Aditi et al., Pharmaceut Anal Acta 2013, 4:10
DOI: 10.4172/2153-2435.1000273

Pharmaceutica Analytica Acta

Review Article Open Access

An Insight in to the Pathogenesis of Diabetic Vascular Diseases: Role of Oxidative Stress and Antioxidants

Aditi[1], Nipun Mahajan[2], Shruti Rawal[3] and Rajesh Katare[3]*

[1]Department of Pharmacology, Lovely School of Pharmaceutical Sciences, Lovely Professional University, Punjab, India
[2]Nipun Mahajan, School of Chemistry, National University of Ireland, Galway, Ireland
[3]Department of Physiology, Otago School of Medical Sciences, University of Otago, New Zealand

Abstract

The profound effects of hyperglycaemia on the vascular tree are the major causes of morbidity and mortality among patients suffering from diabetes. Diabetic Vascular Diseases (DVD) includes accelerated forms of atherosclerosis due to endothelial dysfunction and microangiopathy of retinal vessels. A host of several studies indicate that increased oxidative stress play a pivotal role in the development and progression of diabetic vascular diseases. The metabolic abnormalities due to oxidative stress are linked to the structural and functional changes in the vasculature, consequently resulting in atherosclerosis and diabetic retinopathy. Oxidative stress brings alterations in downstream transcription factors which result in changes in gene expression, myocardial substrate utilization, myocyte growth, endothelial function and myocardial compliance. Based on this, an approach towards investigating new and effective antioxidant therapies could serve as potential therapeutic implications in preventing the deleterious effects of oxidative stress on vasculature.

This review aims to understand the underlying mechanisms involved in the pathogenesis of vascular complications in diabetes with special emphasis on the role of oxidative stress towards development of these complications and also describe the role of antioxidants as therapeutic interventions for DVD.

Keywords: Hyperglycaemia; Oxidative stress; Endothelial dysfunction; Atherosclerosis; Diabetic retinopathy

Introduction

Diabetes mellitus is a metabolic disorder, characterized by defective or deficient insulin secretory process, glucose underutilization and increased blood sugar. It is congenital or acquired inability to transport sugar from blood stream into the cells. Multiple etiologies have been found which segregates diabetes into two major forms: Type I or insulin dependent diabetes mellitus (IDDM) and Type II or non-insulin dependent diabetes mellitus (NIDDM) [1]. Type I diabetes is an autoimmune disease in which patient's immune system react against islet antigens and destroy the beta cell. Type II diabetes is a polygenic syndrome characterized by insulin resistance with more severe β-cell deficiency [1]. Both the types are associated with characteristic long term complications. The number of people with diabetes is increasing rapidly due to aging population, growth of population size, urbanization and high prevalence of obesity and sedentary lifestyle [2]. As per International Diabetes Federation, about 365 million people suffered from diabetes in 2011 and this number is expected to rise upto 552 million by 2030 [3].

Diabetic vascular diseases (DVD) are the most serious microvascular and macrovascular complications of diabetes. Vascular complications in diabetes include accelerated forms of atherosclerosis due to endothelial dysfunction and microangiopathy of retinal vessels. The underlying molecular mechanisms for DVD are still debatable but hyperglycaemia-induced oxidative stress has been proposed as the major precipitating factor in various studies [4-6].

This review article highlights the molecular mechanisms behind the development of vascular complications in diabetes with main focus on the role of oxidative stress as well as the implication of antioxidants for the prevention of DVD.

Metabolic Status in Diabetes

The metabolic effects of insulin is closely related to its effect on the vascular system, such that the effect of insulin on the endothelium augments its metabolic effect [7]. The major role of insulin in the vascular system is to stimulate the production of endothelial derived Nitric Oxide (NO) which mediates vasodilation [8]. In normal circumstances, insulin mediated activation of insulin receptors in the endothelium and glucose processing organs such as adipose tissue and skeletal muscle, leads to a activation of downstream signaling pathways.

Initially phosphorylation of Insulin Receptor Substrate (IRS) activates phosphotidylinositol-3-kinase (PI3K) [9], which then generates phosphotidylinositol-3,4,5-triphosphate (PIP3). PIP3 becomes phosphorylated to activate a serine kinase phosphoinositide-dependent kinase (PDK) which ultimately activates Akt, a serine/threonine protein kinase. Akt directly phosphorylate endothelial NO synthase (eNOS) in the endothelium and GLUT-4 translocation in glucose processing organs [10], leading to vasodilation which facilitates the glucose uptake. Alteration in insulin signaling along with other metabolic disturbances such as increase in the levels of free fatty acids (FFA) causes inhibition of IRS phosphorylation, thereby inhibiting the downstream signaling and ultimately causing endothelial dysfunction and insulin resistance, as shown in Figure 1 [11].

***Corresponding author:** Rajesh Katare, Department of Physiology Heart Otago, Otago School of Medical Sciences, University of Otago, New Zealand, Tel: +64-3-4797292; Fax: +64-3-4797323; E-mail: rajesh.katare@otago.ac.nz

Received October 18, 2013; **Accepted** November 25, 2013; **Published** November 27, 2013

Citation: Aditi, Mahajan N, Rawal S, Katare R (2013) An Insight in to the Pathogenesis of Diabetic Vascular Diseases: Role of Oxidative Stress and Antioxidants. Pharmaceut Anal Acta 4: 273. doi: 10.4172/2153-2435.1000273

