Negative Association of Serum IL-6 and IL-17 with Type-II Diabetes Retinopathy

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ABSTRACT

Background: Diabetes mellitus (DM) is a health concern which leads to complications such as retinopathy. Pakistan has 6.9 million people living with DM and this toll will be doubled by 2025. **Objective:** To determine serum IL-6 and IL-17 of type 2 diabetes mellitus (T2DM) patients with retinopathy. **Methods:** In this cross-sectional case-control study, 212 subjects enrolled which were categorized into 3 groups. Group-I included 30 subjects without diabetes, group-II consisted of 30 subjects with T2DM without retinopathy and group-III consisted of 152 subjects with T2DM and retinopathy. Serum IL-6 and IL-17 levels were determined by ELISA. Data was analysed using SPSS 17.0 and one way ANOVA to observe group mean differences. **Results:** Longer mean duration of disease was detected in group-III than group-II ($p=0.007$). Highest IL-6 level was detected in group-II and highest IL-17 level was detected in group-I. For IL-6, significant differences were detected among groups in total, between Group-I and Group-III and between Group-II and Group-III ($p<0.0001$ each). Regarding IL-17, significant differences were found among groups in total ($p=0.002$) and between Group-I and Group-III ($p=0.001$). No significant difference in the percentages of HbA1c observed between groups. **Conclusions:** Age, gender and duration of diabetes contribute to T2DM retinopathy. Serum IL-6 and IL-17 were inversely associated with T2DM retinopathy.

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INTRODUCTION

Diabetes mellitus (DM) is a chronic disease which is present all over the world and leads to many complications such as retinopathy. Type-2 diabetes mellitus (T2DM) is relatively more common and it is one of the leading causes of morbidity and mortality. World prevalence of diabetes was 285 million in 2010, and will increase to 439 million by 2030. More than 80% of its burden is in low and middle income countries (1,2). In Pakistan, more than 6.9 million people are affected with diabetes and by the year 2025 it could affect more than 11.5 million people (3,4).

Nowadays, children of 8 years or even younger are suffering from T2DM. The rise in T2DM is associated with increased prevalence of obesity, and change in dietary and lifestyle patterns. There is more childhood T2DM in Japan, Taiwan and the USA. In 20 years T2DM may account for the 60% of non-communicable diseases in developing world (4,5). As compared to Western population, Asians are less obese, less overweight and low BMI but they have higher prevalence of DM. Increased childhood obesity and abdominal obesity are important risk factors of T2DM in Asians (5).

In diabetes, hyper reactive platelets interact with damaged vessels and cause micro thrombosis of small vessels that leads to diabetes retinopathy (DR) which is a horrifying prospect. The number of people at risk to develop DR would double in the next 30 years (6,7). People with high white cell count and raised inflammatory markers i.e. IL-6 and CRP, may develop T2DM in 20 and 4 years' time respectively (8,9).

Th17 is a subclass of T cells that produces IL-17. IL-6 and TGF-beta are required for IL-17 production and IL-23 for Th17 maintenance. Natural Killer T cells express IL-23 receptor and produces IL-17 which is independent of IL-6. IL-17 Foxp3 Treg cells are produced in peripheral circulation and contribute in antimicrobial defense and checks autoimmunity and inflammation (10,11). Th17 cells have been associated with autoimmunity, cancer, insulin resistance, type-1 diabetes (TID), etc. In TID increased level of IL-17 is detrimental for islet cells (12). IL-17 is also increased in active uveitis and decreases after treatment (13). IFN-γ produces IL-27 in the target tissue therefore alleviate uveitis by antagonizing Th17 cells (14).

Anti-IL-6 receptor antibody (Taclomide) is being used in many diseases e.g. RA. Similarly, IL-23/IL-17 axis can be a therapeutic target for diabetic complications and autoimmunity (15). Therefore, a study was designed to determine serum level of IL-6 and IL-17 in DR patients.

