Redox imbalance stress in diabetes mellitus: Role of the polyol pathway

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Abstract
In diabetes mellitus, the polyol pathway is highly active and consumes approximately 30% glucose in the body. This pathway contains 2 reactions catalyzed by aldose reductase (AR) and sorbitol dehydrogenase, respectively. AR reduces glucose to sorbitol at the expense of NADPH, while sorbitol dehydrogenase converts sorbitol to fructose at the expense of NAD⁺, leading to NADH production. Consumption of NADPH, accumulation of sorbitol, and generation of fructose and NADH have all been implicated in the pathogenesis of diabetes and its complications. In this review, the roles of this pathway in NADH/NAD⁺ redox imbalance stress and oxidative stress in diabetes are highlighted. A potential intervention using nicotinamide riboside to restore redox balance as an approach to fighting diabetes is also discussed.

KEYWORDS
diabetes mellitus, fructose, NADH/NAD⁺, oxidative stress, polyol pathway, redox imbalance stress

1 | INTRODUCTION

Diabetes mellitus is a debilitating disease. It impairs the biological function of many organs in the body. The underlying mechanism of diabetic pathogenesis is hyperglycemia-induced chronic glucotoxicity,1-6 which impairs numerous pathways in the biological metabolome. During development and progression of diabetes, many pathways are upregulated in an attempt to handle the overflow of glucose in the body. These pathways include the polyol pathway,7-12 the glycation pathway,13-15 the protein kinase c pathway,16-19 the hexosamine pathway,20-22 and the enediol/alpha-ketoaldehyde pathway.23-25 It is now believed that all the pathways converge on elevation of reactive oxygen species (ROS) by a variety of ROS generation systems.25-28

Under normoglycemic conditions, the major purpose of glucose combustion is to produce energy in the form of ATP, and to produce NADPH and ribose via the pentose phosphate pathway (Figure 1A). Excess glucose can be further stored in the body as either glycogen or fatty acids (Figure 1A).29 As glucose metabolism involves electron extraction, storage, and transportation, nearly all the biochemical reactions in glucose metabolism are actually redox reactions. For example, splitting of glucose to 2 molecules of pyruvate during glycolysis stores the extracted electrons in NADH, as does the pyruvate dehydrogenase complex pathway whereby pyruvate is decarboxylated to form acetyl-CoA. After entry of acetyl-CoA into the Krebs cycle, electrons are stored in both NADH and FADH₂. These electron donors then donate their electrons to complex I (NADH) or complex II (FADH₂) in the mitochondrial electron transport chain. Oxygen is only used at the last step whereby complex IV transports electrons from cytochrome c to oxygen.

As glucose provides electrons that are mainly stored in NADH, the higher the blood glucose levels, the higher the NADH contents. This can tilt the redox balance between NADH and NAD⁺ toward the side of NADH, resulting in redox imbalance.6,30 This is indeed what occurs in diabetes31,32 and the polyol pathway is known to
play a major role in breaking the redox balance between NADH and NAD\textsuperscript{+}.\textsuperscript{33-36}

\section*{2 | THE POLYOL PATHWAY}

The polyol pathway consists of 2 reactions catalyzed by 2 respective enzymes.\textsuperscript{7,10,35} As shown in Figure 1B, the first reaction is reduction of glucose to sorbitol, which is catalyzed by aldose reductase (AR). This reaction is the rate-limiting reaction\textsuperscript{37} in this pathway and also converts NADPH to NADH. The second reaction converts sorbitol to fructose and is catalyzed by sorbitol dehydrogenase, which makes NADH from NAD\textsuperscript{+}. So the overall products of the polyol pathway are sorbitol, fructose, and NADH. NADH production results from the consumption of NADPH. Because nearly 30% of blood glucose can flux through the polyol pathway in diabetes,\textsuperscript{38,39} this pathway has been thought to be the major pathway contributing to NADH/NAD\textsuperscript{+} redox imbalance in diabetes.\textsuperscript{7,8,26,34} I will now dissect each of the pathway’s components (Figure 2) and their role in redox imbalance stress and diabetes mellitus.

