ed.; Humana Press: Totowa, NJ, USA, 2008; pp. 3–27. ISBN 978-1-934115-83-1.
12. Isner, J.M.; Asahara, T. Angiogenesis and Vasculogenesis as Therapeutic Strategies for Postnatal Neovascularization. J. Clin. Investig. 1999, 103, 1231–1236.
13. Crawford, T.N.; Alfaro, D.V., 3rd; Kerrison, J.B.; Jablon, E.P. Diabetic Retinopathy and Angiogenesis. Curr. Diabetes Rev. 2009, 5, 8–13.
14. Capitão, M.; Soares, R. Angiogenesis and Inflammation Crosstalk in Diabetic Retinopathy. J. Cell. Biochem. 2016, 117, 2443–2453.
15. Gupta, N.; Mansoor, S.; Sharma, A.; Sapkal, A.; Sheth, J.; Falatoonzadeh, P.; Kuppermann, B.; Kenney, M. Diabetic Retinopathy and VEGF. Open Ophthalmol. J. 2013, 7, 4–10.
16. Campbell, M.; Doyle, S.L. Current Perspectives on Established and Novel Therapies for Pathological Neovascularization in Retinal Disease. Biochem. Pharmacol. 2019, 164, 321–325.
17. Praidou, A.; Androudi, S.; Brazitikos, P.; Karakiulakis, G.; Papakonstantinou, E.; Dimitrakos, S. Angiogenic Growth Factors and Their Inhibitors in Diabetic Retinopathy. Curr. Diabetes Rev. 2010, 6, 304–312.
18. Barber, A.J.; Lieth, E.; Khin, S.A.; Antonetti, D.A.; Buchanan, A.G.; Gardner, T.W. Neural Apoptosis in the Retina during Experimental and Human Diabetes. J. Clin. Investig. 1998, 102, 783–791.
19. Kern, T.S.; Barber, A.J. Retinal Ganglion Cells in Diabetes. J. Physiol. 2008, 586, 4401–4408.
20. Mohamed, Q.; Gillies, M.C.; Wong, T.Y. Management of Diabetic Retinopathy: A Systematic Review. JAMA 2007, 298, 902–916.
21. Fong, D.S.; Girach, A.; Boney, A. Visual Side Effects of Successful Scatter Laser Photocoagulation Surgery for Proliferative Diabetic Retinopathy: A Literature Review. Retina

2007, 27, 816–824.

22. Gross, J.G.; Glassman, A.R.; Jampol, L.M.; Inusah, S.; Aiello, L.P.; Antoszyk, A.N.; Baker, C.W.; Berger, B.B.; Bressler, N.M.; Browning, D. Panretinal Photocoagulation vs Intravitreous Ranibizumab for Proliferative Diabetic Retinopathy: A Randomized Clinical Trial. JAMA 2015, 314, 2137–2146.
23. Sivaprasad, S.; Prevost, A.T.; Vasconcelos, J.C.; Riddell, A.; Murphy, C.; Kelly, J.; Bainbridge, J.; Tudor-Edwards, R.; Hopkins, D.; Hykin, P. Clinical Efficacy of Intravitreal Aflibercept versus Panretinal Photocoagulation for Best Corrected Visual Acuity in Patients with Proliferative Diabetic Retinopathy at 52 Weeks (CLARITY): A Multicentre, Single-Blinded, Randomised, Controlled, Phase 2b, Non-Inferiority Trial. Lancet 2017, 389, 2193–2203.
24. Preti, R.C.; Ramirez, L.M.; Monteiro, M.L.; Carra, M.K.; Pelayes, D.E.; Takahashi, W.Y. Contrast Sensitivity Evaluation in High Risk Proliferative Diabetic Retinopathy Treated with Panretinal Photocoagulation Associated or Not with Intravitreal Bevacizumab Injections: A Randomised Clinical Trial. Br. J. Ophthalmol. 2013, 97, 885–889.
25. McCannel, C.A. Meta-Analysis of Endophthalmitis after Intravitreal Injection of Anti-Vascular Endothelial Growth Factor Agents: Causative Organisms and Possible Prevention Strategies. Retina 2011, 31, 654–661.
26. Wubben, T.J.; Johnson, M.W. Anti-Vascular Endothelial Growth Factor Therapy for Diabetic Retinopathy: Consequences of Inadvertent Treatment Interruptions. Am. J. Ophthalmol. 2019, 204, 13–18.
27. Zehden, J.A.; Mortensen, X.M.; Reddy, A.; Zhang, A.Y. Systemic and Ocular Adverse Events with Intravitreal Anti-VEGF Therapy Used in the Treatment of Diabetic Retinopathy: A Review. Curr. Diabetes Rep. 2022, 22, 525–536.
28. Gonzalez, V.H.; Campbell, J.; Holekamp, N.M.; Kiss, S.; Loewenstein, A.; Augustin, A.J.; Ma, J.; Ho, A.C.; Patel, V.; Whitcup, S.M. Early and Long-Term Responses to Anti-Vascular Endothelial Growth Factor Therapy in Diabetic Macular Edema: Analysis of Protocol I Data. Am. J. Ophthalmol. 2016, 172, 72–79.
29. Faselis, C.; Katsimardou, A.; Imprialos, K.; Deligkaris, P.; Kallistratos, M.; Dimitriadis, K. Microvascular Complications of Type 2 Diabetes Mellitus. Curr. Vasc. Pharmacol. 2020, 18, 117–124.
30. Tesfaye, S.; Selvarajah, D. Advances in the Epidemiology, Pathogenesis and Management of Diabetic Peripheral Neuropathy: Advances in Epidemiology, Pathogenesis and Management of DPN. Diabetes Metab. Res. Rev. 2012, 28, 8–14.
31. Iqbal, Z.; Azmi, S.; Yadav, R.; Ferdousi, M.; Kumar, M.; Cuthbertson, D.J.; Lim, J.; Malik, R.A.; Alam, U. Diabetic Peripheral Neuropathy: Epidemiology, Diagnosis, and Pharmacotherapy. Clin.

