The_Relationships_Between_Sorbitol_Dehydrogenase.pdf

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Original Article

The Relationships Between Sorbitol Dehydrogenase (SDH) Level and Diabetic Rethinopathy in Diabetes Melitus Type-2 Patients

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ABSTRACT

Background: The conversion of sorbitol accumulation to fructose by SDH triggers the osmotic damage in retinal endothelial cells and pericyte through the activation of advanced glycation end products (AGEs), oxidative-nitrosative stress, Protein Kinase C (PKC) pathway activation, inflammation, and the imbalance of growth factor. The osmotic damage eventually leads to DR (Diabetic Rethinopathy). Methods: This is a case-control study. DM type 2 patients who had the direct ophthalmoscopy and fundus imaging in dr. Mohammad Hoesin Central General Hospital opthalmology outpatient in Palembang was selected as a subject in this study.Patient's blood sample was collected from a mediancubital vein for 3 mL and stored in ethylene diaminetetraacetic acid (EDTA) coated tube for SDH assay by ELISA. Results: The average level of SDH in DR subjects was 13,3 ±7,8 ng/mLand the average level of SDH in Non DR was 10,7±2,3 ng/mL, p=0,044.There was no significant difference in subjects with DR and subjects in control group in level of SDH by chi square-test, which the level of SDH was devided into two groups, higher than 11,18 ng/mL and lower than 11,18 ng/mL by ROC curve. Conclusion: There was significant difference in subjects with DR and subjects in control group in level of SDH. The average of SDH level in DR subjects were more higher than Non DR subjects.

Introduction

Diabetic retinopathy (DR) has the potential to cause blindness in diabetes mellitus (DM) patients. The probability of this complication is escalating along with the duration of DM[1,2,3]. This complication prevalence in DM patients is 28,5 % with a threat to eye vision capability for about 30%, and 15% of them are blind2,3. The Diab Care Asia report in 2008, involving 1758 DM patients in 18 primary and secondary health service in Indonesia, revealed that 42% of DM patients will get retinopathy complication, in which about 6,4% is proliferative DR[4].

Blindness caused by DR is related to the obstruction and damage in micro blood vessels in the retina. Chronic hyperglycemia condition triggers the cascade of physiology and biochemical alteration which leads to microvascular damage and retina disfunction5. The Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS) stated that there is strong relevance between chronic hyperglycemia with DR, but the mechanism is not yet clear5,6. Some of the biochemical pathways regarding the potential links between hyperglycemia and DR were already investigated. Under the hyperglycemic condition, glucose flux will increase via polyol pathway, where the aldose reductase (AR) enzyme will deplete the glucose supply as they are converted to sorbitol, and finally, are converted to fructose by sorbitol dehydrogenase (SDH)[5].

Quick conversion of sorbitol accumulation to fructose by SDH triggers the osmotic damage in retinal endothelial cells and pericyte through the activation of advanced glycation end products (AGEs), oxidative-nitrosative stress, Protein Kinase C (PKC) pathway activation, inflammation, and the imbalance of growth factor. The osmotic damage eventually leads to DR[5,6]. The experimental study revealed some important connection between DR and SDH, which have an important role in the second part of polyol pathway[5,2]. Amano et al (2007) showed that SDHwas overexpressed in mammalian pericyte culture after exposed to high dose of glucose and eventually stimulated reactive oxygen. AR inhibitor and antioxidant significantly block the bad effects of excess SDH by

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preventing the loss of pericyte and vascular hyperpermeability. Loss of pericyte and vascular hyperpermeability are the initial characteristic of DR in streptozotocin-induced DM rats[8].

Methods

This is a case-control study. DM type 2 patients who had the direct ophthalmoscopy and fundus imaging in dr. Mohammad Hoesin Central General Hospital opthalmology outpatient in Palembang was selected as a subject in this study, from July 2014 – June 2016. The study had ethical clearence from Bioethics and Humaniora Unit Faculty of Medicine Sriwijaya University, Indonesia. Inclusion factor for DR group subjects was: (1) had DR based on ETDRS criteria and confirmed by direct ophthalmoscopy and fundus imaging; (2) aged 45-65 years old; (3)DM type 2 patients without any DR symptoms after direct ophthalmoscopy were considered as control. Every group has40 subjects and their age, gender, and the DM duration were recorded.

Patient's blood sample was collected from a mediancubital vein for 3 mL and stored in ethylene diaminetetraacetic acid (EDTA) coated tube for SDH assay.Blood samples were centrifuged 10.000 rpm for 10 minutes. Supernatan was collected. Solid phase sandwich ELISA (HumanSDH ELISA kit, Abcam) were used to analysis concentration of SDH. Add samples and standards and incubate the plate at 37oC for 90 minutes, do not wash. Add biotinylated antibodies and incubate the plate at 37oC for 60 minutes, wash plate 3 times with PBS 0,01 M. Add ABC working solution and incubate the plate at 37°C for 30 minutes. Wash plate 5 times with PBS 0,01 M. Add TMB colour developing agent and incubate the plate at 37°C in dark for 20 minutes. Add TMB stop solution and read the OD absorbance at 450nm in a microplate reader. The standard curve was plotted as the OD 450 of each standard solution vs the concentration of standard solution. The human SDH concentration of the samples was interpolated from the standard curve.