\subsection*{2.1 | Aldose reductase}

The physiological function of this enzyme still remains murky, but it is usually thought that the enzyme, under normal physiological conditions, can degrade toxic aldehyde byproducts formed by lipid peroxidation such as 4-hydroxy-nonenal (HNE) and its glutathione conjugates (GSH-HNE).\textsuperscript{40,41} However, its ability to catalyze glucose reduction is nearly negligible under physiological conditions due to the high $K_m$ of its reaction with glucose.\textsuperscript{42} In contrast, when the glucose level is high, this enzyme and the polyol pathway becomes a major pathway in disposing of glucose.\textsuperscript{7,35-37,43}

The role of AR in diabetes has been well elucidated by using its inhibitors and by AR knockout animal models. It has been found that AR inhibitors can ameliorate diabetes mellitus.\textsuperscript{44,45} In fact, numerous AR inhibitors have been tested and evaluated.\textsuperscript{46-50} For example, the AR inhibitor zopolrestato can lower acetate utilization in the diabetic heart,\textsuperscript{45} indicating increased glucose combustion via the glycolytic pathway and the Krebs cycle, that otherwise is inhibited in diabetes. Another example is the use of AR inhibitor sorbinil,\textsuperscript{51} which has been clinically used to stabilize diabetic corneal epithelial disorders.\textsuperscript{52} One caveat of inhibiting the polyol pathway is that it could be overinhibited, leading to increased protein glycation by glucose.\textsuperscript{53}

With respect to AR deletion or knockout studies, it has been demonstrated that AR deletion from mice could inhibit diabetes-induced retinal capillary degeneration mediated by superoxide production.\textsuperscript{54} It has also been demonstrated that the AR knockout mouse is resistant to the development of diabetic nephropathy.\textsuperscript{55}

\subsection*{2.2 | Consumption of NADPH and redox imbalance of NADPH and NADP\textsuperscript{+}}

As glucose flux through the polyol pathway consumes NADPH, it has been suggested that the level of NADPH could be significantly decrease...
decreased.\textsuperscript{56} Indeed, we have found that this is the case in diabetic lung and pancreas,\textsuperscript{31,57} whereby NADPH content is lower than that in controls. It has been established that there is about a 15% decrease in NADPH in the diabetic lens.\textsuperscript{35} The NADPH decrease could further impair the GSH/GSSG redox balance, as GSSG reduction by glutathione reductase requires NADPH as a cofactor.\textsuperscript{58,59} NADPH is also involved in the biosynthesis of biological molecules such as fatty acids and nitric oxide, so its decrease or depletion should have deleterious effects on many anabolic pathways.\textsuperscript{60} Additionally, from a chemical point of view, the polyol pathway can also compete with glutathione reductase for NADPH,\textsuperscript{61,62} leading to further impairment in glucose metabolism.

\subsection*{2.3 Accumulation of sorbitol}

In certain tissues such as retina, sorbitol dehydrogenase content is low,\textsuperscript{63} so sorbitol formed from glucose reduction can accumulate.\textsuperscript{35} This accumulation can change cellular membrane osmotic pressure and triggers osmotic stress.\textsuperscript{39} This osmotic stress has been thought to be the main underlying mechanism for diabetic retinopathy\textsuperscript{64,65} and has also been implicated in diabetic kidney dysfunction or nephropathy.\textsuperscript{9} It should be noted that even in the same organ, different cell populations may have different levels of sorbitol dehydrogenase;\textsuperscript{66} hence, the effect of sorbitol on diabetic tissue is differential.

\subsection*{2.4 NADH overproduction and NAD\textsuperscript{+} depletion}

The second reaction of the polyol pathway involves NADH production from NAD\textsuperscript{+}. This pathway has therefore been regarded as the major source of NADH/NAD\textsuperscript{+} redox imbalance.\textsuperscript{5,6,26,32} On one hand, NADH is overproduced, which could lead to reductive stress followed by oxidative stress.\textsuperscript{26,28} This is because elevated levels of NADH could overwhelm mitochondrial complex I, leading to more ROS production from the mitochondrial electron transport chain.\textsuperscript{26} Additionally, excess NADH can also inhibit the glycolytic pathway, the pyruvate dehydrogenase complex, and the Krebs cycle,\textsuperscript{12,67} leading to more flux of glucose through the polyol pathway. On the other hand, an NAD\textsuperscript{+} decrease also imposes deleterious effects on a variety of metabolic pathways.\textsuperscript{6} A major one is the sirtuin pathway,\textsuperscript{8} which is responsible for protein deacetylation.\textsuperscript{58} A decrease in NAD\textsuperscript{+} would inactivate sirtuins, leading to over-acetylation of proteins and less efficient glucose metabolism.\textsuperscript{69-71}

In the case of NADH/NAD\textsuperscript{+} redox imbalance, it has been demonstrated that restoring the redox balance by supplementing with an NAD\textsuperscript{+} precursor or analogue is a valuable approach.\textsuperscript{72} In this regard, the recently identified precursor nicotinamide riboside is very promising as this chemical is more tolerant and has fewer side-effects than niacin.\textsuperscript{73} For example, it has been reported that nicotinamide riboside can ameliorate diabetes and diabetic neuropathy in mice, and can enhance metabolism and prevent development of obesity induced by a high fat diet.\textsuperscript{74,75}

