REVIEW

Metabolic Memory in Diabetes – Mechanistic Insights and the Impact of Cardiovascular Medication

Raluca SOSDEAN[1,2,3], Loredana N. IONICA[3,4,*], Adrian P. MERCE[3,5], Danina M. MUNTEAN[3,4], Adrian STURZA[3,4]

ABSTRACT

The prevalence of diabetes mellitus is increasing worldwide. Endothelial dysfunction plays a critical role in the pathophysiology of diabetes-related vascular complications. Several studies have shown that restoring blood glucose levels failed to reduce the incidence of major cardiovascular events in diabetic population, hence confirming the idea of "metabolic/hyperglycemic memory". The major pathomechanism is, most likely, represented by the overproduction of reactive oxygen species (ROS). The purpose of this minireview is to summarize current knowledge about the mechanisms of metabolic memory and the impact of cardiovascular medication on this phenomenon, respectively.

Keywords: diabetes mellitus, metabolic memory, oxidative stress, cardiovascular medication.

REZUMAT

Diabetul zaharat prezintă o creștere alarmantă a prevalenței la nivel mondial. Disfuncția endotelială joacă un rol esențial în patogeneza complicațiilor vasculare ale diabetului zaharat. Mai multe studii au arătat că normalizarea glicemiei nu a reușit să reducă incidența evenimentelor cardiovasculare majore la populația diabetică, confirmând astfel conceptul de „memorie metabolică/ hiperglicemică". Mecanismul de bază incriminat este, cel mai probabil, supraproducția speciilor reactive de oxigen. Scopul acestui articol este de a rezuma cunoștințele actuale despre mecanismele responsabile de memoria metabolică și, respectiv, ale impactului medicației cardiovasculare asupra acestui fenomen.

Cuvinte cheie: diabet zaharat, memorie metabolică, stress oxidativ, medicație cardiovasculară.

INTRODUCTION

Diabetes mellitus (DM) is a major and developing public health concern that is associated with decreased life expectancy and increased morbidity as a consequence of the related complications. DM induces micro- and macrovascular complications that may become evident even after a good glycemic control has been accomplished. This happens mostly through the „metabolic memory" phenomenon. Potential mechanisms responsible for this „memory" include non-enzymatic glycation of cellular proteins and lipids and the increased generation of cellular reactive oxygen and nitrogen species, particularly those originating at the level of glycated mitochondrial proteins, which may act in concert to maintain stress signaling[1]. Intensive glycemia lowering treatment may not be sufficient to prevent these complications especially in patients with diabetes type 2 and severe insulin resistance. Diabetes Control and Complications Trial (DCCT) showed that in type 1 diabetes, where insulin resistance is not dominant, early and intensive insulin treatment led to a significant cardiovascular risk and major cardiac events reduction during the trial and even years after. These results were sustained in the *Epidemiology of Diabetes Interventions and Complications* (EDIC) trial, showing a beneficial impact on the progression to ma-

[1] Department of Cardiology – Cardiology II, „Victor Babes" University of Medicine and Pharmacy, Timisoara, Romania
[2] Research Center for Cardiovascular Diseases, Institute of Cardiovascular Diseases, Timisoara, Romania
[3] Center for Translational Research and Systems Medicine, „Victor Babes" University of Medicine and Pharmacy, Timisoara, Romania
[4] Department of Functional Sciences – Pathophysiology, „Victor Babes" University of Medicine and Pharmacy, Timisoara, Romania
[5] Department of Cardiology – Cardiovascular Surgery, „Victor Babes" University of Medicine and Pharmacy, Timisoara, Romania

Contact address:
Loredana N. IONICA, Department of Functional Sciences – Pathophysiology, Center for Translational Research and Systems Medicine, „Victor Babes" University of Medicine and Pharmacy, 2 Eftimie Murgu Square, 300041, Timisoara, Romania.
E-mail: ionica.loredana@umft.ro

crovascular complications and long- term risk of impaired glomerular filtration rate. On the other hand, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial had an excess in cardiovascular mortality in the intensive treatment arm in patients with diabetes type 2. The explanation may be that in extremely insulin resistant patients, high insulin doses might have a proatherogenic effect because of the loss of liver gluconeogenetic reduction ability along with the maintenance of lipogenesis enhancement ability. This highlights the importance of drugs targeting several points of the metabolic memory pathways.