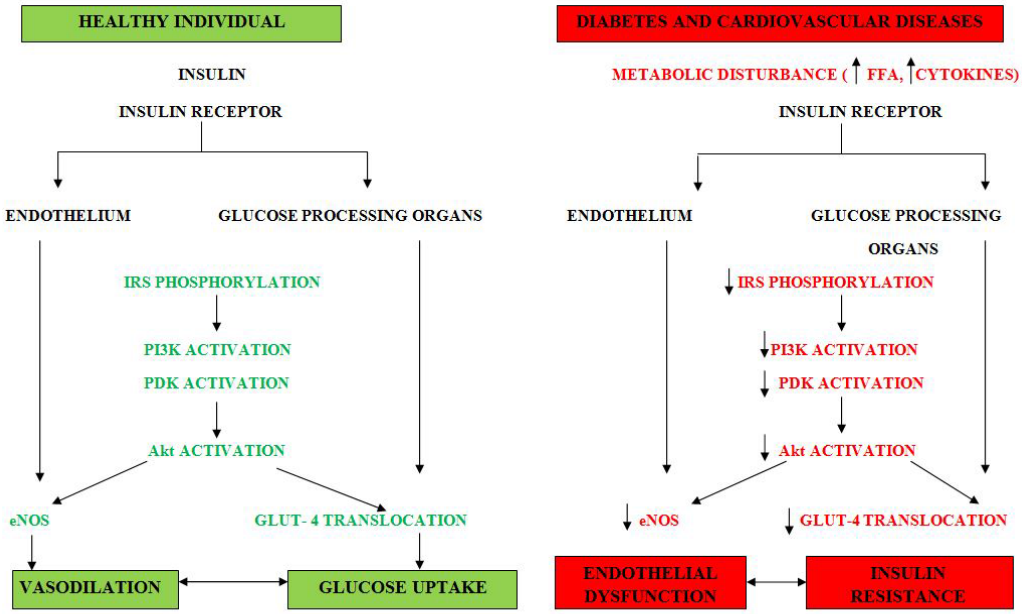

Figure 1: Altered metabolic status and endothelial dysfunction in diabetes.

Complications in Diabetes

In chronic hyperglycaemia, the sugar that normally serves as substrate, fuel and signal takes on the darker role of toxin [12] and is the major cause of the harmful effects of diabetes on various tissues of body [13]. The deleterious effects include macrovascular complications such as coronary artery disease, stroke and peripheral artery disease and microvascular complications such as retinopathy, nephropathy and neuropathy [14,15].

Vascular Complications in Diabetes

Among the several listed complications, effects of diabetes on the vascular tree are the major causes of mortality and morbidity in both types of diabetes. In light of this fact, it becomes more important to understand the relation between diabetes and vascular diseases. The vascular complications of diabetes include accelerated forms of atherosclerosis, increased risk of myocardial infarction, stroke and microangiopathy of renal and retinal vessels [16].

The central pathogenic mechanism for the vascular complications is the process of atherosclerosis which serves as a major risk factor for myocardial infarction, ischemic heart disease and stroke. Diabetes, as a metabolic syndrome, leads to abdominal obesity and hyperlipidemia which in turn promote vascular complications independent of atherosclerosis [17]. Finally, high glucose in diabetes can itself directly affect the myocardium and hence an independent cause of heart failure [18,19]. Recent clinical studies demonstrated that the risk of myocardial infarction (MI) in people with diabetes is equivalent to risk in non-diabetics with a previous history of MI [20]. In view of such facts American Heart Association and American Diabetes Association has recommended that diabetes should be considered as coronary artery disease risk equivalent rather than a risk factor [21].

Risk of stroke related dementia and stroke related mortality is also elevated in diabetic patients [22]. The DCCT trial demonstrated 42% risk reduction in all cardiovascular events and 57% reduction in stroke and death from CVD following intensive treatment of Type I diabetic patients [23].

Besides these macrovascualr complications, microvascualr complications involving smaller blood vessels like renal and retinal vasculature result in equally devastating consequences. Retinal complications termed as retinopathy, eventually leading to blindness, and begins to develop as early as seven years before the clinical diagnosis of diabetes and thus is the earliest complication of diabetes [24]. Evidences suggest that incidence of diabetic retinopathy can be reduced in 90% of the cases with early treatment [25].

Cardiovascular Complications in Diabetes

Cardiovascular diseases accounts for upto 80% of premature mortality in diabetic patients [26]. The major cardiovascular diseases related to diabetes include atherosclerosis which is a major risk factor for Coronary Artery Disease (CAD) [27]. Enhanced myocardial dysfunction in diabetes leads to accelerated heart failure independent of CAD and is more specifically termed as diabetic cardiomyopathy [28]. In addition prolonged hypertension, chronic uncontrolled hyperglycemia, microvascular diseases, glycosylation of myocardial protein and autonomic neuropathy aggravate the development of congestive heart failure in diabetic heart [29].

The cardiovascular complications of diabetes were earlier considered to be caused by slowly progressing structural changes. But with the emergence of modern techniques, it is now clear that cardiac dysfunction occurs soon after the development of metabolic abnormalities and much before the development of any structural changes. This suggest that complex events occurring at cellular and molecular level plays a major role in the development of cardiovascular dysfunction in diabetes [30,31].

Retinal Complications in Diabetes

Diabetic retinopathy is the most common and tissue specific

microvascular complication of diabetes. Its effect as impairment of vision is well established but its importance beyond visual impairment remains to be explored. Studies reveal that people with diabetic retinopathy have high risk of developing systemic vascular complications like CAD, heart failure and nephropathy which is attributed to a common genetic link between retinopathy and other systemic vascular complications [32-34].

Vascular and neuronal degeneration are the prime changes that manifest themselves as diabetic retinopathy [35,36]. The features of diabetic retinopathy include increase in vascular permeability, neovascularisation, retinal cell apoptosis and leukocyte adhesion [37,38].

Several factors like accumulation of advanced glycation end products (AGE), polyol pathway, Protein kinase C activation, increased expression of growth factors and oxidative stress have been implicated in the pathogenesis of diabetic retinopathy [24]. Out of these, oxidative stress plays a crucial role in mediating the vascular dysfunction associated with diabetic retinal changes [39,40].

9. Role of Oxidative Stress in Diabetic Vascular Complications

Oxidative stress is defined as excess formation or insufficient removal of highly reactive molecules such as reactive oxygen species (ROS) and reactive nitrogen species (RNS) which includes free radicals such as superoxide (O_2-), hydroxyl (OH•), peroxyl (•RO_2), hydroperoxyl (•HRO_2-) as well as non-radical species such as hydrogen peroxide (H_2O_2) and hypochlorous acid (HOCl) [41]. ROS generated under physiological conditions is required for cell signalling and defence mechanisms but excess generation of ROS play an important role in the pathological event. In diabetes, ROS is the major determinant for the poor prognosis of vascular complications [42]. The molecular alterations leading to increased ROS/RNS production include increased expression of NADPH oxidase, formation of advanced glycation end products (AGEs) and activation of protein kinase-C, endothelial nitric oxide synthase uncoupling (eNOS) and polyol pathway [42,43]. Overproduction of ROS/RNS cause damage to cell structures, nucleic acid, lipids and proteins [44,45]. Oxidative stress can also result in damage to protein transporters, increase the concentration of intracellular calcium and lipid peroxidation [46]. These events lead to activation of stress sensitive pathways like NF-κB, p38-MAPK, JNK/SAPK that are ultimately responsible for insulin resistance, β-cell dysfunction and other diabetic complications, shown in Figure 1. These events are further augmented by the marked reduction in the endogenous antioxidants systems such as SOD, glutathione (GSH) and catalase [47-49].

