Genetic Markers SOD1, GPX1, &CAT Distribution and Their Pattern of Linkage in The Pathogenesis of Cataract in Type 2 Diabetic Patients of Pakistan

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ABSTRACT

Introduction: Cataract is one of the major causes of blindness throughout the world (WHO, 2017). The occurrence of cataract is higher in diabetic patients due to the overproduction of ROS which ultimately develops oxidative stress (Ito*et al.,* 2019). The primary antioxidant enzymes SOD1, CAT and GPX1 play a significant role in the dissociation of reactive metabolites inside the lens which provides protection from oxidative stress (Ighodaro andAkinloye, 2018).

Objectives: Present study comprised of following objectives:

- To examine the distribution of promotor sequence *GPX1* (*rs1800668)*, *CAT* (*rs1001179*) and *SOD1* 50 bp Indel variants among four groups of study.
- To evaluate the role of three genetic variant with risk cataractogenesis in type 2 diabetes.
- To assess the association of haplotypes and the pattern of linkage disequilibrium

Methodology: It was a large case-control study. The study was categorized in four groups of subjects (total n=680): type 2 diabetes mellitus (T2DM), diabetic cataract (DC) group, senile cataract (SC) group and controls. Each group contains n=170 blood samples. DNA isolation was performed by salting out protocol. After that genotyping of *SOD1* 50 bp Indel variant was undergone by conventional PCR, while *GPX1* (*rs1800668)* and *CAT* (*rs1001179*) variants were screened by allele specific polymerase chain reaction (AS-PCR). Statistical testing was conducted using SPSS version 20.0 and SNPstats software. Chisquare, odds ratio, genetic models and haplotypes were used to check the presence of association and role of mutants. While, bioinformatic analysis was carried out by Haploview version 7.0 software for the investigation of linkage disequilibrium.

Results: *GPX1* (*rs1800668)* variant elaborated a significant role to the higher susceptibility of T2DM ($\chi2$=14.0, p<0.001) and opacification of lens in the state of hyperglycaemia ($\chi2$=23.0, p<0.001). Mutant T allele of *GPX1 C/T* variant indicated a significant role for the risk of diabetic cataract (p<0.001). However, no statistical association was observed in the genetic distribution of *SOD1* 50 bp and *CAT* (*rs1001179*) variants in studied group of population. Though, a significantly higher frequency of C/T genotype (DC=0.60 and SC=0.23) and T/T genotype (CC=0.23 and CT=0.05) of *CAT* variant (rs1001179) was found in diabetic cataract group. Nevertheless, among the patients of senile cataract group, the C/C genotype was frequently detected in higher probability (SC=0.71 and DC=0.16) than diabetic cataract group. Depiction of risk was indicated by the haplotype CTI, TTI and CTD in the pathogenesis of T2DM (OR<1.0), but no statistical significance was observed in comparison to controls. While, the haplotype CTD showed a probability of insignificant risk with diabetic cataract in comparison to senile cataract group (OR=3.60). A significant

protective role of haplotypes TCI, TCD and TTI was observed against the pathogenicity of diabetic cataract ($p<0.01$). In linkage disequilibrium, haploblock CTC-CTT demonstrated the significant pattern of linkage ($D'=1.0$) and co-inheritance (LD=13.84) with accelerated risk of cataractogenesis in the pathogenesis of type 2 diabetes mellitus.

Conclusions: *GPX1* (*rs1800668)* variant may serve the role of a potential antioxidant biomarker. Since, GPX1 enzyme performs an important function in the modulation of oxidative stress. The polymorphism may create hinderance in developing resistance for oxidative stress which ultimately induces the formation of opacities and accelerates aging. Pharmacogenomic studies and genotype-phenotype correlation of antioxidant biomarker would be beneficial in future as a therapeutic target for eradicating the risk of cataract in T2DM.

Keywords: Oxidative stress, antioxidant enzymes, cataractogenesis, hyperglycaemia

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