1. PATHOGENESIS OF METABOLIC MEMORY: THE CLASSIC ENZYMATIC PATHWAYS

Several clinical and epidemiological studies in diabetic patients have shown a close relationship between hyperglycemia and vascular oxidative stress, which contributes to a significant reduction in the bioavailability of nitric oxide (NO)[2]. Chronic hyperglycemia triggers immediate direct biochemical changes in endothelial function and indirect effects via the synthesis of growth factors and vasoactive agents, resulting in vascular permeability alteration.

Furthermore, its deleterious effect is mediated through the activation of a couple of metabolic pathways. The main pathways that have been classically shown to mediate hyperglycemia-induced tissue damage are as follows: increased intracellular formation of the advanced glycation end products (AGEs), increased expression for AGEs' receptors and their activating ligands, activation of protein kinase C (PKC) and overactivity of the hexosamine pathway[3]. In addition, several lines of evidence have indicated that all these mechanisms are triggered by a single upstream event, namely the mitochondrial overproduction of reactive oxygen species (ROS) and the subsequent augmented intracellular oxidative stress[4] (Figure 1).

1.1. The advanced glycation endproducts

One of the mechanisms that is responsible for the accelerated atherosclerosis in diabetes is the non-enzymatic reaction between glucose and proteins or lipoproteins in the arterial wall, with the subsequent formation of advanced glycation endproducts (AGEs)[5].

AGEs are a broad and heterogenous group of compounds generated when a sugar reactive carbonyl group interacts with an amino acid nucleophilic amino group during the classic Maillard reaction. The degree of non- enzymatic glycation is mainly determined by the glucose concentration and the time the tissues are exposed to it[6]. Structures lose some of their properties, such as structural proteins, enzymes and nucleic acids[7]. Also, AGEs have specific membrane receptors (RAGE) on certain types of cells. There are specific types of receptors on the surface of endothelial cells, that binds AGEs. One of the best studied AGE receptor is RAGE8tumor necrosis factor-α (TNF-α. RAGE activation promotes inflammatory responses, apoptosis, expression of adhesion molecules such as VCAM-1, which enhances monocyte attachment and transendothelial migration across the endothelial cell layer, oxidative stress. Evidence suggests that AGEs and the receptor called „RAGE" may be involved in the metabolic memory fenomenon. The interaction between AGE and RAGE causes an increased production of ROS, cytokines such as (interleukin-6) IL-6, (tumor necrosis factor-α) TNF-alfa, growth factors- IGF-1, transforming growth factor beta (TGF b).

Furthermore, Rosca et al demonstrated that glycated mitochondrial respiratory chain complexes were more likely to produce superoxide, regardless of the degree of hyperglycemia[9].

The production of mitochondrial AGE can be an irreversible process and may be responsible for the long-term development of metabolic memory. Importantly, the reversal of hyperglycemia does not reverse the inflammatory process and oxidative stress (which remain high). In the EDIC study, Genuth et al observed that AGEs are long-term indicators of microvascular disease progression with the subsequent progression of diabetic retinopathy[9].

1.2 The protein kinase C system

Another significant change caused by hyperglycemia is the activation of the protein kinase C (PKC) system. Elevated glucose levels induce diacylglycerol de novo synthesis leading to PKC activation, which is considered a major pathway in diabetes mellitus induced vascular remodeling[11].

PKC belongs to the serine-threonine kinase family and is an important cell signal transduction player for various cytokines. Evidence shows that enhanced PKC isoform activity can also result from interactions between AGEs and their cell-surface receptors[12].

Ganz et al demonstrated that overactivity of PKC has been associated with decreased NO production in smooth muscle cells. Furthermore, it has been shown to inhibit insulin-stimulated expression of endothelial NO synthase (eNOS) in cultured endothelial cells[13].

