Relationship of cytokines and AGE products in diabetic and non-diabetic patients with cataract

Sadaf Hamid,[1] Anjuman Gul,[2] Qamar Hamid [3]

[1] Department of Anatomy, Jinnah Sindh Medical University, Rafique Hariri Road, Karachi, Pakistan;
[2] Department of Biochemistry, College of Medicine, Qassim University, Kingdom of Saudi Arabia;
[3] Department of Anatomy, Lyari Medical College, Karachi, Pakistan.

Abstract:

Objectives: Cytokines are important mediators of inflammatory and immune responses. The aim of this study was to investigate the changes in cytokines concentration (IL-6, IL-8 and TNF-α) and serum advanced glycation end products (sAGEs) in senile diabetics with or without cataract and non-diabetic patients with cataract.

Methodology: The study included 124 subjects (sixty or over sixty years age), distributed as four groups thirty senile diabetic patients with cataract (Group I) (16 female and 14 male), thirty senile non-diabetic patients with cataract (Group II) (15 female and 15 male), thirty three senile diabetic patients without any complication (Group III) (16 female and 17 male), thirty one apparently normal healthy individuals (Group IV) (16 female and 15 male), age, sex and weight matched with senile control subjects were investigated. Patients were selected on clinical grounds from Eye Ward Jinnah Postgraduate Medical Centre.

Results: Interleukin-6 (IL-6), interleukin-8 (IL-8) and tumor necrosis factor-α (TNF-α) levels were significantly increased ($P < 0.001$) in Group I and III as compared to Group II and IV. Fasting blood glucose, glycosylated hemoglobin, serum fructosamine, malondialdehyde (MDA), sAGEs, IL-6, IL-8 and TNF-α levels were significantly increased ($P < 0.001$) in Group I as compared to Group II and the levels were almost same in Group II and IV. There was a significant decrease in serum vitamin E and total antioxidant status ($p< 0.001$) in Group I and Group III as compared to Group II and Group IV.

Conclusion: The results of the present study thus demonstrated that levels increased in both condition but are more severe in diabetic patients with cataract that may be a predictor for cataractogenesis and the levels were almost same in Group II and IV.

Key words: Diabetes, cataract, cytokines, Interleukin, tumor necrosis factor.

Correspondence:

Dr Sadaf Hamid,
Associate Professor,
Department of Anatomy,
Sindh Medical College,
Jinnah Sindh Medical University,
Rafiqi H.J Shaheed Road, Karachi-75510,
Pakistan.
Tel: 92-204776
Fax: 92201372
Email: sadafhamid2001@yahoo.co.in

Introduction

Diabetes mellitus is one of the rising health alarms of Pakistan. Over 12% of the Pakistani population in the age group of 25 years and above suffer from this disease and about 10% from impaired glucose tolerance.[1, 2] Cataract is the most common cause of blindness in the world. The incidence of cataract has increased dramatically over the past 2 decades. [3] IL-6, IL-8 and TNF-α and certain chemokines which are supposed to be intermediates of inflammation have been anticipated to be involved in the events causing diabetes and complications. [4] IL-6, a major proinflammatory cytokine, is produced in a variety of tissues. [5] Several studies have demonstrated elevated levels of IL-6 among individuals both with features of the insulin resistance syndrome and clinically overt type 2 diabetes. [6] Elevated serum IL-8 levels were found in type 1 and type 2 diabetic subjects and it is suggested that this cytokine might also contribute to the development of diabetic macroangiopathy. [7] IL-8's primary function is to recruit neutrophils to phagocytose the antigen which trigger the antigen pattern toll-like receptors. [8] Chronic elevated glucose level in diabetes increases monocyte adhesion to aortic endothelial cells which is mediated primarily through induction of IL-8. [9] Insulin resistance and TNF-α overexpression in adipose tissue and skeletal muscle are important features of human obesity, related to each other, as TNF-α induces insulin resistance by acting via autocrine-paracrine pathway. AGEs have been reported to accelerate in aging, cardiovascular complications and cataract formation in diabetic and non-diabetic patients. [10] AGEs are the heterogeneous group of compounds that have multiple biological effects on various cell types including endothelial cells, macrophages and smooth muscle cells and these effects are mediated by interacting with receptors for AGE. [11] Among many other causes, diabetes is considered a major risk factor for the development of cataract and it has been reported that cataract reaches maturity almost 10 years earlier in the presence of diabetes. [12] Cataract is a major complication of diabetes and is a cause of impaired vision and blindness worldwide and often referred as senile cataract to indicate that it is more common in advanced age. [13] Several different pathogenetic mechanisms have been proposed to explain the accelerated cataractogenesis of diabetes including increased polyol pathway flux, [14] elevated oxygen free radical formation [15] and the advanced glycation process. [16] There are several studies which report that serum AGEs increases in senile diabetic patients but whether cataract formation contributes to increase AGEs in these patients is not known. Objective of this study is to determine the extent of cytokines (IL-6, IL-8 and TNF-α) and AGEs in senile diabetic and non-diabetic patients with cataract.