\subsection*{2.5 Fructose}

As the polyol pathway consumes approximately 30% of blood glucose in diabetes,\textsuperscript{39} fructose is overproduced in the body. Overproduction of fructose can lead to severe metabolic consequences. On one hand, fructose can chemically glycate proteins,\textsuperscript{76} leading to protein dysfunction. It is known that fructose can be further metabolized to produce 3-deoxyglucose and fructose-3-phosphate, both of which are very potent nonenzymatic glycation agents.\textsuperscript{76} On the other hand, as fructose metabolism by fructokinase, with the consumption of ATP, can bypass the regulation of the glycolytic pathway,\textsuperscript{77,78} acetyl-CoA could be overproduced\textsuperscript{78} and ATP could be depleted.\textsuperscript{79} Acetyl-CoA overproduction could cause non-alcoholic fatty liver disease (NAFLD), as acetyl-CoA is the precursor of fatty acid,\textsuperscript{77,80-82} while ATP depletion could cause cell death. Additionally, overproduction of acetyl-CoA can result in more protein acetylation, leading to protein functional impairment.\textsuperscript{83-85} Protein acetylation can worsen when sirtuin proteins are inactive due to lack of NAD\textsuperscript{+} in diabetes.\textsuperscript{6,86} Therefore, fructose accumulation due to activation of the polyol pathway by hyperglycemia can accentuate diabetes and its complications.

\subsection*{2.6 Effect of redox imbalance on sirtuins}

Sirtuins are protein deacetylases that use NAD\textsuperscript{+} as their substrate.\textsuperscript{87} So when NAD\textsuperscript{+} levels decrease during diabetes, sirtuin activities will be decreased,\textsuperscript{69,88} and this can also be modulated by decreased expression of sirtuin proteins. Indeed, numerous studies including ours, have demonstrated attenuated expression of sirtuin proteins in diabetes.\textsuperscript{31,57,88,89} As a consequence, protein acetylation is increased (Figure 3A), leading to functional changes of numerous proteins.\textsuperscript{83,90} Accordingly, studies have demonstrated that supplementing with NAD\textsuperscript{+} precursors or analogous can serve as an approach for enhancing sirtuin activity, thereby augmenting protein deacetylation, which can lead to amelioration of diabetes.\textsuperscript{70,71,91}

\subsection*{2.7 Effect of redox imbalance on poly-ADP-ribosylase function}

In diabetes, it is usually thought that DNA damage occurs first, which triggers the upregulation of poly-ADP-ribosylase (PARP) activity.\textsuperscript{72,92,93} This upregulation can deplete NAD\textsuperscript{+}, as PARP also uses NAD\textsuperscript{+} as its substrate during repair of damaged DNA.\textsuperscript{94-96} Indeed, PARP knockout mouse has been found to be resistant to diabetes development\textsuperscript{97,98} and inhibition of PARP can also retard the development of diabetes.\textsuperscript{99-102} On the other hand, it is also possible that decreased levels of NAD\textsuperscript{+} caused by activation of the polyol pathway could impair PRAP activity, leading to accentuation of diabetes, as it is likely that damaged DNA would not get repaired promptly. Nonetheless, the crosstalk between the polyol pathway and the PARP pathway will need to be further investigated. This author tends to believe that the 2 pathways may form a vicious cycle that will worsen the situation during progression of diabetes.
2.8 | Redox imbalance and oxidative stress

One of the major consequences of NADH/NAD⁺ redox imbalance is oversupply of electron donors to the mitochondrial electron transport chain.²⁶ Oversupply of NADH would overwhelm complex I, which relays electrons from NADH to CoQ.³² One feature of complex I electron transport is that the more electrons it transports, the more superoxide it will produce.¹⁰³-¹⁰⁶ This is because more electrons could leak and partially reduce oxygen, leading to overproduction of superoxide which is the precursor of all the ROS.¹⁰⁷-¹¹⁰ Hence, oversupply of NADH in diabetes driven by constant hyperglycemia can devastate cells with enhanced oxidative stress, impaired mitochondrial function, and increased cell death, as has been demonstrated by numerous investigators.¹⁷,²⁷,²⁸,¹¹¹-¹¹⁸

2.9 | Targeting redox imbalance as an approach for diabetes therapy

It is reasonable to say that diabetes is a redox imbalance disease.³² Hence restoration of NADH/NAD⁺ redox balance may serve to combat diabetes. One approach, as mentioned above, is supplementing with NAD⁺ precursors or analogues (Figure 3B). In particular, the utilization of nicotinamide riboside in a variety of experimental settings has demonstrated the beneficial effects of this compound.¹⁰,⁷⁴,⁷⁵,¹¹⁹ Additionally, plant extracts or compounds that are antioxidants in nature have also been evaluated for their effects in mitigating oxidative stress and promoting cell survival.¹²⁰-¹²³ As these compounds can counteract the deleterious effects of the activated polyol pathway that is responsible for redox imbalance in diabetes, an understanding of how they work in alleviating diabetes and its complications should provide insights into the design of novel strategies for fighting this epidemic and devastating disease.