Several lines of evidence have also supported that

PKC activation increases the expression of transforming growth factor beta (TGF-beta), which promotes thickening of the capillary basement membrane, reported to occur in early stages of diabetes. In addition, it promotes vascular endothelial growth factor excess, increasing the production of thromboxane and endothelin-1 (ET-1) and decreases production of prostacyclin[14].

Takagi et al. reported that the expression of endothelin-1 is increased in the retina of diabetic rats and that intravitreous injection of endothelin-1 receptor antagonist prevented the decrease in retinal blood flow in diabetic rats[15]. Moreover, Shiba et al demonstrated that the decrease in retinal blood flow in diabetic rats was normalized by PKC inhibitors[16].

A study of aortic rings in rats with diabetes by Koya et al showed that acetylcholine-dependent relaxation was restored by the addition of PKC inhibitors[17,18].

1.3 The polyol pathway

Normally, most glucose is metabolized by glycolytic and pentose shunt pathways. Under hyperglycemia conditions, the pathways of polyol and hexosamine are activated[19]. In the polyol pathway, sorbitol is formed by aldose reductase, the first and rate-limiting step leading to the conversion of NADPH to NADP+. NADPH is a crucial cofactor in the synthesis of glutathione that is impaired by the polyol pathway. The conversion of sorbitol to fructose (via the activity of sorbitol dehydrogenase) results in an increased NADH/NAD+ ratio that drives the production of advanced glycation end products as well as the de novo production of diacyglycerol (DAG)[20].

Several mechanisms related to the hyperglycemia-induced polyol pathway have been proposed, with the most representative being an increase in redox stress due to the consumption of NADPH. Because NADPH is a cofactor needed to regenerate reduced glutathione (GSH) and GSH is an essential scavenger of reactive oxygen species (ROS), this could induce intracellular oxidative stress.

Vikramadithyan et al demonstrated that the overexpression of human aldose reductase increased atherosclerosis in diabetic mice and decreased the expression of genes that control glutathione regeneration. It has been also demonstrated that decreased glutathionylation of cellular proteins is related to decreased NO availability in diabetic rats. Restoration of NO levels in diabetic animals improves the glutathionylation of cellular proteins, inhibits the activity of aldose reductase and prevents the accumulation of sorbitol[20].

1.4 The hexosamine pathway

Recent studies have shown that the hexosamine pathway, previously known exclusively as a biosynthetic pathway for amino sugars, has regulatory functions. These include induction of gene expression such as growth factors in smooth muscle cells or renal mesangial cells and also of insulin resistance. Several lines of evidence suggest that the activation of TGF-b is regulated by the hexosamine pathway[21]. High glucose levels in cultured mesangial cells induced the production of TGF-b. During intracellular glucose metabolism, the redirection of fructose-6-phosphate from the glycolytic pathway to the hexosamine pathway (HSP) can ultimately induce increased transcription of proinflammatory cytokines, insulin desensitizationand oxidative stress— all of which are prominent features contributing to retinal neuronal apoptosis[22].

Given the reported role of the hexosamine pathway in the regulation of genes related to injury and fibrosis, Leighton et al. hypothesized that the hexosamine pathway is important in inflammation and may regulate the expression of nuclear factor kappa-light chain-enhancer of activated B cells (NF-κB) dependent genes such as vascular cell adhesion molecule 1 (VCAM-1), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α)[23].

2. THE ROLE OF MITOCHONDRIAL DYSFUNCTION

Glycation of mitochondrial proteins may contribute to the „metabolic memory" phenomenon. Independent of actual glycemia, glycated mitochondria can initiate a vicious cycle of mitochondrial DNA (mtDNA) damage, functional decline, increased ROS generation, and cellular injury, thereby maintaining activation of the pathways involved in the pathogenesis of diabetic complications. Mitochondrial dysfunction has been linked to retinal vascular cell loss, a common complication of diabetic retinopathy. Hyperglycemia has been shown to elicit mitochondrial fragmentation and dysfunction in retinal endothelial cells, which may lead to apoptosis. In this respect, Wang et al. conducted a study using rat retinal endothelial cells to investigate the effect of metabolic memory on mitochondrial oxidative damage-induced diabetic retinopathy. They demonstrated that high glucose triggered mitochondrial damage, increased apoptosis, and ROS generation even after cells were returned to normal glucose conditions, indicating that retinal cells possess metabolic memory[24].