Oxidative Stress Mediated Endothelial Dysfunction

Endothelial dysfunction is the prime manifestation of vascular complications in diabetes [50]. It involves the loss of activity of NO, leading to increase in the activity of NF-κB, that causes increased production of chemokines and cytokines which are ultimately responsible for atherosclerotic changes [51]. Besides mediating vasodilation, NO also cause inhibition of monocyte adhesion, inhibition of vascular smooth muscle cell proliferation, inhibition of platelet adhesion and activation of intrinsic coagulation pathway [52]. All these factors have an important role in the pathogenesis of atherosclerosis [53]. Therefore, decreased production of NO in diabetes is one of the major molecular factor leading to vascular complications.

Diabetes induced oxidative stress further deteriorates the situation as excess superoxide radical react with available NO, thereby generating cytotoxic peroxynitrite (ONOO-) [54]. Formation of peroxynitrite inturn inactivates NO leading to decreased NO as explained above [52]. In addition to the inactivation of NO, ONOO-also alters the function of other biomolecules by mediating protein nitration and lipid peroxidation. Protein nitration inhibits potassium channels that normally mediate vascular relaxation [55]. ONOO-further causes oxidation of tetrahydrobiopterin, which is a cofactor for nitric oxide synthase (NOS). This leads to uncoupling of NOS which then produces superoxide radical instead of NO, thereby leading to increased risk of vascular complications [56]. In addition to superoxide radical, increased production of hydrogen peroxide by high glucose leads to apoptosis and pathological angiogenesis in endothelial cells [57].

Pro-atherosclerotic Effects of Oxidative Stress

Beside oxidative stress, dyslipidemia is also a common metabolic disturbance associated with diabetes, as 97% of diabetics are dyslipidemic [58-60]. Atherogenic dyslipidemia, is characterised by increased levels of very low density lipoprotein (VLDL), low density lipoprotein (LDL) and decreased high density lipoprotein (HDL) [61,62].

Oxidative stress due to diabetes leads to oxidation of the LDL particles, producing oxidized LDL which are pro-atherogenic, and behave as foreign particle to the immune system. It thus, produces abnormal biological response leading to plaque formation (Figure 2), in atherosclerosis and other associated vascular dysfunctions in diabetes [63,64].

Oxidation of LDL particles also leads to loss of recognition by cellular LDL receptors and these are preferentially taken up by vascular wall macrophages. As a result, the vascular cell become lipid-laden that leads to atherosclerotic lesions in early stage. In the later stages, the fatty streaks originate in the arteries and causes arterial insufficiency and occlusion [65]. It is well demonstrated that patients with diabetes have lipid rich atherosclerotic plaque that is more vulnerable to rupture than the plaque found in those without diabetes [66].

Oxidative stress in diabetes increases the formation of AGE (vide infra) [67], which in turn leads to glycation of LDL and HDL particles that eventually changes the half-life of LDL and HDL. Increase in half-life of LDL increases its pro-atherogenic potential and decrease in half-life of HDL decreases its protective effect against atherogenesis [68-70] (Figure 3).

Oxidative Stress in the Development of Microangiopathy

Retinopathy is the common clinical implication due to diabetes induced microangiopathy. Increased production of AGE and its expression on its receptor RAGE in retinal microvasculature in people with diabetes leads to increased protein kinase C (PKC) [71,72]. This PKC increase the oxidative stress in retina which in turn increases the accumulation of AGE in retinal microvasculature [67]. This positive feedback system leads to consequences such as retinal cell apoptosis, neovascularisation, activation of NF-κB, microaneurysm and loss of pericytes [71,73]. Reduced histological changes of retinopathy following treatment with aminoguanidine, an AGE inhibitor further confirms the crucial role of AGE in the development of diabetic microangiopathy [74,75].

Activation of PKC, is one of the major pathway implicated in the pathogenesis of diabetic microangiopathy [76]. In addition to being activated by increased accumulation of AGE, PKC is also activated by diacyl glycerol (DAG), which has been shown to be markedly increased in diabetes [77,78]. Increased DAG levels activate several isoforms of

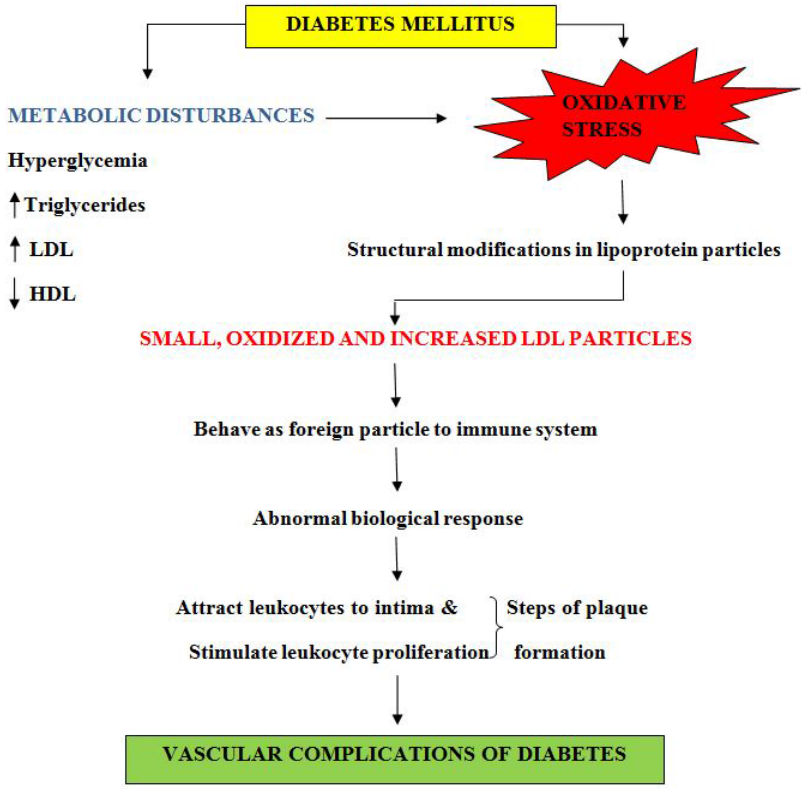

Figure 2: Atherogenic dyslipidemia in diabetes leading to vascular complications and involvement of oxidative stress.

