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Hyperglycemia combined hyperlipidemia, a critical factor influences increased production of advanced glycation and lipoxidation end products, and thus worsens the pathology of diabetic microvascular disease

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Statement of the Problem: Diabetic Retinopathy (DR), a form of microangiopathy, is one of the leading causes of blindness across the world. Among the different biochemical pathways implicated in the pathogenesis of DR, the process of formation and accumulation of Advanced Glycation end Products (AGEs) and their mode of actions have been considered as major initiator of retinal micro vascular complications in type 2 diabetes mellitus (DM). AGEs are non-enzymatically glycated and oxidized proteins or lipids, which accumulate in the vessel wall, where they may perturb vascular endothelial and pericyte cell structure and function. Apart from hyper-glycemic events, irreversibly proteins are also modified by non-enzymatic reaction of reactive carbonyl species, produced by lipid peroxidation and lipid metabolism among diabetic individuals. However, the term Advanced Lipoxidation End products (ALEs) comprises modified protein adducts, derived from malondialdehyde as well as other lipid peroxidation products.

Methodology & Theoretical Orientation: In the present study, we have investigated whether AGEs and its late oxidative products in normal individuals without diabetes (HC), patients of type 2 DM without retinopathy (DNR) and patients of DR i.e. in non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR) were significantly different. We have also measured serum lipoproteins, cholesterol, triglycerides, hexanoyl-lysine (HEL), and malondialdehyde (MDA) protein adduct (a potential ALE species) to understand the cross-talk of diabetes associated hyperlipidemia and ALEs in the occurrence of NPDR. Enzyme linked immunosorbent assay, spectrophotometry and flow cytometry techniques were employed to measure different glyco or lipoxidative products, lipids and reactive oxygen species from blood.

Findings: Serum AGEs and Nε-CML level was significantly elevated in subjects with PDR and NPDR compared to DNR subjects. Further vitreous AGEs and Nε-CML level was found extensively high among PDR subjects compared to control group. Reactive oxygen species production was found strikingly high among NPDR and PDR subjects as compared to DNR group. Serum and cellular total thiol level was decreased remarkably in NPDR and PDR subjects than those were considered as DNR. A robust linear relationship was observed in between MDA protein adduct and LDL or cholesterol or triglyceride level, and HEL and LDL or cholesterol or triglyceride level among MNPDR subjects.

Conclusion & Significance: Our findings suggest that AGEs mediated ROS are the key modulator for the development of NPDR among poorly controlled type 2 diabetic subjects whereas AGEs under persistent oxidative stress and deprived antioxidant state might instigate the pathogenic process of retinopathy from non-proliferative to proliferative state. Hyperlipidemia is also an important factor associated with increased ALEs formation in NPDR. Increased ALEs generation was found to be associated with the decreased availability of principle cellular reductants in NPDR, suggesting their detrimental role in the occurrence of early NPDR.

Biography

Subhadip Choudhuri is investigating the role of different lipoproteins, advanced glycation and lipoxidation end products, cell migration and adhesion molecules in the development of diabetic microvascular diseases. Major area of research interest includes investigating the cellular and molecular mechanism involved in the metabolic deregulation and pathophysiology of pre-diabetes & type 2 diabetes mellitus and related microvascular dysfunction. He is the Fellow of National Academy of Biochemistry (American Association of Clinical Chemistry). He has completed his PhD in Biochemistry from University of Calcutta in 2013. He is the Reviewer of several international journals and has 20 international publications in high impact journals. At present, he is a Chief Biochemist and Research Scientist at GD Hospital and Diabetes Institute, Kolkata.

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