Brownlee has recently pointed to an excess of superoxide anion, a reactive species, in the mitochondria of endothelial cells in response to hyperglycemia with the subsequent diabetic complications[25]. Superoxide is the major oxygen free radical generated by the mitochondria, which is eventually transformed to more reactive species that may cause various degree of cellular damage.

3. THERAPEUTIC APPROACHES TO AMELIORATE METABOLIC MEMORY PHENOMENON

Besides the antidiabetic drugs, several classes of cardiovascular drugs are used to control cardiovascular disease and the associated cardiovascular risk factors: hypertension, dyslipidemia, and thus are preferred in diabetic patients[26]. Drugs with multiple targets, including metabolic memory are very useful in diabetes and its complications management, where early intensive glycemic control plus hypertension and hyperlipemia management are needed[27].

3.1 Renin-Angiotensin-Aldosterone System (RAAS) blockers

RAAS upregulation and imbalance is evident in diabetic patients and exert deleterious effects on the cardiovascular system by promoting accelerated atherosclerosis, cardiac remodeling (hypertrophy, fibrosis, apoptosis), inflammation, increased oxidative stress, defective angiogenesis mostly through angiotensin II and aldosterone. Reversal of these effects is therefore warranted[26]. Besides the beneficial effect of a substantial blood pressure lowering, and cardiac remodeling, the studies proved that both angiotensin-converting enzyme inhibitors (ACE inhibitors) and angiotensin-I (AT-1) receptor blockers target the metabolic memory pathways and work as antioxidants, having a protective effect in patients with diabetes[3].

Yoshida et al. demonstrated that the AT-1 receptor blocker, telmisartan downregulates RAGE mRNA levels through activation of the peroxisome proliferator activated receptor-gamma in the liver and reduces AGE-induced C-reactive protein production, in a dose-dependent manner. This may have a protective vascular effect in diabetic patients. This effect was not observed in their study with the AT-1 receptor blocker candersartan[1,28]. In the same manner, the studies also showed beneficial effects of RAAS blockade for diabetic retinopathy by targeting metabolic memory. In the *Diabetic Retinopathy Candesartan Trials* (DIRECT), candersartan proved to reduce severe retinopathy in both diabetes type 1 and 2, even if the end-points were not met[29,30]. These effects were due not only to blood pressure lowering but also to reduction of AGEs and vascular endothelial growth factor (VEGF) overexpression as explained later by Miller et al.[31]. They proved that candersartan restored glyoxalase-I activity and reduced NO in cultured bovine retinal endothelial cells and bovine retinal pericytes. This was demonstrated also *in vivo,* in diabetic Ren-2 rats, along with a decrease in retinal acellular capillaries and inflammation. Silva et al. demonstrated a beneficial effect of losartan in hypertensive and diabetic rats in which a high rate of apoptosis was detected in the retina, in cells displaying neural and glial markers. Mitochondrial function was dramatically affected, and superoxide production was increased. Losartan had a neuroprotective effect by re-establishing mitochondrial function and oxidative redox[32]. Zhang et al. demonstrated in diabetic rats that AT1 and AT2 receptors are implicated in the modulation of VEGF expression and that the use of valsartan attenuated the expression of this growth factor in the retina, thus having a protective effect in this complication[33].

Simão et al. investigated the effects of the direct renin inhibitor, aliskiren in retinal pigment epithelial cells treated with high glucose concentrations. Exposure to angiotensin II induced hyperproduction of proangiogenic factors (VEGF) and increased the production of reactive oxygen species. Aliskiren reduced the levels of oxidative stress and promoted the production of anti-angiogenic factors, thus protecting retinal cells from the undesired effects of high glucose concentrations and angiotensin II[34]. In a recent review, Alshahrani summarized the antioxidant, anti-inflammatory and antiatherosclerotic properties of aliskiren in several organ damage including the kidney, heart and brain, that are independent of its blood pressure lowering properties. There are several preclinical studies that demonstrated the renal protective effect of aliskiren, alone or combined with other drugs, in diabetic rats. The described mechanisms included the decrease in aldosterone levels, thus inhibiting its oxidative and profibrotic actions and increasing renal NO and cyclic guanosine monophosphate.