3 | CONCLUDING REMARKS

The active polyol pathway in diabetes mellitus is a major contributor to NADH/NAD⁺ redox imbalance due to its ability to convert NADPH to NADH. Not only can excess NADH induce oxidative stress via generation of ROS through the mitochondrial electron transport chain and other pathways, but lowered NADPH content can also induce oxidative stress by impairing glutathione metabolism. Approaches to restoration of redox balance by targeting the polyol pathway have been explored and should remain a research focus in order to provide novel strategies for fighting diabetes and its complications.

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CONFLICT OF INTEREST

None.

REFERENCES

1. Del Prato S. Role of glucotoxicity and lipotoxicity in the pathophysiology of type 2 diabetes mellitus and emerging treatment strategies. Diabet Med. 2009;26:1185–1192.
2. Brahma MK, Pepin ME, Wende AR. My sweetheart is broken: role of glucose in diabetic cardiomyopathy. Diabetes Metab J. 2017;41:1–9.
3. Kaiser N, Leibowitz G, Nesher R. Glucotoxicity and beta-cell failure in type 2 diabetes mellitus. J Pediatr Endocrinol Metab. 2003;16:5–22.
4. Brunner Y, Schwartz D, Priego-Capote F, Coute Y, Sanchez JC. Glucotoxicity and pancreatic proteomics. J Proteomics. 2009;71:576–591.
5. Zheng H, Wu J, Jin Z, Yan LJ. Protein Modifications as manifestations of hyperglycemic glucotoxicity in diabetes and its complications. Biochem Insights. 2016;9:1–9.

6. Luo X, Wu J, Jing S, Yan LJ. Hyperglycemic stress and carbon stress in diabetic glucotoxicity. Aging Dis. 2016;7:90–110.

7. Chung SS, Ho EC, Lam KS, Chung SK. Contribution of polyol pathway to diabetes-induced oxidative stress. J Am Soc Nephrol. 2003;14(8 Suppl. 3):S233–S236.

8. Dunlop M. Aldose reductase and the role of the polyol pathway in diabetic nephropathy. Kidney Int Suppl. 2000;77:S3–S12.

9. Hotta N. New concepts and insights on pathogenesis and treatment of diabetic complications: polyol pathway and its inhibition. Nigoya J Med Sci. 1997;60:89–110.

10. Lee AY, Chung SS. Contributions of polyol pathway to oxidative stress in diabetic cataract. FASEB J. 1999;13:23–30.

11. Li Q, Hwang YC, Ananthakrishnan R, Oates PJ, Guberski D, Ramasamy R. Polyol pathway and modulation of ischemia-reperfusion injury in type 2 diabetic BBZ rat hearts. Cardiovasc Diabetol. 2008;7:33.

12. Tang WH, Wu S, Wong TM, Chung SK. Polyol pathway mediates iron-induced oxidative injury in ischemic-reperfusion rat heart. Free Radic Biol Med. 2008;45:602–610.

13. Lyons TJ, Jenkins AJ. Glycation, oxidation, and lipoxidation in the development of the complications of diabetes: a carboxyl stress hypothesis. Diabetes Rev (Austr). 1997;5:365–391.

14. Vlassara H, Striker GE. Advanced glycation endproducts in diabetes and diabetic complications. Endocrinol Metab Clin North Am. 2013;42:697–719.

15. Wolff SP, Jiang ZY, Hunt JV. Protein glycation and oxidative stress to oxidative stress. J Diabetes Investig. 2010;1:90–96.

16. Lieberman M, Marks AD. Marks’ Basic Medical Biochemistry: A Clinical Approach (4th ed.). Philadelphia, PA: Wolters Kluwer/Lippincott Williams & Wilkins; 2013.

17. Luo X, Li R, Yan LJ. Roles of pyruvate, NADH, and mitochondrial complex I in redox balance and imbalance in β cell function and dysfunction. J Diabetes Res. 2015;2015:12. https://doi.org/10.1159/2015/512618.

18. Wu J, Jin Z, Yan LJ. Redox imbalance and mitochondrial abnormalities in the diabetic lung. Redox Biol. 2017;11:51–59.

19. Wu J, Jin Z, Zheng H, Yan LJ. Sources and implications of NADH/NAD+ redox imbalance in diabetes and its complications. Diabetes Metab Syndr Obes. 2016;9:145–153.

20. Ido Y, Williamson JR. Hyperglycemic cytokisolic reductive stress ‘pseudohypoxia’: implications for diabetic retinopathy. Invest Ophthalmol Vis Sci. 1997;38:1467–1470.