Ther. 2018, 40, 828–849.

32. Gandhi, M.; Fargo, E.; Prasad-Reddy, L.; Mahoney, K.M.; Isaacs, D. Diabetes: How to Manage Diabetic Peripheral Neuropathy. Drugs Context 2022, 11, 1–13.
33. Nitta, K.; Masakane, I.; Hanafusa, N.; Taniguchi, M.; Hasegawa, T.; Nakai, S.; Goto, S.; Wada, A.; Hamano, T.; Hoshino, J.; et al. Annual Dialysis Data Report 2017, JSDT Renal Data Registry. Ren. Replace. Ther. 2019, 5, 53.
34. Rossing, K.; Christensen, P.K.; Hovind, P.; Tarnow, L.; Rossing, P.; Parving, H.-H. Progression of Nephropathy in Type 2 Diabetic Patients. Kidney Int. 2004, 66, 1596–1605.
35. Sagoo, M.K.; Gnudi, L. Diabetic Nephropathy: An Overview. In Diabetic Nephropathy; Gnudi, L., Long, D.A., Eds.; Methods in Molecular Biology; Springer: New York, NY, USA, 2020; Volume 2067, pp. 3–7. ISBN 978-1-4939-9840-1.
36. Nakhoul, F.; Nakhoul, N.; Asleh, R.; Miller-Lotan, R.; Levy, A.P. Is the Hp 2-2 Diabetic Mouse Model a Good Model to Study Diabetic Nephropathy? Diabetes Res. Clin. Pract. 2013, 100, 289–297.
37. Gnudi, L.; Gentile, G.; Ruggenenti, P. The Patient with Diabetes Mellitus. In Oxford Textbook of Clinical Nephrology; Turner, N., Lameire, N., Goldsmith, D.J., Winearls, C.G., Himmelfarb, J., Remuzzi, G., Eds.; Oxford University Press: Oxford, UK, 2015; pp. 1199–1247. ISBN 978-0-19-959254-8.
38. Jia, G.; Hill, M.A.; Sowers, J.R. Diabetic Cardiomyopathy: An Update of Mechanisms Contributing to This Clinical Entity. Circ. Res. 2018, 122, 624–638.
39. Wagenknecht, L.E.; Zaccaro, D.; Espeland, M.A.; Karter, A.J.; O'Leary, D.H.; Haffner, S.M. Diabetes and Progression of Carotid Atherosclerosis: The Insulin Resistance Atherosclerosis Study. Arterioscler. Thromb. Vasc. Biol. 2003, 23, 1035–1041.
40. Folsom, A.R.; Rasmussen, M.L.; Chambless, L.E.; Howard, G.; Cooper, L.S.; Schmidt, M.I.; Heiss, G. Prospective Associations of Fasting Insulin, Body Fat Distribution, and Diabetes with Risk of Ischemic Stroke. The Atherosclerosis Risk in Communities (ARIC) Study Investigators. Diabetes Care 1999, 22, 1077–1083.
41. Ergul, A.; Kelly-Cobbs, A.; Abdalla, M.; Fagan, S.C. Cerebrovascular Complications of Diabetes: Focus on Stroke. Endocrine Metab. Immune Disord.-Drug Targets 2012, 12, 148–158.
42. Lusis, A.J. Atherosclerosis. Nature 2000, 407, 233–241.
43. Borghetti, G.; von Lewinski, D.; Eaton, D.M.; Sourij, H.; Houser, S.R.; Wallner, M. Diabetic Cardiomyopathy: Current and Future Therapies. Beyond Glycemic Control. Front. Physiol. 2018, 9, 1514.