The data was analyzed using SPSS 22. The relationship between SDH level and DR cases was analyzed by chi square, with 95% confidence interval. The data was shown descriptively in narration, table, and percentage.

Results:

There was no significant difference in subjects with DR and subjects in control group in gender, mean age, dan the DM duration(table 1).

Table 1. Subject's general characteristic in DR group and control group.

Characteristic	DR group (%)	Control group (%)	p
Gender			
• Male	22 (55)	20 (50)	0,89*
• Female	18 (45)	20 (50)	
Age (year)	55,95±6,78	55,85±5,95	0,96**
DM duration			
• ≥ 5 years	29 (72,5)	28 (70)	0,76*#
• <5 years	11 (27,5)	12 (30)	

*Chi-square test, *# Fisher exact test, ** Unpaired T-test

There was significant difference in subjects with DR and subjects in control group in level of SDH. The average of SDH level in DR subjects were more higher than Non DR subjects (Table 2).

Table 2. SDH Level in DR and Non DR Subjects

	DR	Non DR	p value*
Level of SDH (ng/mL) ± SD	13,3 ± 7,8	10,7±2,3	0,044

*p<0,05, Mann Whitney Test

There was no significant difference in subjects with DR and subjects in control group in level of SDH by chi square-test, which the level of SDH was devided into two groups, higher than 11,18 ng/mL and lower than 11,18 ng/mL by ROC curve (Table 3).

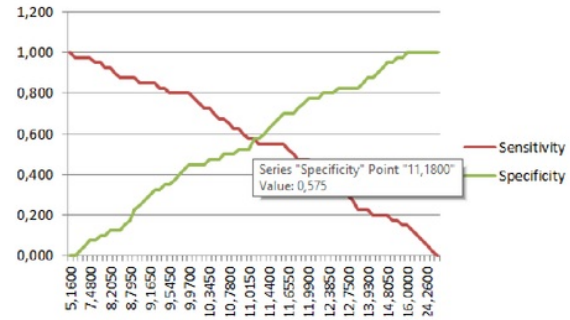

Figure 1. Cut of Point SDH Level by ROC Curve

Table 3. The Relationships Between SDH Level in DR and Non DR subjects

	DR (%)	Non DR (%)	p value*
SDH Level ≥ 11,18 ng/mL	23 (57,5)	17 (42,5)	0,18
SDH Level < 11,18 ng/mL	17 (42,5)	23 (57,5)	

*p<0,05, Chi square test

Discussion

Preston et al observed increased serum sorbitol in patients with type 2 DM and normal people. Mixed-meal tolerance test also showed increased sorbitol serum at meal times and during fasting.9 But the serum fructose level was more significantly increase in post prandial than fasting. Other study showed increased eritrocyte sorbitol at meals and fasting.10 Sorbitol (serum or erythrocytes) is a strong marker on polyol pathways rather than fructose, and less likely to be affected by acute metabolic status changes.

The polyol pathway is based on the enzyme aldose reductase.11,12,13,14Aldose reductase reduces toxic aldehydes in the cell to inactive alcohols, which is its normalfunction.10,13When glucose concentration in the cell becomes too high, aldose reductase also reduces that glucose to sorbitol, using nicotinamide adenine

dinucleotide phosphate (NADPH) as a cofactor. NADPH is an essential cofactor for regenerating critical intracellular antioxidants, and is then reduced to glutathione (GSSG). Sorbitol is then oxidised to fructose by the enzyme sorbitol dehydrogenase, which uses nicotinamide adenine dinucleotide (NAD+) as a cofactor.11,12,13,14Sorbitol is an alcohol, and is highly hydrophilic.10,13Therefore it does not diffuse easily through the cell membrane and accumulate intracellularly. Sorbitol is also more difficult to metabolise.The buildup of sorbitol has damaging effects in cells, including osmotic damage.10,13Oxidative stress results from the oxidation of sorbitol to fructose because NAD+ is converted to NADH, which is the substrate for NADH oxidase that generates reactive oxygen species (ROS).15,16Oxidative stress is the critical factor in the development of diabetic complications, including diabetic retinopathy.15Oxidative stress and the resultant tissue damage are the hallmarks of chronic disease and cell death.