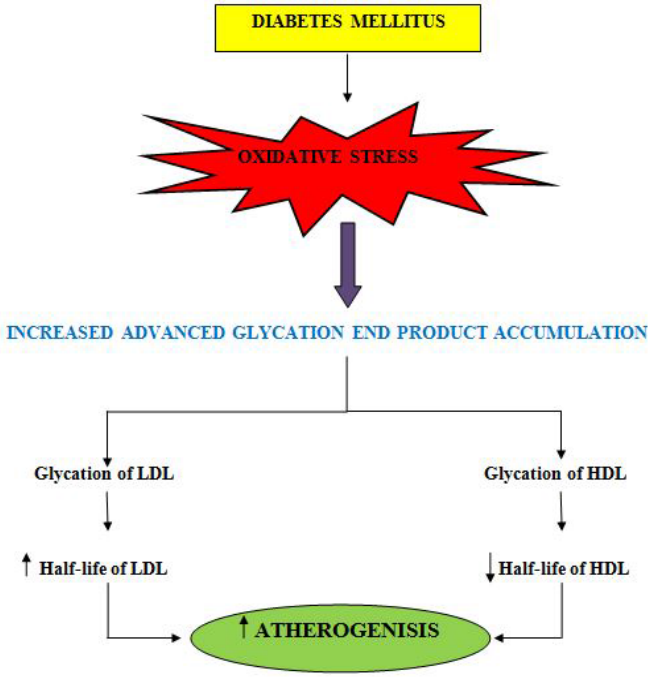

Figure 3: Role of glycation of lipoproteins in the etiology of atherosclerosis and the involvement of oxidative stress.

PKC, among which PKC-β is the major one activated in vasculature and retina [76]. PKC isoform regulates vascular permeability, blood flow and neovascularisation and increased PKC activation can therefore lead to changes such as increase in permeability of retinal vessel, neovascularisation and endothelial proliferation [79,80].

Oxidative stress also induces microangiopathy through indirect mechanisms like increased expression of vascular endothelial growth factor (VEGF), a proangiogenic factor as observed in diabetic retinopathy [81]. Physiologically, VEGF has a key role in embryonic and early postnatal vasculogenesis and angiogenesis. In adults, it occurs at several sites in the vascular bed and is a potent vasodilator. It has the capacity to promote formation of collateral vessels that has role in ischemic injury and wound healing [82]. In the pathological states such as oxidative stress, the physiological roles of VEGF take the darker side and its excess activation leads to consequences like hyperpermeability of retinal membrane, angiogenesis [83]. These changes are responsible for visual loss in case of diabetic retinopathy (Figure 4).

In addition to retinopathy, we recently demonstrated diabetes induced microangiopathy in the bone marrow due to increased intracellular oxidative stress [84]. Bone marrow microangiopathy lead to the endothelial cell dysfunction, leaky endothelial cell barrier, thereby affecting the survival of bone marrow stem cells. Treating the diabetic animals with anti-oxidant Benfotiamine markedly reduced the microangiopathy, thereby confirming the role of oxidative stress in the development of microangiopathy [84]. Further, we also demonstrated that diabetes induces bone marrow endothelial cells barrier dysfunction through activation of RhoA-Rho-assocaited kinase pathway, a potent activator of oxidative stress [85].

These evidences provide a clear role for oxidative stress in the development of diabetes induced microangiopathy, thereby suggesting the potential therapeutic role for anti-oxidants in people with diabetes to prevent or delay the development of vascular complications.

Role of Antioxidants in Preventing DVD

Diabetes has reached epidemic proportion fuelled by an aging population and rapidly increasing obesity. Among the varieties of complications associated with diabetes, vascular complications are the leading cause of death and disability among the people with diabetes [26]. While, by convention, the focus of the drug therapy in diabetes mellitus is on the glycaemic control, there is an urgent need towards addressing the associated complications due to diabetes. Hyperglycaemia-generated ROS appears to be an important element in the genesis of severe diabetic complications including atherosclerosis

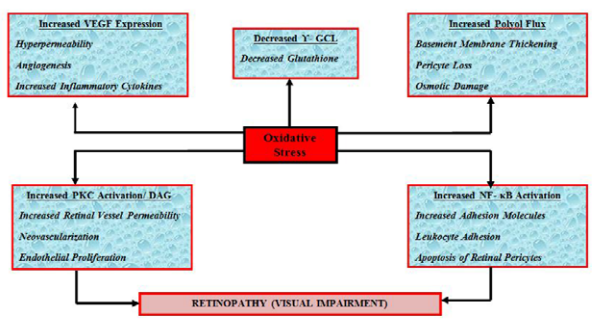

Figure 4: Role of oxidative stress in the development of retinal complications in diabetes.

and microangiopathy. Antioxidants have emerged as an effective therapy in the prevention of DVD. Besides their role in inhibiting the activity of ROS, antioxidants have been reported to exhibit protective effects through various mechanisms [86]. A well-established role of oxidative stress is also supported by the various epidemiological, experimental as well as clinical studies, showing protective effects following long term administration of antioxidants by several mechanisms [79,87-91].

Among various antioxidants reported to exert beneficial effects against diabetic vascular damage, antioxidants such as vitamin C, vitamin E, β-carotene, α-lipoic acid, bioflavonoids, as well as phenolic constituents present in various medicinal plants have been well recognized. Lynch et al. [92] demonstrated the protective role of as Vitamin C in the development of atherosclerosis via inhibition of oxidation of LDL, in addition to its well-recognized role in neutralizing the ROS. Vitamin E supplementation has also been reported to possess beneficial role in preventing and delaying the onset of cardiovascular events in diabetic patients by reducing lipoproteins and reducing the activity of oxidative stress enzymes such as glutathione peroxidise GSH-Px) and glutathione S-transferase (GST) [93,94]. Another natural antioxidant, Rosmarinic acid, has been found to protect aortic endothelial function and structural alterations in diabetic rats by through its anti-inflammatory and antioxidant properties [95].