3.2 Lipid lowering drugs

Lipid-lowering drugs including statins, ezetimibe, niacin, PCSK9 inhibitors may be effective in reversing the „metabolic memory" phenomenon in diabetes but more clinical studies are needed in this regard.

Cerielo et al. demonstrated in 20 patients suffering from type 2 diabetes that high fat load and glucose induced through oxidative stress enhancement, a decrease in endothelial function and an increase in inflammatory markers such as C-reactive protein, intercellular adhesion molecule-1, interleukin-6 and nitrotyrosine. Irbesartan and atorvastatin both separately, but even better in combination, reverted these undesired effects[35].

On the other hand, Carillo-Ibarra et al evaluated the effects of ezetimibe/simvastatin and rosuvastatin on oxidative DNA damage in patients with diabetic polyneuropathy in a study that included 74 patients and found no significant differences in DNA biomarkers in the three groups- placebo, ezetimibe/simvastatin and rosuvastatin, between baseline and final levels, after treatment[36].

Fibrates, acting as PPAR-α agonists demonstrated to improve endothelial protective effects of HDL cholesterol in diabetic patients with dislypidemia.These induce an increase in progenitor cells maturation and differentiation, improving endothelial dysfunction and increasing NO levels and availability[37].

Zhao et al. demonstrated that fenofibrate exerts an important anti-inflammatory effect suppresses the cellular metabolic memory of high glucose-induced stress in animal models of diabetic retinopathy, through the NAD+ dependent deacetylase sirtuin 1 which is inhibited in hyperglycemic conditions. The decrease of sirtuin1 activity was negatively correlated with the expression of nuclear factorκB. Fenofibrate seems to increase the expression of sirtuin1 in hyperglycemia induced metabolic memory through the peroxisome proliferatoractivated receptor α. Because of these actions this may be a promising treatment for diabetic complications[38].

CONCLUSIONS

Microvascular and macrovascular complications may continue to evolve even when normal glucose levels are maintained in patients with diabetes mellitus. The term „metabolic memory" refers to this phenomenon which appears to be a major clinical issue with potential life-threatening consequences. Although the molecular processes behind this process are unknown, inflammation, oxidative stress, and epigenetic modification are all indicators of „metabolic memory" in diabetes mellitus. Early, aggressive treatment of hyperglycemia may „program" the metabolic memory. In diabetic patients, early and intensive care of glycemia, blood pressure, and lipid abnormalities may lower the risk of chronic complications and premature death.

Compliance with ethics requirements:

The authors declare no conflict of interest regarding this article. The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from all the patients included in the study.

Acknowledgement: Research supported by the university internal grant no. 6POSTDOC/1871/12.02.2020.

References:

