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Mini Review

Advanced Glycation End Products: Do They Play a Role in the Cataract Formation?

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Abstract

Prevalence of diabetes is gradually increasing worldwide. Ocular diseases including cataract occur at an earlier age with a frequency higher than the non-diabetes subjects. Hence cataract was demonstrated as the most common cause of visual impairment in older-onset diabetic patients. Furthermore, risk after the phacoemulsification cataract surgery remains high among such patients. Various molecular mechanisms have been demonstrated for degenerative changes in the lens. Advanced glycation end product (AGE) accumulation was also evidenced in older-onset diabetic patients with cataract. AGE might have a role in degenerative changes in the lens which is found to be occurring early in the diabetic patients. The AGE with its receptor interaction might be involved in ageing, oxidative stress, inflammation and fibrotic changes. This review article discusses the role of AGE in the cataractous lens formation.

Keywords: *Cataract; Advanced Glycation End Product; Diabetes Mellitus; Antioxidants; Transforming Growth Factor-Beta*

Introduction

The global prevalence of diabetes was expected to reach 4.4% by 2030 [1]. In Patients with diabetes, cataract like ocular disease occurs at an early age with a frequency higher than the non-diabetes subjects. Further, the incidence of cataract was found high with duration of diabetes [2]. Hence, cataract is considered as one of the most common causes of visual impairment in older diabetic patients. Approximately 20% of patients who have had surgical treatment for cataract have diabetes [3]. Epidemiological study during the last decade found that 8.3% cataract surgery was conducted in type 1 diabetes patients while that in type 2 patients it was 24.9%. Advanced glycation end product (AGE) might have a role in degenerative changes in the lens which is found to be occurring early in the diabetic patients. The AGE with its receptor interaction might be involved in ageing, oxidative stress, inflammation and fibrotic changes. Oxidative stress associated lipid peroxidation level was significantly high in the lens of diabetic patients than in the senile subjects [4,5]. This review article discusses the role of AGE in the cataractous lens formation.

Role of Advanced glycation end products in cataract formation

Many molecular mechanisms were put forward for the incidence of cataract in diabetes. The three major mechanisms were non-enzymatic glycation of lens proteins, oxidative stress and osmotic stress associated with an activated polyol pathway. Though the non-enzymatic glycation of lens proteins was demonstrated as well, the role of AGE in cataract has not yet been established. AGE has been associated with a broad spectrum of human diseases. Among the diseases demonstrated so far cardiovascular, cancer and neurodegenerative diseases remain the major [6,7]. Recently a group of senile ocular diseases like cataract, glaucoma and age-related macular degeneration were also found to be associated with AGE [8,9]. AGEs are non-enzymatic glycation end product on tissue proteins. They enter the body either through food or is formed inside during ageing. In diabetes, their level was correlated to the hyperglycemic status as well as the duration of diabetes. Hence, pathological conditions in chronic diabetes have a direct link to the AGE level and thereby, the organ damages.

AGE are formed during a high temperature cooking such as broiling at 225°C or frying at 177°C of high fatty food of animal source [10]. Despite their poor bioavailability from food, a long period of ingestion of food rich in AGE may lead to their accumulation in the body. Endogenously they are formed as a rapid non-enzymatic reaction between the ketone or aldehyde group of sugar with free amino groups of either free amino acids or proteins. An intermediate labile Schiff base is formed first which is further converted slowly to stable Amadori-products. A wide variety of AGEs are demonstrated in humans. N-ε-carboxy-ethyl-lysine, pentosidine and N-ε-carboxy-methyl-lysine are the major AGEs among others. Since the lipid peroxidation, as well as oxidative stress, was mainly involved in the rearrangement of the labile Schiff base, conditions like diabetes were reported as a risk factor for the formation of AGE.