The antioxidant and anti-atherogenic properties of taurine have been known from past two decades [96,97]. A study by Wang et al. [98] demonstrated the protective effects of Taurine against diabetes-mediated vascular endothelial dysfunction by downregulating the expression of lectin-like oxLDL receptor-1 (LOX-1) a well-known receptor for intercellular adhesion molecule-1 (ICAM-1) in the aorta. In line with these findings, the beneficial role of taurine on diabetic vasculature was extensively evaluated by other experimental and clinical studies [99,100]. Zhu et al. [101] investigated the rescue potential of lycopene, a potent antioxidant compound, in endothelial dysfunction by reducing the oxidative stress, hence indicating its use in preventing DVD associated with endothelial dysfunction.

Ginko biloba, known to be rich in antioxidant constituents is recently reported to exhibit beneficial effects in diabetic retinopathy by improving retinal capillary blood flow rate in type II diabetic individuals [102,103]. Recently, Kumar et al. [104,105] investigated the retinoprotective properties of *Moringa oleifera* in STZ-diabetic rats. *M. oleifera* exhibit its retinoprotective effect via antioxidant, anti-inflammatory, and anti-angiogenic mechanisms, which is attributed to its antioxidant constituents. Similarly, another naturally occurring phenolic antioxidant, Resveratrol, found in wine has been demonstrated to decrease vascular lesions and VEGF induction in retinas of diabetic mice, suggesting its mitigating role in diabetic retinopathy [106]. Citrus fruits are rich in flavanoids that have high antioxidant potential. Hesperetin, a dietary flavanoid, found in many citrus fruits is reported to possess ameliorative effect in diabetes induced vasculopathy via anti-angiogenic mechanism by inhibition in the expression of VEGF and PKC-β [105]. In another study106 these authors also reported the ameliorative effect of hesperetin in diabetic retinopathy via inhibiting retinal oxidative stress, neovascularisation as well as apoptosis in STZ-induced diabetic rats.

In addition to the pharmacological management of oxidative stress to combat the vascular complications of diabetes, recent advances in the understanding of underlying molecular mechanisms has resulted in the development of novel therapies for the treatment of DVD. This includes gene therapy for modulation of pro-survival genes [107] and most recently the therapeutic modulation of microRNAs for the post-

transcriptional regulation of genes involved in the development of DVD [108]. While these studies have provided promising results in the pre-clinical setting, a translation research in larger diabetic population will be required to investigate the therapeutic outcome of these novel therapeutic modalities.

Funding

This work was funded by the project grants from Heart Foundation NZ, Otago Medical Resarch Foundation, Lottery Health NZ and University of Otago Research Grants.