21. Williamson JR, Chang K, Frangos M, et al. Hyperglycemic pseudohypoxia and diabetic complications. Diabetes. 1993;42:801–813.

22. Kador PF, Kinoshita JH. Role of aldose reductase in the development of diabetes-associated complications. Am J Med. 1985;79:8–12.

23. Chung SS, Chung SK. Aldose reductase in diabetic microvascular complications. Curr Drug Targets. 2005;6:475–486.

24. Yabe-Nishimura C. Aldose reductase in glucose toxicity: a potential target for the prevention of diabetic complications. Pharmacol Rev. 1998;50:21–33.

25. Gonzalez RG, Barnett P, Aguayo J, Cheng HM, Chylack LT Jr. Direct measurement of polyol pathway activity in the ocular lens. Diabetes. 1984;33:196–199.

26. Fantus IG. The pathogenesis of the chronic complications of the diabetes mellitus. Endocrinol Rounds. 2002;2:1–8.

27. Srivastava SK, Yadav UC, Reddy AB, et al. Aldose reductase inhibition suppresses oxidative stress-induced inflammatory disorders. Chem Biol Interact. 2011;191:330–338.

28. Maccari R, Ottana R. Targeting aldose reductase for the treatment of diabetes complications and inflammatory diseases: new insights and future directions. J Med Chem. 2015;58:2047–2067.

29. Brownlee M. The pathobiology of diabetic complications: a unifying mechanism. Diabetes. 2005;54:1615–1625.

30. Kador PF. The role of aldose reductase in the development of diabetic complications. Med Res Rev. 1988;8:325–352.

31. Demir Y, Isik M, Gulcin I, Beydemir S. Phenolic compounds inhibit the aldose reductase enzyme from the sheep kidney. J Biochem Mol Toxicol. 2017;31(9).

32. Trueblood N, Ramasamy R. Aldose reductase inhibition improves altered glucose metabolism of isolated diabetic rat hearts. Am J Physiol. 1998;275:H75–H83.

33. Hao X, Han Z, Li Y, et al. Synthesis and structure-activity relationship studies of phenolic hydroxyl derivatives based on quinoxaline-2,3-dione as aldose reductase inhibitors with antioxidant activity. Bioorg Med Chem. 2017;27:887–892.

34. Han Z, Hao X, Ma B, Zhu C. A series of pyrido[2,3-b]pyrazin-3(4H)-one derivatives as aldose reductase inhibitors with antioxidant activity. Eur J Med Chem. 2016;121:308–317.

35. Zhi S, Hao X, Zhang S, Qin X, Chen X, Zhu C. Synthesis of benzothiazadine derivatives exhibiting dual activity as aldose reductase inhibitors and antioxidant agents. Bioorg Med Chem Lett. 2016;26:2880–2885.

36. Zhi S, Zhang S, Hao X, et al. Pyridothiadiazine derivatives as aldose reductase inhibitors having antioxidant activity. J Enzyme Inhib Med Chem. 2016;31:126–130.
50. Zou Y, Qin X, Hao X, et al. Phenolic 4-hydroxy and 3,5-dihydroxy derivatives of 3-phenoxyquinolin-2(1H)-one as potent aldose reductase inhibitors with antioxidant activity. Bioorg Med Chem Lett. 2015;25:3924–3927.

51. Datiles MB, Kador PF, Kashima K, Kinoshita JH, Sinha A. The effects of sorbinil, an aldose reductase inhibitor, on the corneal endothelium in galactosemic dogs. Invest Ophthalmol Vis Sci. 1990;31:2201–2204.

52. Narayanan S. Aldose reductase and its inhibition in the control of diabetic complications. Ann Clin Lab Sci. 1993;23:148–158.

53. Jagdale AD, Bavkar LN, Kashira K, Sinha A. The effects of sorbinil, an aldose reductase inhibitor, on the corneal endothelium in galactosemic dogs. Invest Ophthalmol Vis Sci. 1990;31:2201–2204.

54. Tang J, Du Y, Petras JM, Shleibani N, Kern TS. Deletion of aldose reductase from mice inhibits diabetes-induced retinal capillary degeneration and superoxide generation. PLoS ONE. 2013;8:e62081.

55. Liu Y, Luo Y, Zhang T, et al. Genetic deficiency of aldose reductase counteracts the development of diabetic nephropathy in C57BL/6 mice. Diabetologia. 2011;54:1242–1251.

56. Díaz-Flores M, Ibanez-Hernandez MA, Galvan RE, et al. Glucose-6-phosphate dehydrogenase activity and NADPH/NADP+ ratio in liver and pancreas are dependent on the severity of hyperglycemia in rat. Life Sci. 2006;78:2601–2607.