MATERIALS AND METHODS

Subjects. This cross-sectional case control study, was performed in the Department of Immunology, University of Health Sciences (UHS) Lahore, Pakistan. Study was approved by Ethical Committee and Advanced Studies and Research Board of UHS. It included 212 subjects: Group-I (30 healthy controls), Group-II (30 diabetes patients without retinopathy) and Group-III (152 diabetes patients with retinopathy). Subjects of either sex and between 20-75 years were selected. The patients had diabetes of 5-25 years duration. HbA1c and duration of diabetes was noted at the time of sample collection. Eye examination was performed by consultant ophthalmologist. Subjects having infection in the last two weeks and chronic infection like TB, and autoimmunity were excluded.

IL-6 and IL-17 ELISA. IL-6 and IL-17 were detected according to manufacturer's instructions (KOMA BIOTECH INC., KOREA). Plates were read at 450 nm using microtiter plate reader (BioRad, USA). Manufacturer claimed no cross reactivity of IL-6 and IL-17 with CNTF, CT, G-CSF, sIL-6R, IL-11, IL-12, and Leptin.

Data Analysis. Data was analysed using SPSS 17.0, Mean ± SD, frequencies and percentages were used for qualitative variables. Tables were presented for both qualitative and quantitative variables. One way ANOVA was used to observe group mean differences, Post Hoc Tukey test was used for which group means differs, Pearson correlation test was used for correlation between quantitative variables and Pearson Chi-Square test was applied for associations between qualitative variables. A p value of ≤ 0.05 was considered statistically significant.

RESULTS

The demographic data of studied population is shown in Table 1. More females were in Group-II (83%) and Group-III (66%) compared to Group-I (30%) ($p<0.0001$ each). On comparison of gender distribution there were significant differences among three groups ($p=0.0029$), between Group-I and Group-II ($p<0.0001$) and between Group-I and Group-III ($p<0.0001$) and there was no significant difference between Group-II and Group-III.

Table 1. Demographic data of the subjects.

Variables/Parameters	Group-I Healthy Subjects (30)	Group-II Diabetes without Retinopathy (30)	Group-III Diabetes with Retinopathy (152)
Male n (%)	21 (70)	05 (16.66)	51 (33.55)
Female n (%)	09 (30)	25 (83.33)	101 (66.44)
Age range (years)	28-64	35-75	20-70
(mean ± SD)	34.66 ± 8.78	49.46 ± 9.94	50.88 ± 8.90
HbA1c (%)	NA*	5.9-12.6	5.5-15.4
Duration of diabetes (range)			
5-10 years n (%)	NA*	25 (11.79)	84 (39.62)
More than 10 years (%)	NA*	05 (2.35)	68 (32.07)

*NA= not applicable

Increased age of subjects was found in Group-III (50 years) and Group-II (49 years) compared to Group-I (34 years) ($p<0.0001$ each). On comparison of age, there were significant differences among three groups, between Group-I and Group-II and between

Group-I and Group-III (p<0.0001 each) and there was no significant difference between Group-II and Group-III.

Table 2. Comparisons of different variables in different groups.

Variable	Group-I (n=30)	Group-II (n=30)	Group-III (n=152)	P Value
Gender				0.0029*[1]
Male n, (%)	21 (70)	5 (16.6)	51 (33.55)	<0.0001*[2]
Female n, (%)	9 (30)	25 (83.33)	101 (66.44)	<0.0001*[3]
				0.0868 [4]
Min / Max Mean ± SD of Age (years)	24.0 / 64.0 34.66 ± 8.78	27.0 / 75.0 49.46 ± 9.94	20.0 / 75.0 50.88 ± 8.90	<0.0001*[1] <0.0001*[2] <0.001*[3] 0.4365 [4]
Min/ Max Mean ± SD duration of disease (years)	NA#	5.0 / 20.0 7.76 ± 4.14	2.0 / 26.0 10.51 ± 5.24	0.0073*[4]
Min/ Max Mean ± SD HbA1C (%)	NA#	5.90 / 12.60 8.54 ± 2.06	5.20 / 15.40 8.83 ± 2.35	0.6044[4]