References

1. Del Guerra S, Lupi R, Marselli L, Masini M, Bugliani M, et al. (2005) Functional and molecular defects of pancreatic islets in human type 2 diabetes. Diabetes 54: 727-735.
2. Wild S, Roglic G, Green A, Sicree R, King H (2004) Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care 27: 1047-1053.
3. Whiting DR, Guariguata L, Weil C, Shaw J (2011) IDF diabetes atlas: global estimates of the prevalence of diabetes for 2011 and 2030. Diabetes Res Clin Pract 94: 311-321.
4. Madonna R, De Caterina R (2011) Cellular and molecular mechanisms of vascular injury in diabetes--part I: pathways of vascular disease in diabetes. Vascul Pharmacol 54: 68-74.
5. Pitocco D, Tesauro M, Alessandro R, Ghirlanda G, Cardillo C (2013) Oxidative stress in diabetes: implications for vascular and other complications. Int J Mol Sci 14: 21525-21550.
6. Fiorentino TV, Prioletta A, Zuo P, Folli F (2013) Hyperglycemia-induced oxidative stress and its role in diabetes mellitus related cardiovascular diseases. Curr Pharm Des 19: 5695-5703.
7. Dunger DB (1995) Insulin and insulin-like growth factors in diabetes mellitus. Arch Dis Child 72: 469-471.
8. Baron AD, Clark MG (1997) Role of blood flow in the regulation of muscle glucose uptake. Annu Rev Nutr 17: 487-499.
9. Niswender KD, Morrison CD, Clegg DJ, Olson R, Baskin DG, et al. (2003) Insulin activation of phosphatidylinositol 3-kinase in the hypothalamic arcuate nucleus: a key mediator of insulin-induced anorexia. Diabetes 52: 227-231.
10. Fulton D, Gratton JP, McCabe TJ, Fontana J, Fujio Y, et al. (1999) Regulation of endothelium-derived nitric oxide production by the protein kinase Akt. Nature 399: 597-601.
11. Kim JA, Montagnani M, Koh KK, Quon MJ (2006) Reciprocal relationships between insulin resistance and endothelial dysfunction: Molecular and pathophysiological mechanisms. Circulation113:1888-1904.
12. Bouhanick B, Barigou M, Kantambadouno JB, Chamontin B (2013) Glycaemic control and complications of diabetes: what about?. Presse Med 42: 849-854.
13. Kawahito S, Kitahata H, Oshita S (2009) Problems associated with glucose toxicity: role of hyperglycemia-induced oxidative stress. World J Gastroenterol 15: 4137-4142.
14. Reusch JE (2003) Diabetes, microvascular complications, and cardiovascular complications: what is it about glucose? J Clin Invest 112: 986-988.
15. Yamagishi S, Imaizumi T (2005) Diabetic vascular complications: Pathophysiology, biochemical basis and potential therapeutic strategy. Curr Pharm Des11:2279-2299.
16. Deedwania PC (2004) Diabetes is a vascular disease: the role of endothelial dysfunction in pathophysiology of cardiovascular disease in diabetes. Cardiol Clin 22: 505-509, v.
17. Almdal T, Scharling H, Jensen JS, Vestergaard H (2004) The independent effect of type 2 diabetes mellitus on ischemic heart disease, stroke, and death: a population-based study of 13,000 men and women with 20 years of follow-up. Arch Intern Med 164: 1422-1426.
18. Creager MA, Luscher TF, Cosentino F, Beckman JA (2003) Diabetes and vascular disease: Pathophysiology, clinical consequences, and medical therapy: Part i. Circulation108:1527-1532.
19. Kamalesh M (2007) Heart failure in diabetes and related conditions. J Card Fail 13: 861-873.
20. Kuusisto J, Laakso M (2013) Update on type 2 diabetes as a cardiovascular disease risk equivalent. Curr Cardiol Rep 15: 331.
21. Buse JB, Ginsberg HN, Bakris GL, Clark NG, Costa F, et al.(2007). Primary prevention of cardiovascular diseases in people with diabetes mellitus: A scientific statement from the american heart association and the american diabetes association. Circulation115: 114-126.
22. Beckman JA, Creager MA, Libby P (2002) Diabetes and atherosclerosis: epidemiology, pathophysiology, and management. JAMA 287: 2570-2581.
23. Nathan DM, Cleary PA, Backlund JY, Genuth SM, Lachin JM, et al. (2005) Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N Engl J Med 353: 2643-2653.
24. Fong DS, Aiello L, Gardner TW, King GL, Blankenship G, et al. (2004) Retinopathy in diabetes. Diabetes Care 27 Suppl 1: S84-87.
25. Tapp RJ, Shaw JE, Harper CA, de Courten MP, Balkau B, et al. (2003) The prevalence of and factors associated with diabetic retinopathy in the Australian population. Diabetes Care 26: 1731-1737.
26. Winer N, Sowers JR (2004) Epidemiology of diabetes. J Clin Pharmacol 44: 397-405.
27. Smith JW, Marcus FI, Serokman R (1984) Prognosis of patients with diabetes mellitus after acute myocardial infarction. Am J Cardiol 54: 718-721.
28. Spector KS (1998) Diabetic cardiomyopathy. Clin Cardiol 21: 885-887.
29. Regan TJ (1983) Congestive heart failure in the diabetic. Annu Rev Med 34: 161-168.
30. Katare R, Caporali A, Emanueli C, Madeddu P (2010) Benfotiamine improves functional recovery of the infarcted heart via activation of pro-survival g6pd/akt signaling pathway and modulation of neurohormonal response. Journal of molecular and cellular cardiology 49: 625-638.
31. Katare RG, Caporali A, Oikawa A, Meloni M, Emanueli C, et al. (2010) Vitamin b1 analog benfotiamine prevents diabetes-induced diastolic dysfunction and heart failure through akt/pim-1-mediated survival pathway. Circ Heart Fail 3: 294-305.
32. Cheung N, Wang JJ, Klein R, Couper DJ, Sharrett AR, et al. (2007) Diabetic retinopathy and the risk of coronary heart disease: the Atherosclerosis Risk in Communities Study. Diabetes Care 30: 1742-1746.
33. Cheung N, Wong TY (2008) Diabetic retinopathy and systemic vascular complications. Prog Retin Eye Res 27: 161-176.
34. Cheung N, Rogers S, Couper DJ, Klein R, Sharrett AR, et al. (2007) Is diabetic retinopathy an independent risk factor for ischemic stroke? Stroke 38: 398-401.
35. Ozawa Y, Kurihara T, Sasaki M, Ban N, Yuki K, et al. (2011) Neural degeneration in the retina of the streptozotocin-induced type 1 diabetes model. Exp Diabetes Res 2011: 108328.
36. Sasaki M, Ozawa Y, Kurihara T, Kubota S, Yuki K, et al. (2010) Neurodegenerative influence of oxidative stress in the retina of a murine model of diabetes. Diabetologia 53: 971-979.
37. Al-Shabrawey M, Smith S (2010) Prediction of diabetic retinopathy: role of oxidative stress and relevance of apoptotic biomarkers. EPMA J 1: 56-72.
38. Barber AJ, Gardner TW, Abcouwer SF (2011) The significance of vascular and neural apoptosis to the pathology of diabetic retinopathy. Invest Ophthalmol Vis Sci 52: 1156-1163.
39. Evans JL, Goldfine ID, Maddux BA, Grodsky GM (2002) Oxidative stress and stress-activated signaling pathways: a unifying hypothesis of type 2 diabetes. Endocr Rev 23: 599-622.
40. Pan HZ, Zhang H, Chang D, Li H, Sui H (2008) The change of oxidative stress products in diabetes mellitus and diabetic retinopathy. Br J Ophthalmol 92: 548-551.
41. Apel K, Hirt H (2004) Reactive oxygen species: metabolism, oxidative stress, and signal transduction. Annu Rev Plant Biol 55: 373-399.
42. Johansen JS, Harris AK, Rychly DJ, Ergul A (2005) Oxidative stress and the use of antioxidants in diabetes: linking basic science to clinical practice. Cardiovasc Diabetol 4: 5.

43. DjordjeviÄ‡ VB, ZvezdanoviÄ‡ L, CosiÄ‡ V (2008) Oxidative stress in human diseases. Srp Arh Celok Lek 136 Suppl 2: 158-165.

44. Dandona P, Thusu K, Cook S, Snyder B, Makowski J, et al. (1996) Oxidative damage to DNA in diabetes mellitus. Lancet 347: 444-445.

45. Valko M, Leibfritz D, Moncol J, Cronin MT, Mazur M, et al. (2007) Free radicals and antioxidants in normal physiological functions and human disease. Int J Biochem Cell Biol 39: 44-84.

46. Halliwell B, Chirico S (1993) Lipid peroxidation: its mechanism, measurement, and significance. Am J Clin Nutr 57: 715S-724S.

47. Hashim A, Khan MS, Khan MS, Baig MH, Ahmad S (2013) Antioxidant and Î± -amylase inhibitory property of phyllanthus virgatus L.: an in vitro and molecular interaction study. Biomed Res Int 2013: 729393.

48. Kaul N, Siveski-Iliskovic N, Hill M, Khaper N, Seneviratne C, et al. (1996) Probucol treatment reverses antioxidant and functional deficit in diabetic cardiomyopathy. Mol Cell Biochem 160-161: 283-8.

49. Linke A, Adams V, Schulze PC, Erbs S, Gielen S, et al.(2005) Antioxidative effects of exercise training in patients with chronic heart failure: Increase in radical scavenger enzyme activity in skeletal muscle. Circulation111:1763-1770.

50. Sena CM, Pereira AM, Seiça R (2013) Endothelial dysfunction - A major mediator of diabetic vascular disease. Biochim Biophys Acta 1832: 2216-2231.