57. Wu J, Luo X, Thangthaeng N, et al. Pancreatic mitochondrial complex I exhibits aberrant hyperactivity in diabetes. Biochem Biophys Rep. 2017;11:119–129.

58. Bravi MC, Pietrangelo P, Laurenti O, et al. Polyol pathway activation and glutathione redox status in non-insulin-dependent diabetic patients. Metabolism. 1997;46:1194–1198.

59. Yan LJ, Christians ES, Liu L, Xiao S, Sohal RS, Benjamin IJ. Mouse homeostasis and increases mitochondrial oxidative damage. EMBO J. 2002;21:5164–5172.

60. Mapanga RF, Essop MF. Damaging effects of hyperglycemia on cardiovascular function: spotlight on glucose metabolic pathways. Am J Physiol Heart Circ Physiol. 2016;310:H153–H173.

61. Cumble BC, Hermayer KL. Current concepts in targeted therapies for the pathophysiology of diabetic microvascular complications. Vasc Health Risk Manag. 2007;3:823–832.

62. Ravindranath TM, Mong PY, Ananthakrishnan R, et al. Novel role for aldose reductase in mediating acute inflammatory responses in the lung. J Immunol. 1999;163:8128–8137.

63. Aldebar Y, El-Gendi SM, Kamel A, Mohieldein A. Aldo-keto reductase and sorbitol dehydrogenase enzymes in Egyptian diabetic patients with and without proliferative diabetic retinopathy. Clin Exp Ophthalmol. 2013;9:303–309.

64. Kinoshita JH. Cataracts in galactosemia. The Jonas S. Friedenwald Memorial Lecture. Invest Ophthalmol. 1965;4:786–799.

65. Robison WG Jr, Kador PF, Kinoshita JH. Retinal capillaries: basement membrane thickening by galactosemia prevented with aldose reductase inhibitor. Science. 1983;221:1177–1179.

66. Oates PJ. Polyol pathway and diabetic peripheral neuropathy. Int Rev Neurobiol. 2002;50:325–392.

67. Hwang YC, Bakr S, Ellery CA, Oates PJ, Ramsamy R. Sorbitol dehydrogenase: a novel target for adjunctive protection of ischemic myocardium. FASEB J. 2003;17:2331–2333.

68. Morris BJ. Seven sirtuins for seven deadly diseases of aging. Free Radic Biol Med. 2013;56:133–171.

69. Yang T, Sauve AA. NAD metabolism and sirtuins: metabolic regulation of protein deacetylation in stress and toxicity. AAPS J. 2006;8:E632–E643.

70. Turkmen K, Karagoz A, Kucuk A. Sirtuins as novel players in the pathogenesis of diabetes mellitus. World J Diabetes. 2014;5:894–900.

71. Kitada M, Kume S, Kanasaki K, Takeda-Watanabe A, Koya D. Sirtuins as possible drug targets in type 2 diabetes. Curr Drug Targets. 2013;14:622–636.

72. Lee CF, Chavez JD, Garcia-Menendez L, et al. Normalization of NAD+ redox balance as a therapy for heart failure. Circulation. 2016;134:883–894.

73. Bogan KL, Brenner C. Nicotinic acid, nicotinamide, and nicotinamide riboside: a molecular evaluation of NAD+ precursor vitamins in human nutrition. Annu Rev Nutr. 2008;28:115–130.

74. Canto C, Houtkooper RH, Pirinen E, et al. The NAD+ precursor nicotinamide riboside enhances oxidative metabolism and protects against high-fat diet-induced obesity. Cell Metab. 2012;15:838–847.

75. Trammell SA, Weidemann BJ, Chadda A, et al. Nicotinamide riboside opposes type 2 diabetes and neuroinflammation in mice. Sci Rep. 2016;6:26933.

76. Gugliucci A. Formation of fructose-mediated advanced glycation end products and their roles in metabolic and inflammatory diseases. Adv Nutr. 2017;8:54–62.

77. Jegatheesan P, De Bandt JP. Fructose and NAFLD: the multifaceted aspects of fructose metabolism. Nutrients. 2017;9(3).

78. Diggle CP, Shires M, Leitch D, et al. Ketohexokinase: expression and localization of the principal fructose-metabolizing enzyme. J Histochem Cytochem. 2009;57:763–774.

79. Johnson RJ, Rodriguez-Iturbe B, Roncal-Jimenez C, et al. Hypermosality drives hypertension and CKD–water and salt revisited. Nat Rev Nephrol. 2014;10:415–420.

80. Lanaspa MA, Ishimoto T, Li N, et al. Endogenous fructose production and metabolism in the liver contributes to the development of metabolic syndrome. Nat Commun. 2013;4:2434.