Materials and Methods

Study design

This is a case control (comparative study) carried out at Ziauddin University. Patients were selected on clinical grounds from Eye Ward Jinnah Postgraduate Medical Centre, Karachi.

Patients

Clinically confirmed cases of senile diabetic and non-diabetic patients with and without cataract were selected. Study subjects were classified in to four groups:

1. Group I: Senile diabetic patients with cataract.
2. Group II: Senile non-diabetic patients with cataract.
3. Group III: Senile diabetic patients without any complication.
4. Group IV: Apparently normal healthy individuals.

Study Protocol

Duration of diabetes and its complications were recorded. Duration of the disease was defined as the time that had elapsed between the patients' initial diagnosis of diabetes and their present visit to the clinic. The weight of patients was given with reference to their height as their body mass index (BMI), which is defined as weight (kg) divided by the square of their height in meters (m^2). Sex, weight, duration of diabetes, duration of complication in diabetic and non-diabetic patients, type of diabetes and type of treatments received were also recorded. Physical examination including measurement of blood pressure was done. Individuals were classified as having diabetes mellitus if any of the following criteria were met: [17] fasting serum glucose levels of $\leq$7.0 mmol/L (126 mg/dl), random glucose levels $\leq$11.1mmol/L (200

mg/dl). They were labeled as impaired glucose tolerant or borderline if fasting blood glucose was between 6.9 to 7.0 mmol/l and random blood glucose ≥7.8 mmol/l but ≤11.1 mmol/l. Diabetic patients were diagnosed if fasting blood glucose was ≥7.0 mmol/l and random was ≥11.1 mmol/l. Current use of medications prescribed to treat diabetes (e.g. insulin or drugs), or a positive response to the question "has a doctor ever told you that you had diabetes i.e. (sugar in the blood)?" The local ethical committee approved the protocol and written informed consent was obtained from each patient after the nature of the study had been fully explained.

Exclusion Criteria

- Patients below the age of sixty years.
- Patients with more than one complication.
- Patients having a history of ocular trauma, uveitis or glaucoma.
- Patients having a history of other macrovascular disease like angina, stroke, intermittent claudication, vascular surgery or amputation for atherosclerotic disease or one or more absent foot pulses on examination were excluded from study.

Inclusion Criteria

The patients, who were sixty or over sixty years with cataract were included. Patients having history of blurred vision, double vision and spots were examined by slit lamp to determine the cataract. Patients having cataract either in one or both eyes were included in the study. Diabetic patients without any complications were also included and investigated.

Control subjects

The study included thirty one apparently normal, age, sex and weight matched senile control subjects. Senile control subjects were having no history of diabetes and any other major illness like macrovascular disease, cataract, retinopathy, tuberculosis, rheumatoid arthritis, liver diseases or malignancy were selected.