1. Testa R, Bonfigli AR, Prattichizzo F, La Sala L, De Nigris V, Ceriello A. The "Metabolic Memory" Theory and the Early Treatment of Hyperglycemia in Prevention of Diabetic Complications. Vol. 9, Nutrients. 2017.
2. Guzik TJ, Mussa S, Gastaldi D, Sadowski J, Ratnatunga C, Pillai R, et al. Mechanisms of increased vascular superoxide production in human diabetes mellitus: Role of NAD(P)H oxidase and endothelial nitric oxide synthase. Circulation. 2002;105(14):1656–62.
3. F Giacco MB. Oxidative stress and diabetic complications. Giacco F1, Brownlee M. Circ Res. 2010;
4. Brownlee M. The pathobiology of diabetic complications: A unifying mechanism. In: Diabetes. 2005. p. 1615–25.
5. Brouwers O, Niessen PM, Haenen G, Miyata T, Brownlee M, Stehouwer CD, et al. Hyperglycaemia-induced impairment of endothelium-dependent vasorelaxation in rat mesenteric arteries is mediated by intracellular methylglyoxal levels in a pathway dependent on oxidative stress. Diabetologia. 2010;53(5):989–1000.
6. M. N, A. S, B. S, T. G, T. H, C. G, et al. Effects of low- and high-advanced glycation endproduct meals on macro- and microvascular endothelial function and oxidative stress in patients with type 2 diabetes mellitus. American Journal of Clinical Nutrition. 2007.
7. Yamagishi SI. Advanced Glycation End-Products. In: Brenner's Encyclopedia of Genetics: Second Edition. 2013. p. 36–8.
8. Tanaka N, Yonekura H, Yamagishi SI, Fujimori H, Yamamoto Y, Yamamoto H. The receptor for advanced glycation end products is induced by the glycation products themselves and tumor necrosis factor-α through nuclear factor-κB, and by 17β-Estradiol through sp-1 in human vascular endothelial cells. J Biol Chem. 2000;275(33): 25781–90.
9. Wang H, Liu J, Wu L. Methylglyoxal-induced mitochondrial dysfunction in vascular smooth muscle cells. Biochem Pharmacol. 2009; 77(11):1709–16.
10. Shamoon H, Cleary P, Barnie A, Genuth S, Maffin C, Tamborlane W, et al. Epidemiology of Diabetes Interventions and Complications (EDIC): Design, implementation, and preliminary results of a long-term follow-up of the Diabetes Control and Complications Trial cohort. Diabetes Care. 1999;22(1):99–111.
11. Xia P, Inoguchi T, Kern TS, Engerman RL, Oates PJ, King GL. Characterization of the mechanism for the chronic activation of diacylglycerol-protein kinase C pathway in diabetes and hypergalactosemia. Diabetes. 1994;43(9):1122–9.
12. Steinberg SF. Structural basis of protein kinase C isoform function. Vol. 88, Physiological Reviews. 2008. p. 1341–78.
13. Ganz MB, Seftel A. Glucose-induced changes in protein kinase C and nitric oxide are prevented by vitamin E. Am J Physiol - Endocrinol Metab. 2000;278(1 41-1).
14. Pugliese G, Pricci F, Pugliese F, Mene P, Lenti L, Andrean D, et al. Mechanisms of glucose-enhanced extracellular matrix accumulation in rat glomerular mesangial cells. Diabetes. 1994;43(3):478–90.
15. Takagi C, Bursell SE, Lin YW, Takagi H, Duh E, Jiang Z, et al. Regulation of retinal hemodynamics in diabetic rats by increased ex-