81. Choi Y, Abdelmegeed MA, Song BJ. Diet high in fructose promotes liver steatosis and hepatocyte apoptosis in C57BL/6J female mice: role of disturbed lipid homeostasis and increased oxidative stress. Food Chem Toxicol. 2017;103:111–121.

82. Ishimoto T, Lanaspa MA, Rivard CJ, et al. High-fat and high-sucrose (western) diet induces steatohepatitis that is dependent on fructokinase. Hepatology. 2013;58:1632–1643.

83. Wagner GR, Hirschey MD. Nonenzymatic protein acylation as a carbon stress regulated by sirtuin deacetylases. Mol Cell. 2014;54:5–16.

84. Baeza J, Smalllegan MJ, Denu JM. Site-specific reactivity of nonenzymatic lysine acetylation. ACS Chem Biol. 2015;10:122–128.

85. Paik WK, Pearson D, Lee HW, Kim S. Nonenzymatic acetylation of histones with acetyl-CoA. Biochim Biophys Acta. 1970;213:513–522.

86. Madsen AS, Andersen C, Dao MD, et al. Investigating the Sensitivity of NAD+-dependent Sirtuin Decylation Activities to NADH. J Biol Chem. 2016;291:7128–7141.

87. Hall JA, Dominy JE, Lee Y, PuisysP. The sirtuin family’s role in aging and age-associated pathologies. J Clin Invest. 2013;123:973–979.

88. de Kreutzenberg SV, Ceolotto G, Papparella I, et al. Downregulation of the longevity-associated protein sirtuin 1 in insulin resistance and metabolic syndrome: potential biochemical mechanisms. Diabetes. 2010;59:1006–1015.

89. Caton PW, Richardson SJ, Kewlitch J, et al. Sirtuin 3 regulates mouse pancreatic beta cell function and is suppressed in pancreatic islets isolated from human type 2 diabetic patients. Diabetologia. 2013;56:1068–1077.