Sample Collection

All medication was stopped at least two days before the blood was drawn. Fifteen to twenty ml of blood samples were obtained in fasting state after a 10-h overnight fast. Samples were withdrawn by venous puncture and distributed equally into two tubes containing EDTA or heparin (for glucose estimation) and one tube with no anti-coagulant (for serum collection). The samples were then immediately stored on ice until processed. Glycosylated hemoglobin was estimated within 8 days. Clotted blood was centrifuged at 1,500 rpm for 30 min and the serum was separated and frozen at -70°C until analysis. Samples were thawed and analyzed in batches.

Biochemical estimations

Blood glucose was determined by glucose oxidase method, glycosylated hemoglobin (HbA1C) was determined by using the HbA1C kit (Bio Systems Reagents and Instruments, Barcelona, Spain). The serum fructosamine was determined by using a fructosamine kit (Quimica Clinia Aplicada, Spain). Total serum protein was determined by Biuret Method of Reinhold. [18] The quantity of total antioxidant capacity was measured according to the Randox kit procedure (Randox, UK). ABTS (2, 2'-Azino-di-[3-ethylbenzthiazoline sulphonate]) is incubated with a peroxidase (metmyoglobin) and H_2O_2 to produce the radical cation ABTS. This is relatively stable and is of bluish-green color, and was measured at 600 nm. Antioxidants in the added sample cause suppression of this color production to a degree which is proportional to their concentration. [19] MDA of the serum sample was reacted with thiobarbituric acid to form a pink-colored pigment, the absorbance of which was measured at 535 nm. [20] Vitamin E was measured on the basis of the reduction of ferric ions to ferrous ions by α-tocopherol and subsequent formation of a pink-colored complex with bathophenanthroline which was measured colorimetrically at 536 nm. [21] The serum fructose concentration was measured by the colorimeteric method. [22] The amount of AGE was determined by noncompetitive ELISA using rabbit polyclonal antibodies to AGE (Abcam, UK).[23] The IL-6, IL-8 and TNF- α concentrations were measured from stored frozen serum samples using a commercially available high-sensitivity ELISA test [IL-6 ELISA kit (DRG-EIA 4640), IL-8 ELISA kit (DRG-EIA 4700) and TNF-α ELISA kit (DRG-EIA 4641)] were obtained from DRG instruments GmbH, Germany.

Statistical analysis

Data was analyzed using Statistical Package for Social Sciences (SPSS, v 10.0). Mean, standard deviation (SD) and standard error of mean (SEM) were calculated. The statistical significance of the difference between two means of various parameters between different groups was evaluated by student's t test. The difference was regarded as highly significant if the P value was less than 0.001, statistically significant if the P value was less than 0.05 and non-significant if the P value was greater than 0.05.

Results

Fasting blood glucose, glycosylated hemoglobin, serum fructosamine significantly increased ($P < 0.001$) in Group I and Group III as compared to Group II and Group IV (Table 3). Table 3 also demonstrated that the level of MDA and serum AGEs significantly increased ($p < 0.001$) in Group I and Group III as compared to Group II and Group IV. There was a significant decrease in serum vitamin E and total antioxidant status ($p< 0.001$) in Group I and Group III as compared to Group II and Group IV. IL-6, IL-8 and TNF-α levels significantly increased ($P < 0.001$) in Group I and Group III as compared to Group II and Group IV (Table 2). There was no significant difference between male and female blood concentrations. Data also showed no significant difference between Group II and Group IV blood levels.

Table 1. Physical features of senile diabetic and non-diabetic patients with and without cataract

The values are expressed as mean, ± standard deviation, ± standard error of mean. Units and numbers of cases are shown in parentheses.