pression and action of endothelin-1. Investig Ophthalmol Vis Sci. 1996;37(12):2504–18.
16. Shiba T, Inoguchi T, Sportsman JR, Heath WF, Bursell S, King GL. Correlation of diacylglycerol level and protein kinase C activity in rat retina to retinal circulation. Am J Physiol - Endocrinol Metab. 1993;265(5 28-5).
17. Koya D, Jirousek MR, Lin YW, Ishii H, Kuboki K, King GL. Characterization of protein kinase C β isoform activation on the gene expression of transforming growth factor-β, extracellular matrix components, and prostanoids in the glomeruli of diabetic rats. J Clin Invest. 1997;100(1):115–26.
18. KOYA D, HANEDA M, NAKAGAWA H, ISSHIKI K, SATO H, MAEDA S, et al. Amelioration of accelerated diabetic mesangial expansion by treatment with a PKC β inhibitor in diabetic db/db mice, a rodent model for type 2 diabetes. FASEB J. 2000;14(3):439–47.
19. Pugliese G, Tilton RG, Williamson JR. Glucose–induced metabolic imbalances in the pathogenesis of diabetic vascular disease. Diabetes Metab Rev. 1991;7(1):35–59.
20. Vikramadithyan RK, Hu Y, Noh HL, Liang CP, Hallam K, Tall AR, et al. Human aldose reductase expression accelerates diabetic atherosclerosis in transgenic mice. J Clin Invest. 2005;115(9):2434–43.
21. Sayeski PP, Kudlow JE. Glucose metabolism to glucosamine is necessary for glucose stimulation of transforming growth factor-α gene transcription. J Biol Chem. 1996;271(25):15237–43.
22. Schleicher ED, Weigert C. Role of the hexosamine biosynthetic pathway in diabetic nephropathy. Kidney International, Supplement. 2000.
23. James LR, Tang D, Ingram A, Ly H, Thai K, Cai L, et al. Flux through the hexosamine pathway is a determinant of nuclear factor κB-dependent promoter activation. Diabetes. 2002;51(4):1146–56.
24. Wang Z, Zhao H, Guan W, Kang X, Tai X, Shen Y. Metabolic memory in mitochondrial oxidative damage triggers diabetic retinopathy. BMC Ophthalmol. 2018;18(1).
25. Brownlee M. Biochemistry and molecular cell biology of diabetic complications. Vol. 414, Nature. 2001. p. 813–20.
26. Bernardi S, Michelli A, Zuolo G, Candido R, Fabris B. Update on RAAS Modulation for the Treatment of Diabetic Cardiovascular Disease. Journal of Diabetes Research. 2016.
27. Wu Y, Tang L, Chen B. Oxidative stress: Implications for the development of diabetic retinopathy and antioxidant therapeutic perspectives. Vol. 2014, Oxidative Medicine and Cellular Longevity. 2014.
28. Yoshida T, Yamagishi S, Nakamura K, Matsui T, Imaizumi T, Takeuchi M, et al. Telmisartan inhibits AGE-induced C-reactive protein production through downregulation of the receptor for AGE via peroxisome proliferator-activated receptor-gamma activation. Diabetologia. 2006;49(12):3094–9.
29. Sjølie AK, Klein R, Porta M, Orchard T, Fuller J, Parving HH, et al. Effect of candesartan on progression and regression of retinopathy in type 2 diabetes (DIRECT-Protect 2): a randomised placebo-controlled trial. Lancet. 2008;372(9647):1385–93.
30. Chaturvedi N, Porta M, Klein R, Orchard T, Fuller J, Parving HH, et al. Effect of candesartan on prevention (DIRECT-Prevent 1) and progression (DIRECT-Protect 1) of retinopathy in type 1 diabetes: randomised, placebo-controlled trials. Lancet. 2008;372(9647):1394–402.
31. Miller AG, Tan G, Binger KJ, Pickering RJ, Thomas MC, Nagaraj RH, et al. Candesartan attenuates diabetic retinal vascular pathology by restoring glyoxalase-I function. Diabetes. 2010;59(12):3208–15.
32. Silva KC, Rosales MAB, Biswas SK, De Faria JBL, De Faria JML. Diabetic retinal neurodegeneration is associated with mitochondrial oxidative stress and is improved by an angiotensin receptor blocker in a model combining hypertension and diabetes. Diabetes. 2009;
33. Zhang X, Lassila M, Cooper ME, Cao Z. Retinal Expression of Vascular Endothelial Growth Factor Is Mediated by Angiotensin Type 1 and Type 2 Receptors. Hypertension. 2004;43(2 I):276–81.
34. Simão S, Santos DF, Silva GA. Aliskiren decreases oxidative stress and angiogenic markers in retinal pigment epithelium cells. Angiogenesis. 2017;20(1):175–81.
35. Ceriello A, Assaloni R, Da Ros R, Maier A, Piconi L, Quagliaro L, et al. Effect of atorvastatin and irbesartan, alone and in combination, on postprandial endothelial dysfunction, oxidative stress, and inflammation in type 2 diabetic patients. Circulation. 2005;111(19):2518–24.
36. Carrillo-Ibarra S, Miranda-Díaz AG, Sifuentes-Franco S, Cardona-Muñoz EG, Rodríguez-Carrizalez AD, Villegas-Rivera G, et al. Effect of statins on oxidative DNA damage in diabetic polyneuropathy. J Circ Biomarkers. 2018;7.
37. Berezin A. Metabolic memory phenomenon in diabetes mellitus: Achieving and perspectives. Vol. 10, Diabetes and Metabolic Syndrome: Clinical Research and Reviews. 2016. p. S176–83.
38. Zhao S, Li J, Wang N, Zheng B, Li T, Gu Q, et al. Fenofibrate suppresses cellular metabolic memory of high glucose in diabetic retinopathy via a sirtuin 1-dependent signalling pathway. Mol Med Rep. 2015;12(4):6112–8.