90. Hirschey MD, Shimazu T, Jing E, et al. SIRT3 deficiency and mitochondrial protein hyperacetylation accelerate the development of the metabolic syndrome. Mol Cell. 2011;44:177–190.
91. Huynh FK, Hershberger KA, Hirschey MD. Targeting sirtuins for the treatment of diabetes. Diabetes Metab (Lond). 2013;3:245–257.
92. Hassa PO, Haenni SS, Elser M, Hottiger MO. Nuclear ADP-ribosylation reactions in mammalian cells: where are we today and where are we going? Microbiol Mol Biol Rev. 2006;70:789–829.
93. Mueller-Dieckmann C, Kernstock S, Lisurek M, et al. The structure of human ADP-ribosylhydrolase 3 (ARH3) provides insights into the reversibility of protein ADP-ribosylation. Proc Natl Acad Sci U S A. 2006;103:15026–15031.
94. Dolle C, Rack JG, Ziegler M. NAD and ADP-ribose metabolism in mitochondria. FEBS J. 2013;280:3530–3541.
95. Du X, Matsumura T, Edelstein D, et al. Inhibition of GAPDH activity by poly(ADP-ribose) polymerase activates three major pathways of hyperglycemic damage in endothelial cells. J Clin Invest. 2003;112:1049–1057.
96. Horvath EM, Magenheim R, Kugler E, et al. Nitrate stress and poly(ADP-ribose) polymerase activation in healthy and gestational diabetic pregnancies. Diabetologia. 2009;52:1935–1943.
97. Masutani M, Suzuki H, Kamada N, et al. Poly(ADP-ribose) polymerase gene disruption conferred mice resistant to streptozotocin-induced diabetes. Proc Natl Acad Sci U S A. 1999;96:2301–2304.
98. Pieper AA, Brat DJ, Krug DK, et al. Poly(ADP-ribose)-deficient mice are protected from streptozotocin-induced diabetes. Proc Natl Acad Sci U S A. 1999;96:3059–3064.
99. Obrosova IG, Minchenko AG, Frank RN, et al. Poly(ADP-ribose) polymerase inhibitors counteract diabetes- and hypoxia-induced retinal vascular endothelial growth factor overexpression. Int J Mol Med. 2004;14:55–64.
100. Sarras MP Jr, Mason S, McAllister G, Intine RV. Inhibition of poly-ADP ribose polymerase enzyme activity prevents hyperglycemia-induced impairment of angiogenesis during wound healing. Wound Repair Regen. 2014;22:666–670.
101. Long CA, Boulom V, Albadawi H, et al. Poly-ADP-ribose-polymerase inhibition ameliorates hind limb ischemia reperfusion injury in a murine model of type 2 diabetes. Ann Surg. 2013;258:1087–1095.
102. Szkudelski T. Streptozotocin-nicotinamide-induced diabetes in the rat. Characteristics of the experimental model. Exp Biol Med (Maywood). 2012;237:481–490.
103. Treberg JR, Quinlan CL, Brand MD. Evidence for two sites of superoxide production by mitochondrial NADH-ubiquinone oxido-reductase [complex I]. J Biol Chem. 2011;286:27103–27110.
104. Murphy MP. How mitochondria produce reactive oxygen species. Biochem J. 2009;417:1–13.
105. Cooper JM, Mann VM, Krige D, Schapira AH. Human mitochondrial complex I dysfunction. Biochim Biophys Acta. 1992;1101:198–206.
106. Hirst J, King MS, Pryde KR. The production of reactive oxygen species by complex I. Biochem Soc Trans. 2008;36:976–980.
107. Turrens JF. Superoxide production by the mitochondrial respiratory chain. Biosci Rep. 1997;17:3–8.
108. Turrens JF, Alexandre A, Lehninger AL. Ubisemiquinone is the electron donor for superoxide formation by complex III of heart mitochondria. Arch Biochem Biophys. 1985;237:408–414.
109. Laustsen C, Nielsen PM, Norlings T, et al. Antioxidant treatment attenuates lactate production in diabetic nephropathy. Am J Physiol Renal Physiol. 2017;312:F192–F199.
110. Yan LJ. Positive oxidative stress in aging and aging-related disease tolerance. Redox Biol. 2014;2:165–169.
111. Bhatt NM, Aon MA, Tocchetti CG, et al. Restoring redox balance enhances contractility in heart trabeculae from type 2 diabetic rats exposed to high glucose. Am J Physiol Heart Circ Physiol. 2015;308:H291–H302.
112. Tocchetti CG, Stanley BA, Sivakumar V, et al. Impaired mitochondrial energy supply coupled to increased H2O2 emission under energy/redox stress leads to myocardial dysfunction during Type I diabetes. Clin Sci (Lond). 2015;129:561–574.
113. Berlett BS, Stadtman ER. Protein oxidation in aging, disease, and oxidative stress. J Biol Chem. 1997;272:20313–20316.
114. de M Bandeira S, da Fonseca LJ, da S Guedes G, Rabelo LA, Goulart MO. Vasconcelos SM. Oxidative stress as an underlying contributor in the development of chronic complications in diabetes mellitus. Int J Mol Sci. 2013;14:3265–3284.
115. Haldar SR, Chakrabarty A, Chowdhury S, Haldar A, Sengupta S, Bhattacharyya M. Oxidative stress-related genes in type 2 diabetes: association analysis and their clinical impact. Biochem Genet. 2015;53:93–119.
116. Henriksen EJ, Diamond-Stanic MK, Marchionne EM. Oxidative stress and the etiology of insulin resistance and type 2 diabetes. Free Radic Biol Med. 2011;51:993–999.
117. Lenzen S. Oxidative stress: the vulnerable beta-cell. Biochem Soc Trans. 2008;36:343–347.
118. Shah S, Iqbal M, Karam J, Salifu M, McFarlane SI. Oxidative stress, glucose metabolism, and the prevention of type 2 diabetes: pathophysiological insights. Antioxid Redox Signal. 2007;9:911–929.
119. Hamity MV, White SR, Walder RY, Schmidt MS, Brenner C, Hammond DL. Nicotinamide riboside, a form of vitamin B3 and NAD+ precursor, relieves the nociceptive and aversive dimensions of paclitaxel-induced peripheral neuropathy in female rats. Pain. 2017;158:962–972.
120. Parveen K, Ishrat T, Malik S, Kausar MA, Siddiqui WA. Modulatory effects of Pycnogenol in a rat model of insulin-dependent diabetes mellitus: biochemical, histological, and immunohistochemical evidences. Protoplasma. 2013;250:347–360.
121. Ku CR, Lee HJ, Kim SK, Lee EY, Lee MK, Lee EJ. Resveratrol prevents streptozotocin-induced diabetes by inhibiting the apoptosis of pancreatic beta-cell and the cleavage of poly (ADP-ribose) polymerase. Endocr J. 2012;59:103–109.
122. Chanpoo M, Petchpiboonthai H, Panyarachun B, Anupunpitsit V. Effect of curcumin in the amelioration of pancreatic islets in streptozotocin-induced diabetic mice. J Med Assoc Thai. 2010;93(Suppl. 6):S152–S159.
123. Ding Y, Zhang Z, Dai X, et al. Grape seed proanthocyanidins ameliorate pancreatic beta-cell dysfunction and death in low-dose streptozotocin- and high-carbohydrate/high-fat diet-induced diabetic rats partially by regulating endoplasmic reticulum stress. Nutr Metab (Lond). 2013;10:51.

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