*Statistically significant, #NA=not applicable
NA=not applicable, [1]Comparison among three groups, [2] Comparison between group-I and group-II, [3] Comparison between group-I and group-III, [4] Comparison between group-II and group-III

Longer mean duration of disease was observed in Group-III (10.5 years) than Group-II (7.7 years). On comparison of duration of diabetes there was a significant difference between two groups (p=0.007). On comparison of HbA1c between Group-II and Group-III, there was no significant difference (Table 2).

Highest mean ± SD of IL-6 was observed in Group-II (1341.78 ± 294.74 pg/ml), followed by Group-I (1331.98 ± 306.41 pg/ml) and Group-III (718.66 ± 614.02 pg/ml). On comparison there were significant differences among three groups, between Group-I and Group-III and between Group-II and Group-III (p<0.0001 in each) and there was no significant difference between Group-I and Group-II (Figure 1).

Highest mean ± SD of IL-17 was observed in Group-I (718.05 ± 756.55 pg/ml), followed by Group-II (415.01 ± 483.40 pg/ml) and Group-III (375.95 ± 468.19 pg/ml). On comparison there were significant differences among three groups, and between Group-I and Group-III (p=0.002, and 0.001, respectively) and there was no significant difference between Group-I and Group-II, and between Group-II and Group-III (Figure 1).

Logistic regression model was applied to determine associations among various variables. Regarding IL-6, a significant difference was detected between Group-II and Group-III (p=0.009) while age and IL-6 were significant predictors for the development of diabetic retinopathy between Group-I and Group-II (p<0.0001, 0.005, respectively) (Table 3).

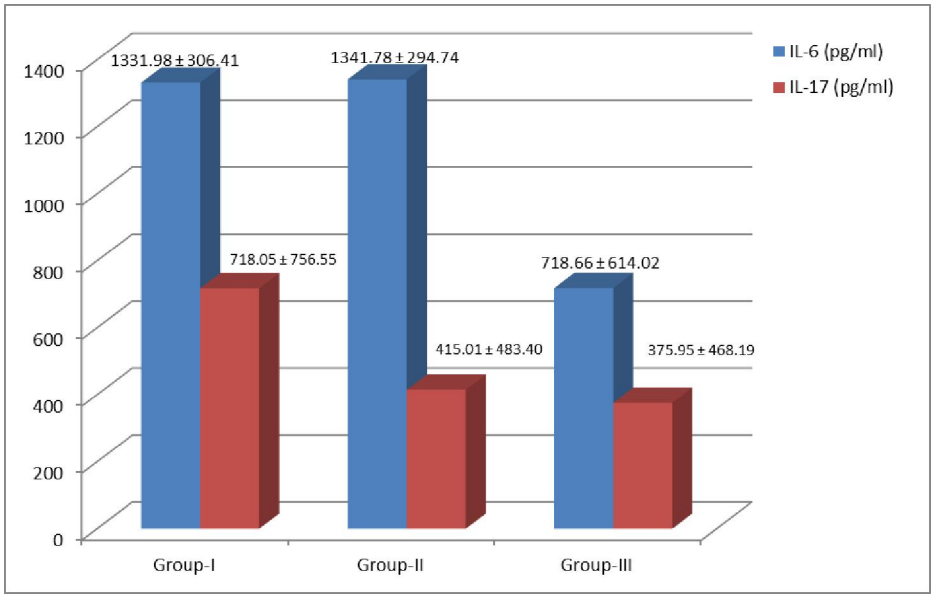

Figure 1. Mean ± SD of IL-6 and IL-17 (pg/ml) cytokines in different groups.
*Statistically significant, [1] Comparison among three groups, [2] Comparison between group-I and group-II, [3] Comparison between group-I and group-III, [4] Comparison between group-II and group-III
IL-6: <0.0001*[1], <0.4255 [2], <0.0001*[3], <0.0001*[4]
IL-17: <0.0026*[1], <0.1456 [2], <0.0014*[3], <0.6791[4]

On comparing IL-17, age was significant predictor between Group-I and Group-II ($p<0.0001$) and none of other parameters were significantly different between Group-II and Group-III (Table 3).