51. Kawashima S, Yokoyama M (2004) Dysfunction of endothelial nitric oxide synthase and atherosclerosis. Arterioscler Thromb Vasc Biol 24: 998-1005.

52. Liu VW, Huang PL (2008) Cardiovascular roles of nitric oxide: a review of insights from nitric oxide synthase gene disrupted mice. Cardiovasc Res 77: 19-29.

53. Kawashima S (2004) Malfunction of vascular control in lifestyle-related diseases: endothelial nitric oxide (NO) synthase/NO system in atherosclerosis. J Pharmacol Sci 96: 411-419.

54. Beckman JA, Goldfine AB, Gordon MB, Creager MA (2001) Ascorbate restores endothelium-dependent vasodilation impaired by acute hyperglycemia in humans. Circulation 103: 1618-1623.

55. Turko IV, Marcondes S, Murad F (2001) Diabetes-associated nitration of tyrosine and inactivation of succinyl-CoA:3-oxoacid CoA-transferase. Am J Physiol Heart Circ Physiol 281: H2289-2294.

56. Maritim AC, Sanders RA, Watkins JB 3rd (2003) Diabetes, oxidative stress, and antioxidants: a review. J Biochem Mol Toxicol 17: 24-38.

57. Taniyama Y, Griendling KK (2003) Reactive oxygen species in the vasculature: molecular and cellular mechanisms. Hypertension 42: 1075-1081.

58. Muntner P, DeSalvo KB, Wildman RP, Raggi P, He J, et al. (2006)Trends in the prevalence, awareness, treatment, and control of cardiovascular disease risk factors among noninstitutionalized patients with a history of myocardial infarction and stroke. Am J Epidemiol 163: 913-920.

59. Lewis SJ, Fox KM, Bullano MF, Grandy S; SHIELD Study Group (2009) Knowledge of heart disease risk among SHIELD respondents with dyslipidemia. Circ Cardiovasc Qual Outcomes 2: 207-212.

60. Parhofer KG (2013) Update dyslipidemia. Internist (Berl) 54: 1089-1103.

61. Adiels M, Olofsson SO, Taskinen MR, Borén J (2008) Overproduction of very low-density lipoproteins is the hallmark of the dyslipidemia in the metabolic syndrome. Arterioscler Thromb Vasc Biol 28: 1225-1236.

62. Beliaeva MI (2013) Modern views of causes of microvascular complications development and progression in type 2 diabetes mellitus and peculiarities of their treatment. Vestn Oftalmol 129: 70-75.

63. Levitan I, Volkov S, Subbaiah PV (2010) Oxidized LDL: diversity, patterns of recognition, and pathophysiology. Antioxid Redox Signal 13: 39-75.

64. Matsuura E, Lopez LR (2004) Are oxidized LDL/beta2-glycoprotein I complexes pathogenic antigens in autoimmune-mediated atherosclerosis? Clin Dev Immunol 11: 103-111.

65. Witztum JL (1993) Role of oxidised low density lipoprotein in atherogenesis. Br Heart J 69: S12-18.

66. Moreno PR, Murcia AM, Palacios IF, Leon MN, Bernardi VH, et al. (2000) Coronary composition and macrophage infiltration in atherectomy specimens from patients with diabetes mellitus. Circulation 102: 2180-2184.

67. Bucciarelli LG, Kaneko M, Ananthakrishnan R, Harja E, Lee LK, et al. (2006) Receptor for advanced-glycation end products: key modulator of myocardial ischemic injury. Circulation 113: 1226-1234.

68. Bucala R, Makita Z, Koschinsky T, Cerami A, Vlassara H (1993) Lipid advanced glycosylation: pathway for lipid oxidation in vivo. Proc Natl Acad Sci U S A 90: 6434-6438.

69. Feig JE, Shamir R, Fisher EA (2008) Atheroprotective effects of HDL: beyond reverse cholesterol transport. Curr Drug Targets 9: 196-203.

70. Meurs I, Van Eck M, Van Berkel TJ (2010) High-density lipoprotein: key molecule in cholesterol efflux and the prevention of atherosclerosis. Curr Pharm Des 16: 1445-1467.

71. Stitt AW (2003) The role of advanced glycation in the pathogenesis of diabetic retinopathy. Exp Mol Pathol 75: 95-108.

72. Tan KC, Shiu SW, Chow WS, Leng L, Bucala R, et al. (2006) Association between serum levels of soluble receptor for advanced glycation end products and circulating advanced glycation end products in type 2 diabetes. Diabetologia 49: 2756-2762.

73. Kowluru RA, Koppolu P, Chakrabarti S, Chen S (2003) Diabetes-induced activation of nuclear transcriptional factor in the retina, and its inhibition by antioxidants. Free Radic Res 37: 1169-1180.

74. Hammes HP, Martin S, Federlin K, Geisen K, Brownlee M (1991) Aminoguanidine treatment inhibits the development of experimental diabetic retinopathy. Proc Natl Acad Sci U S A 88: 11555-11558.

75. Luo D, Fan Y, Xu X (2012) The effects of aminoguanidine on retinopathy in STZ-induced diabetic rats. Bioorg Med Chem Lett 22: 4386-4390.

76. Koya D, King GL (1998) Protein kinase C activation and the development of diabetic complications. Diabetes 47: 859-866.

77. Wolf BA, Williamson JR, Easom RA, Chang K, Sherman WR, et al. (1991) Diacylglycerol accumulation and microvascular abnormalities induced by elevated glucose levels. J Clin Invest 87: 31-38.

78. Inoguchi T, Xia P, Kunisaki M, Higashi S, Feener EP, et al. (1994) Insulin's effect on protein kinase C and diacylglycerol induced by diabetes and glucose in vascular tissues. Am J Physiol 267: E369-379.

79. Kowluru RA (2001) Diabetes-induced elevations in retinal oxidative stress, protein kinase C and nitric oxide are interrelated. Acta Diabetol 38: 179-185.

80. Kowluru RA, Tang J, Kern TS (2001) Abnormalities of retinal metabolism in diabetes and experimental galactosemia. VII. Effect of long-term administration of antioxidants on the development of retinopathy. Diabetes 50: 1938-1942.

81. Aiello LP, Wong JS (2000) Role of vascular endothelial growth factor in diabetic vascular complications. Kidney Int Suppl 77: S113-119.