44. Westermeier, F.; Riquelme, J.A.; Pavez, M.; Garrido, V.; Díaz, A.; Verdejo, H.E.; Castro, P.F.; García, L.; Lavandero, S. New Molecular Insights of Insulin in Diabetic Cardiomyopathy. Front. Physiol. 2016, 7, 125.
45. Dal Canto, E.; Ceriello, A.; Rydén, L.; Ferrini, M.; Hansen, T.B.; Schnell, O.; Standl, E.; Beulens, J.W. Diabetes as a Cardiovascular Risk Factor: An Overview of Global Trends of Macro and Micro Vascular Complications. Eur. J. Prev. Cardiol. 2019, 26, 25–32.
46. O'Donnell, M.J.; Xavier, D.; Liu, L.; Zhang, H.; Chin, S.L.; Rao-Melacini, P.; Rangarajan, S.; Islam, S.; Pais, P.; McQueen, M.J.; et al. Risk Factors for Ischaemic and Intracerebral Haemorrhagic Stroke in 22 Countries (the INTERSTROKE Study): A Case-Control Study. Lancet 2010, 376, 112–123.
47. Lau, L.; Lew, J.; Borschmann, K.; Thijs, V.; Ekinci, E.I. Prevalence of Diabetes and Its Effects on Stroke Outcomes: A Meta-analysis and Literature Review. J. Diabetes Investig. 2019, 10, 780–792.
48. Mankovsky, B.N.; Ziegler, D. Stroke in Patients with Diabetes Mellitus. Diabetes Metab. Res. Rev. 2004, 20, 268–287.
49. Tun, N.N.; Arunagirinathan, G.; Munshi, S.K.; Pappachan, J.M. Diabetes Mellitus and Stroke: A Clinical Update. World J. Diabetes 2017, 8, 235.
50. Zinman, B.; Wanner, C.; Lachin, J.M.; Fitchett, D.; Bluhmki, E.; Hantel, S.; Mattheus, M.; Devins, T.; Johansen, O.E.; Woerle, H.J.; et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N. Engl. J. Med. 2015, 373, 2117–2128.
51. Zhou, Y.; Huang, Y.; Ji, X.; Wang, X.; Shen, L.; Wang, Y. Pioglitazone for the Primary and Secondary Prevention of Cardiovascular and Renal Outcomes in Patients with or at High Risk of Type 2 Diabetes Mellitus: A Meta-Analysis. J. Clin. Endocrinol. Metab. 2020, 105, 1670–1681.
52. Committee, C.S. A Randomised, Blinded, Trial of Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE). Lancet 1996, 348, 1329–1339.
53. Dormandy, J.A.; Charbonnel, B.; Eckland, D.J.; Erdmann, E.; Massi-Benedetti, M.; Moules, I.K.; Skene, A.M.; Tan, M.H.; Lefèbvre, P.J.; Murray, G.D.; et al. Secondary Prevention of Macrovascular Events in Patients with Type 2 Diabetes in the PROactive Study (PROspective PioglitAzone Clinical Trial in MacroVascular Events): A Randomised Controlled Trial. Lancet 2005, 366, 1279–1289.