Table 3. Logistic Regression Model.

Variable	Degree of Freedom (DF)	Estimate	Standard Error	Chi-Square	P Value
For Group-II and Group-III					
Age	1	0.0004	0.0008	0.21	0.644
Duration	1	0.0019	0.0015	1.62	0.203
HbA1C	1	0.0006	0.0034	0.04	0.847
IL-6	1	-0.0000	0.0000	6.74	0.009*
IL-17	1	0.0000	0.0000	0.87	0.350
For Group-I and Group-III					
Age	1	0.0174	42.93	0.0027	<0.0001*
IL-6	1	-0.0001	7.74	0.0000	0.0054*
IL-17	1	-0.0001	2.84	0.0000	0.0921

*Statistically significant

DISCUSSION

In the current study, on comparison of gender distribution, there were significant differences among three groups, between Group-I and Group-II, and between Group-I and Group-III but there was no significant difference between Group-II and Group-III. Non-significant value could be because both groups had more females compared to males. Current study is in agreement with Akram *et al*. (2011) (16), Chhutto *et al*. (2009) (2), Ahmadani *et al*. (2008) (17) and Tam *et al*. (2008) (6). Khan *et al*. (2007) (18) and Qidwai *et al*. (2010) (4) are not in agreement with current study as they documented higher prevalence of diabetes in males compared to females, However, majority of studies suggested higher prevalence of diabetes in females compared to males.

In the current study, on comparison of mean ± SD of age, there were significant differences among three groups, between group-II and group-I and between group-III and group-I. There was no significant difference between group-II and group-III which could be because both groups had diabetic patients but DR could be due to environmental factors (19).

Regarding age distribution, current study is in agreement with Chhutto *et al*. (2009) (2), Ahmadani *et al*. (2008) (17), Shaw *et al*. (2010) (1), and Tam et al. 2008 (6). However Akram et al. (2011) (16) is not in agreement with current study because they had lower age limit of 40 years but no limit for maximum age. Study of Zhang *et al.* (2010) (20) is also different because they included patients between 58.9-62.9 years.

In the current study, level of HbA1c in both groups reflected poor diabetes control. Diabetic patients were recruited from public hospital/non-governmental organizations, and they had diabetes of more than 5-years. These patients were from low socio-economic background and their education level was not high which could be the reason for poor diabetes control because education and socioeconomic status has been associated with increased prevalence of diabetes (25).

Regarding duration of diabetes, current study showed significant difference between the two groups and it is in agreement with Ahmadani *et al.* (2008) (17) and Zhang *et al*. (2010) (20). Possible reason for significance of duration of diabetes could be that length of disease could play role in DR. However current study is not in agreement with Jamal-u-Din *et al*. (2006) (7) and Tam *et al.* (2008) (6) because they included newly diagnosed diabetic till up to 15 years and mean ± SD of age of subjects was less, respectively.

In the current study, highest level of IL-6 was observed in Group-II, followed by Group-I and Group-III. On comparison, there were significant differences among the three groups, between Group-I and Group-III and between Group-II and Group-III while there was no significant difference between Group-I and Group-II.