The usage of NAD+ by sorbitol dehydrogenase leads to an increased NADH/NAD+ ratio, which is termed 'pseudohypoxia' and is linked to a number of metabolic and signalling changes that alter cell functions and increased production of ROS within a cell.15,16The excess NADH may become a substrate for NADH oxidase, and this would be a mechanism for the generation of intracellular oxidant species. Altering intracellular tonicity would expose cells to oxidative stress (oxidant-derived tissue injury) through decreased antioxidant defences, and generation of oxidant species that would ultimately initiate and multiply several mechanisms of cellular damage. Decreased NADPH/NADP and increased NADH/NAD+ could potentially account for all of the other biochemical abnormalities seen in diabetic complications,In cells where sorbitol dehydrogenase activity is high, this may result in an increased NADH/ NAD+ ratio. A decreased NADH/NADP ratio can increase oxidative stress by decreasing regeneration of cellular antioxidant (reduced glutathione from oxidised glutathione) and by decreasing availability of NADPH, thereby decreasing the activity of catalase, the enzyme responsible for converting ROS and Hydrogen peroxide (H2O2) into water. By reducing the amount of reduced glutathione, the polyol pathway increases susceptibility to intracellular oxidative stress.10Hyperglycaemia increases the NADH/NAD+ ratio in complication-prone cell populations. An elevated NADH/ NAD+ ratio could significantly affect the health of the retina.16

Produced fructose can become phosphorylated to fructose-3-phosphate which in turn can be broken down to 3-deoxyglucose and 3-deoxyglucosone.11These two compounds are strong glycating agents that can result in the production of advanced glycation end products (AGEs).16AGEs are a heterogeneous group of molecules formed from the non-enzymatic reaction of reducing sugars with free amino groups of proteins, lipids and nucleic acids,and are major pathogenic mediators of almost all diabetic complications. They are found in the retinal vessels of diabetic patients.16AGEs increase leukocyte adhesion to retinal microvascular endothelial cells through intracellular ROS generation. Hyperglycaemia inside the cell increases the synthesis of diacylglycerol, which is a critical activating cofactor for protein kinase-C (PKC). When PKC is activated by intracellular hyperglycaemia, it alters gene expression and protein function.13The factors that promote normal function are decreased, and those that are adverse to normal function are increased, resulting in cell damage.

Conclusion

There was significant difference in subjects with DR and subjects in control group in level of SDH. The average of SDH level in DR subjects were more higher than Non DR subjects.

References

1. Cheung N, Mitchell P, Wong T Y. Diabetic retinopathy. Lancet 2010; 376: 124–36
2. Bandello F, Menchini F. New Insight Into the Pathogenesis of Diabetic Retinopathy. Johns Hopkins Advanced Studies in Ophthalmology. Vol 5 no 1 March 2008
3. Rogers, S.L. et al. Global Prevalence and Major Risk Factor of Diabetic Retinopathy. Diabetes care 35:556-564. 2012
4. Niazi, M.K., et al. Duration of Diabetes as a Significant Factor for Retinopathy. Pak J Ophthalmolo 26(4):182-186. 2010
5. Amano S, Yamagishi S, et al. Polymorphism of Sorbitol Dehydrogenase (SDH) gene and Susceptibility to Diabetic Retinopathy. Medical hypotheses 2003; 60(4): p550-551
6. Scientific Department The Royal College of Ophthalmologist. Diabetic Retinopathy Guidelines. London;2012. www.rcophth.ac.uk
7. Sotoodeh A. The Genetic Study of Diabetic Retinopathy. Department of Ophthalmology, Faculty of Health Sciences, Flinders University, South Australia
8. Carr IM, Markham AF. Molecular Genetic Analysis of The Human Sorbitol Dehydrogenase Gene. Mammalian Genome 6, 645-52 (1995)
9. Preston GM, Calle RA. Short Report: Elevated Serum Sorbitol and not Fructose in Type 2 Diabetic Patients. Biomarker Insights 2010; 5: 33-38
10. Gabbay KH. The sorbitol pathway and the complications of diabetes. New Engl J Med. 1973;288:831–836. http://dx.doi.org/10.1056/NEJM197304192881609
11. Szwergold BS, Kappler F, Brown TR. Identification of fructose 3-phosphate in the lens of diabetic rats. Diabetes. 1986;35:426–432.
12. Gonzales RG, Bornett P, Aguayo J, Cheng HM, Chylock LT. Direct measurement of polyol pathway activity in the ocular lens. Diabetes. 1984;33:196–199. http://dx.doi.org/10.2337/diab.33.2.196
13. Brownlee M. Biochemistry and molecular cell biology of diabetic complications. Nature. 2001;414:813–820. http://dx.doi.org/10.1038/414813a
14. Aronson D. Hyperglycemia and the pathobiology of diabetic complications. Adv Cardiol. 2008;45:1–16. http://dx.doi.org/10.1159/000115118
15. Wiemer NGM, Dubbelman M, Ringens PJ, Polak BCP. Measuring the refractive properties of the diabetic eye during blurred vision and hyperglycaemia using aberrometry and Scheimpflug imaging. Acta Ophthalmol. 2009;87:176–182. http://dx.doi.org/10.1111/j.1755-3768.2008.01212.
16. Duke-Elder S. Changes in refraction in diabetes mellitus. Br J Ophthalmol. 1925; 9:167–187. http://dx.doi.org/10.1136/bjo.9.4.167

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