82. Ahluwalia A, Tarnawski AS (2012) Critical role of hypoxia sensor--HIF-1Î± in VEGF gene activation. Implications for angiogenesis and tissue injury healing. Curr Med Chem 19: 90-97.

83. Simó R, Hernández C (2008) Intravitreous anti-VEGF for diabetic retinopathy: hopes and fears for a new therapeutic strategy. Diabetologia 51: 1574-1580.

84. Oikawa A, Siragusa M, Quaini F, Mangialardi G, Katare RG, et al. (2010) Diabetes mellitus induces bone marrow microangiopathy. Arterioscler Thromb Vasc Biol 30: 498-508.

85. Mangialardi G, Katare R, Oikawa A, Meloni M, Reni C, et al. (2013) Diabetes causes bone marrow endothelial barrier dysfunction by activation of the rhoa-rho-associated kinase signaling pathway. Arterioscler Thromb Vasc Biol 33: 555-564.

86. Zatalia SR, Sanusi H (2013) The role of antioxidants in the pathophysiology, complications, and management of diabetes mellitus. Acta Med Indones 45: 141-147.

87. Kunisaki M, Bursell SE, Clermont AC, Ishii H, Ballas LM, et al. (1995) Vitamin E prevents diabetes-induced abnormal retinal blood flow via the diacylglycerol-protein kinase C pathway. Am J Physiol 269: E239-246.

88. Matough FA, Budin SB, Hamid ZA, Alwahaibi N, Mohamed J (2012) The role of oxidative stress and antioxidants in diabetic complications. Sultan Qaboos Univ Med J 12: 5-18.

89. Folli F, Corradi D, Fanti P, Davalli A, Paez A, et al.(2011) The role of oxidative stress in the pathogenesis of type 2 diabetes mellitus micro- and macrovascular

complications: Avenues for a mechanistic-based therapeutic approach. Curr Diabetes Rev 7: 313-324.

90. Xu YJ, Tappia PS, Neki NS, Dhalla NS (2013) Prevention of diabetes-induced cardiovascular complications upon treatment with antioxidants. Heart Fail Rev .

91. Chaturvedi N (2007) The burden of diabetes and its complications: trends and implications for intervention. Diabetes Res Clin Pract 76 Suppl 1: S3-12.

92. Lynch SM, Gaziano JM, Frei B (1996) Ascorbic acid and atherosclerotic cardiovascular disease. Subcell Biochem 25: 331-367.

93. Baburao Jain A, Anand Jain V (2012) Vitamin E, Its Beneficial Role in Diabetes Mellitus (DM) and Its Complications. J Clin Diagn Res 6: 1624-1628.

94. Boshtam M, Rafiei M, Golshadi ID, Ani M, Shirani Z, et al. (2005) Long term effects of oral vitamin e supplement in type ii diabetic patients. International journal for vitamin and nutrition research. Internationale Zeitschrift fur Vitamin- und Ernahrungsforschung. Int J Vitam Nutr Res 75: 341-346.

95. Sotnikova R, Okruhlicova L, Vlkovicova J, Navarova J, Gajdacova B, et al. (2013) Rosmarinic acid administration attenuates diabetes-induced vascular dysfunction of the rat aorta. J Pharm Pharmacol 65: 713-723.

96. Kondo Y, Murakami S, Oda H, Nagate T (2000) Taurine reduces atherosclerotic lesion development in apolipoprotein E-deficient mice. Adv Exp Med Biol 483: 193-202.

97. Petty MA, Kintz J, DiFrancesco GF (1990) The effects of taurine on atherosclerosis development in cholesterol-fed rabbits. Eur J Pharmacol 180: 119-127.

98. Wang LJ, Yu YH, Zhang LG, Wang Y, Niu N, et al. (2008) Taurine rescues vascular endothelial dysfunction in streptozocin-induced diabetic rats: correlated with downregulation of LOX-1 and ICAM-1 expression on aortas. Eur J Pharmacol 597: 75-80.

99. Ikubo N, Saito M, Tsounapi P, Dimitriadis F, Ohmasa F, et al. (2011) Protective effect of taurine on diabetic rat endothelial dysfunction. Biomed Res 32: 187-193.

100. Moloney MA, Casey RG, O'Donnell DH, Fitzgerald P, Thompson C, et al. (2010) Two weeks taurine supplementation reverses endothelial dysfunction in young male type 1 diabetics. Diab Vasc Dis Res7: 300-310.

101. Zhu J, Wang CG, Xu YG (2011) Lycopene attenuates endothelial dysfunction in streptozotocin-induced diabetic rats by reducing oxidative stress. Pharm Biol 49: 1144-1149.

102. Alekseev IB, Kochergin SA, Vorob'eva IV, Mikhaleva LG (2013) On some pathogenic features of diabetic retinopathy in type II diabetes mellitus and the role of antioxidants and ginkgo biloba. Vestn Oftalmol 129: 89-93.

103. Huang SY, Jeng C, Kao SC, Yu JJ, Liu DZ (2004) Improved haemorrheological properties by ginkgo biloba extract (egb 761) in type 2 diabetes mellitus complicated with retinopathy. Clin Nutr 23: 615-621.

104. Kumar B, Gupta SK, Srinivasan BP, Nag TC, Srivastava S, et al. (2012) Hesperetin ameliorates hyperglycemia induced retinal vasculopathy via anti-angiogenic effects in experimental diabetic rats. Vascul Pharmacol 57: 201-207.

105. Kumar B, Gupta SK, Srinivasan BP, Nag TC, Srivastava S, et al. (2013) Hesperetin rescues retinal oxidative stress, neuroinflammation and apoptosis in diabetic rats. Microvasc Res 87: 65-74.

106. Kim YH, Kim YS, Roh GS, Choi WS, Cho GJ (2012) Resveratrol blocks diabetes-induced early vascular lesions and vascular endothelial growth factor induction in mouse retinas. Acta Ophthalmol 90: e31-37.

107. Katare R, Caporali A, Zentilin L, Avolio E, Sala-Newby G, et al. (2011) Intravenous gene therapy with pim-1 via a cardiotropic viral vector halts the progression of diabetic cardiomyopathy through promotion of prosurvival signaling. Circ Res108:1238-1251.

108. Urbich C, Kuehbacher A, Dimmeler S (2008) Role of microRNAs in vascular diseases, inflammation, and angiogenesis. Cardiovasc Res 79: 581-588.