Many researchers suggested involvement of IL-6 in eye diseases and detected IL-6 in vitreous fluid of eye whereas current study focused on determination of IL-6 in serum e.g. IL-6 in uveitis by Yoshimura *et al*. (2009) (14), high level of vitreous IL-6 in diabetic type-I retinopathy by Mysliwec *et al*. (2008) (23), high level of vitreous IL-6 in proliferative DR by Mocan *et al*. (2006) (24), and Nakamura *et al*. (2003) (25).

However, none of the above mentioned studies can be compared with current study because they were not performed on T2DM patients. In the current work, low level of IL-6 in DR patients could be due to treatment i.e. laser/local eye drops and their regular medications for diabetes. Such treatments may reduce inflammation in general and of

eye in particular because Ohta *et al*. (2000) (15) documented suppression of IL-6 could reduce inflammation and restore ocular immune privilege.

High levels of IL-6 in healthy and diabetic subjects without retinopathy could be the normal level of IL-6. Further, although detailed history of infection in last two weeks was obtained from the studied population but sub-acute infection could be there whereas DR patients were more aggressively treated and therefore, level of IL-6 was low in this group. Similarly, Dongancy *et al*. (2002) (26) claimed raised IL-6 in poorly controlled diabetic patients and Esposito *et al*. (2002) (27) documented after normalization of plasma glucose, IL-6 declined. Further, Shoelson *et al*. (2006) (28) documented high level of inflammatory markers in healthy individuals that indicated their tendency to get diabetes in later part of life.

Another reason of raised IL-6 in control could be the protective aspect of IL-6 which has been confirmed in pre-diabetes condition in transgenic non-obese diabetic mouse (NOD).

NOD mouse overexpress IL-6 cytokine and have decreased fasting glucose levels with delayed onset of diabetes. These animals survive longer as compared to those who do not over express IL-6 gene (29). Further, protective aspect of IL-6 genotype polymorphism was highlighted in retinopathy and nephropathy of type 1 diabetes mellitus patients (30).

In the current study, highest mean ± SD of IL-17 was observed in Group-I followed by Group-II and Group-III. On comparison there were significant differences among the three groups, and between Group-I and Group-III. There was no significant difference between Group-I and Group-II, and between Group-II and Group-III.

Studies in agreement with current study highlighted protective aspect of IL-17 i.e. IL-17 required to recruit protective IFN-γ producing $CD4^+$ T cells into lung, IL-17 produced in lung as normal host response to *Klebsiella pneumonia* and mycobacterium tuberculosis, neutralization of IL-17 enhanced eosinophil in asthma while recombinant IL-17 decreased airway hyperactivity and eosinophil in bronchial lavage (31), tumor-infiltrating IL-17 producing cells in esophageal squamous cell carcinoma have prognostic value (32). However, none of the above mentioned studies were performed in diabetic patients. IL-17 is an initiator of T cell dependent inflammation and causes lupus nephritis and autoantibody overproduction (33). It is in agreement with current study because in Group-II level of IL-17 was comparable to Group-III which suggests that IL-17 decreases after development of DR.

The current study is not in agreement with Zeng *et al*. (2012) (34), Honkane *et al*. (2010) (12), Chi *et al*. (2011) (35) who documented increased levels of IL-17 in T2DM, T1DM, SLE, psoriasis, RA and allergic asthma. Activated iNK produces IFN-γ and dampens Th17 responses; hence ameliorate experimental ocular autoimmunity (13).

In the current study high level of IL-17 in control group could be a protective aspect of IL-17 while low level of IL-17 in patients of DR could be due to their medications. Therefore, possibility of negative association of IL-6 and IL-17 with DR may also be considered.

In conclusion, age, gender and duration of diabetes contribute in the development of type-II diabetes retinopathy whereas serum IL-6 and IL-17 levels were negatively associated with T2DM retinopathy. The differences observed in the level of IL-6 and IL-17 could have been the result of disease manifestations. Studies should be carried out for determination of IL-17 in intra vitreous fluid. Results of the present study need to be verified in further studies to determine its clinical utility.

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