Groups	Age (years)	Sex (F/M)	Weight (Kg)	Height (m)	BMI (Kg/m2)	Duration of Diabetes (yrs)	Duration of complications (yrs)
Senile Control subjects (31)	64.19 ±3.94 ±0.70	16/15	63.61 ±6.82 ±1.22	1.59 ±0.05 ±0.01	25.22 ±2.97 ±0.53	-	-
Diabetic patients without complicati on (33)	64.18 ±3.31 ±0.57	16/17	65.66 ±8.78 ±1.53	1.59 ±0.05 ±0.01	26.00 ±3.70 ±0.64	12.54 ±4.11 ±0.71	-
Diabetic patients with cataract (30)	64.63 ±3.50 ±0.64	16/14	64.67 ±8.11 ±1.48	1.61 ±0.05 ±0.01	24.84 ±2.38 ±0.43	11.03 ±3.79 ±0.69	3.46 ±2.01 ±0.36
Non-diabetic patients with cataract (30)	65.13 ±4.59 ±0.83	15/15	65.73 ±8.06 ±1.47	1.59 ±0.06 ±0.01	25.91 ±3.39 ±0.62	-	-

Table 2. Cytokines levels in Senile Control Subjects, Senile Diabetic Patients without Complication and Senile Diabetic and Non-diabetic Patients with and without Cataract

The values are expressed as mean, ±standard deviation, ± standard error of mean.
Units and numbers of cases are shown in parentheses.

Groups	Interleukin-6 (pg/ml)	Interleukin-8 (pg/ml)	Tumor Necrosis factor-α (pg/ml)
Senile Control subjects (31)	8.60 ±3.78 ±0.68	38.33 ±4.13 ±0.74	2.62 ±0.99 ±0.17
Diabetic patients without complication (33)	19.41[ab] ±4.17 ±0.72	64.46[ab] ±7.53 ±1.31	5.06[ab] ±1.28 ±0.22
Diabetic patients with cataract (30)	20.77[ab] ±3.27 ±0.59	61.07[ab] ±5.46 ±0.99	7.47[ab] ±1.42 ±0.26
Non-diabetic patients with cataract (30)	8.28 ±3.24 ±0.59	38.09 ±3.77 ±0.68	3.53[a] ±0.53 ±0.09

a - Significant as compared to senile control subjects
b - Significant as compared to senile non-diabetic patients with cataract

Table 3. Comparison of Physical Parameters and Blood Analytes of Senile Diabetic and Non-diabetic Patients with Cataract

The values are expressed as mean, ± standard error of mean. Units and numbers of cases are shown in parentheses.

Parameters	Senile diabetic patients With cataract (30)	Senile non-diabetic patients with cataract (30)
Age (years)	64.63 ±0.64	65.13 ±0.83
Sex (F/M)	16/14	15/15
Weight (Kg)	64.67 ±1.48	65.73 ±1.47
Height (m)	1.61 ±0.01	1.59±0.01
BMI (Kg/m2)	24.84 ±0.43	25.91 ±0.62
Systolic BP (mmHg)	121.50 ±1.12	121.67 ±1.40
Diastolic BP (mmHg)	80.67 ±1.01	81.33 ±1.14
Fasting Blood Glucose (mmol/l)	9.35 ±0.28[a]	5.21 ±0.14
Glycosylated Hemoglobin (HBA1c %)	9.51 ±0.29[a]	4.92 ±0.10
Serum Fructosamine (mmol/l)	3.59 ±0.11[a]	2.31 ±0.11
Total Serum Protein (gm/dl)	7.66 ±0.13	7.32 ±0.16
Total Anti-oxidant Status (mmol/L)	1.20 ±0.03[a]	1.36 ±0.02
Malondialdehyde (nM/ml)	13.35 ±0.58[a]	8.95 ±0.39
Vitamin E (mg/dL)	0.93 ±0.06[a]	1.45±0.04

Serum Fructose (µM/ml)	0.64 ±0.03	0.54 ±0.04
s-AGEs (mU/ml)	12.35 ±0.48[a]	10.26 ±0.29
Interleukin-6 (pg/ml)	20.77 ±0.59[a]	8.28 ±0.59
Interleukin-8 (pg/ml)	61.07 ±0.99[a]	38.09 ±0.68
Tumor Necrosis factor-α (pg/ml)	7.47 ±0.26[a]	3.53 ±0.09

a. p-value (< 0.001) significant as compared to senile non-diabetic patients with cataract.