Studies in human have demonstrated a positive correlation between diabetic microvascular complications and the serum AGEs levels. Many studies during last decade had emphasized the role of AGE in cataract formation. However, the complete mechanism remains elusive. Since they are formed and involved in the process of ageing, a direct link can suggest between AGE and cataract. Gul., *et al*. reported that AGE has role in the cataract formation in senile diabetic patients [11]. This was demonstrated by immunoreactivity against AGE in alkali-soluble lens samples. Pokupec., *et al*. hypothesised that the AGE might have a role in degenerative changes in lens which is found to be occurring early in the diabetic patients and will be higher than subjects without diabetes [12]. An ELISA-based measurement of AGEs level in lens crystallins of streptozocin-induced diabetic rat supports the role of AGE in cataract [13].

In a recent review, the receptor for AGEs referred as RAGE mediated molecular mechanism of inflammation and thereby, the oxidative stress has been demonstrated [14]. The AGE-RAGE interaction can cause the activation of nuclear factor kappa B and thus, the release of several pro-inflammatory cytokines, free radicals and chemokines (Figure 1). In addition to the oxidative stress, the pro-inflammatory cytokines were involved in the modification of extracellular matrix [15]. AGEs-RAGE interaction was demonstrated in cultured human lens epithelial cells which could lead to an increase in the transforming growth factor-β1 and β2 mRNA expression. Smad2 and Smad3 are involved in the TGF-β2 mediated downstream signaling pathway. As the age advances, the proteins in the basement membrane of lens were found to be modified chemically and gets accumulated. The AGE content of the capsule proteins was correlated with the TGFβ2-mediated synthesis of α-smooth muscle actin [16]. TGF-beta can also induce apoptotic cell death in human lens epithelial cells and reduces the Bcl-2 expression [17]. Liquid chromatography-Mass spectra based analysis evidenced an increased level of AGEs in cataractous lens capsules than in normal lens capsules. The signaling pathway of TGF-β2/Smad -mediated epithelial-to-mesenchymal transition of cultured lens epithelial cells was proposed as a mechanism for posterior capsule opacification or secondary cataract formation [18]. The AGE-RAGE interaction further aggravates the superoxide and hydrogen peroxide generation in the epithelial cells and oxidative damage to lens fibers [19,20]. Concluding these findings, AGE may have critical role in the initiation or acceleration of cataract in diabetic patients.

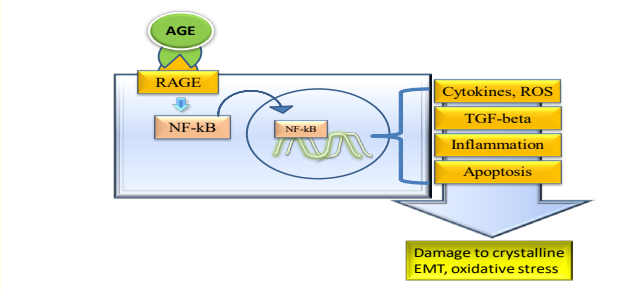

Figure 1: *Advanced glycation end product (AGE) in the cataract formation in cultured lens epithelial cells. AGE interacts with its receptor (RAGE) on lens epithelial cells. AGE-RAGE interaction, in turn, increases the activation of nuclear factor kappa B (NF-kB), which is translocated to nucleus and enhance the expression of cytokines, reactive oxygen species (ROS), apoptosis and transforming growth factor-beta (TGF-β). TGF-β can induce the apoptotic cell death in lens epithelial cells and further promotes the epithelial-to-mesenchymal transition (EMT). ROS can accelerate the cataract by oxidative stress and thus denaturation of lens crystalline, Overall leads to opacities of the lens.*

Conclusion

Exogenous and endogenous advanced glycation end products interact with the receptor and produce aging, oxidative stress, inflammation and fibrotic changes of organs. Oxidative stress and the associated fibrotic changes have long been recognized as one of the risk factors that accelerate the cataractous lens formation. However, the exact role played by AGE in cataract formation is elusive which warrant more future studies. Nevertheless, the role played by AGE in cataract, blockade of AGE-RAGE interaction by anti-RAGE antibody was recommended as a novel strategy to prevent age-associated fibrosis [21]. In general, supplementation of food rich in antioxidants such as vitamin C, vitamin E, carotenoids, trolox and pyridoxine may alleviate the AGE accumulation and thereby the cataract formation.

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