Discussion

The number of people with diabetes is increasing due to population growth, aging, urbanization, and increasing prevalence of obesity and lack of physical inactivity. [24] Previous studies have suggested that the clinical forms of late complications seem to be the same with aging or with diabetes, although it has not been established whether the pathogenic factors involved in the development of the late complications are common and, if so, to what extent. [25, 26] The subjects selected in our study belong to senile group with same age, weight, height and equal number of male and female subjects with or without diabetes. Cataract is one of the earlier complications of diabetes mellitus. Inflammatory mechanisms play a key role in the pathogenesis of diabetes. Individuals who progress to type 2 diabetes display features of low-grade inflammation years in advance of disease onset. This low-grade inflammation has been proposed to be involved in the pathogenetic processes causing type-2 diabetes. [27] Mediators of inflammation such as IL-6, IL-8 and TNF- α have been proposed to be involved in the events causing diabetes. In the present study it was found that the values of IL-6, IL-8 and TNF- α were significantly increased (P<0.001) in Group I and III as compared to Group II and IV. The results of cataract patients are consistent with the studies who found increased levels of IL-6 in cataract lens. [28, 29] Another study by Klein et al. found that IL-6 was significantly associated with age related cataract. [30] Results of this study and previous reports support a possible role for inflammation in diabetogenesis. Another potential mechanism that may explain our results is the relationship between inflammation and endothelial dysfuntion. Altered endothelial permeability and diminished peripheral blood flow may limit insulin delivery and promote insulin resistance in metabolically active tissues. [31, 32] Studies conducted by many others showed increase TNF-α levels in cataract lens that activates NF-kappa B signal pathway that is involved in cataractogenesis. [33, 34]

In the present study it was found that the level of MDA and serum AGEs significantly increased (p < 0.001) and serum vitamin E and total antioxidant status significantly decreased in (p< 0.001) in Group I and Group III as compared to Group II and Group IV. The results of present study are consistent with the previous studies. [35, 36, 37] Oxidative stress is one of the major factors contributing to cataract formation. Oxidative damage of the lens is involved in the genesis of senile cataract and the development of diabetes related pathologic changes. It is clearly known that in people with diabetes, oxidative stress plays an important role in the pathogenesis of early and long-term complications of diabetes. The breakdown products of peroxidized polyunsaturated fatty acids, such as MDA, have been proved to be both sensitive and reliable for evaluation of oxidative stress. An increasing body of evidence suggests that ocular oxidative stress, defined as an imbalance between oxidants and antioxidants, is the key pathophysiological mechanism of senile cataract genesis. [35] Increased generation of the free radicals and decreased antioxidant activity has been proposed to play an important role in cataract formation in senile age group in various earlier and recent studies. AGEs play a pivotal role in loss of lens transparency, i.e., cataract development. Progression of cataract is increased in patients with diabetes mellitus. Some reports have revealed that AGEs accumulate in the lens, causing vision impairment and cataract. In the lens AGEs induce irreversible changes in structural proteins, which lead to lens protein aggregation

and formation of high molecular weight aggregates that scatter light and impede vision. [38] It has been shown that AGEs, by altering the surface charge of the protein, leads to conformational change that in turn may affect protein-protein and protein-water interactions and ultimately, lead to decreased transparency of the eye lens. [39]

Conclusion

Thus, all results in the present study, when taken together suggested that the elevated levels of the proinflammatory cytokines including IL-6, IL-8 and TNF- alpha in cataract, indicated that cytokines may play a role in the development of cataract. However, in our study, the mean values of males and females were not different ($p>0.05$). The results of the present study thus demonstrated that levels increased in both condition but are more severe in diabetic patients with cataract that may be a predictor for cataractogenesis and the levels were almost same in Group II and IV. However, the present study dealt mainly with the concerned parameters in a limited number of patients. More detailed studies involving a larger population section in the community including several other factors are required for a more direct and accurate analysis in future.

Competing interests

The author declares no competing interest.

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