Nephropathic complication of type-2 diabetes is following pattern of autoimmune diseases?

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1. Introduction

The frequency of diabetes mellitus is increasing globally and it is expected that this latent disorder will affect 200 millions of people by 2010 and 300 millions in 2025 [1]. Type-2 is the most prevalent type of the diabetes [2]. Current studies showed that several genetic and environmental parameters are associated with type-2 diabetes [3]. It has been suggested that diabetes is an immune dependent disease in which the pattern of cytokine expression are changed [4]. As an example in type-2 diabetes, peripheral blood monocytes produce inflammatory cytokines [5]. Cytokines and cytokine-receptor axis are recent subject of several studies for their crucial roles in diabetes [3] and the important role of cytokine imbalance in type-2 is reported [6]. Increased serum level of inflammatory cytokines including IL-18 [7], IL-6 [8] and TNF-α [8] is documented in type-2 diabetes. The association of IL-17A and IFN-γ in immunological disorders such as multiple sclerosis [9,10], systemic lupus erythematosus (SLE) [11,12], nephrotic syndrome [13,14], graft rejection [15,16], asthma [11,17] and type-1 diabetes [18,19] is well established. Furthermore, some investigators reported the suppressive effects of IFN-γ on IL-17A via...
The key roles of IL-17A and IFN-γ as inducers of autoimmunity rise questions concerning the impacts of these cytokines on the pathogenesis of some diseases including nephropathic type-2 diabetes. Therefore, this study was aimed to investigate the serum levels of these cytokines in type-2 diabetic patients with nephropathy.

2. Materials and methods

2.1. Subject

Peripheral blood samples were collected from 180 type-2 diabetic patients without nephropathy, 100 type-2 diabetic patients showing nephropathic complications and 100 healthy controls. The patient and control groups were selected within Rafsanjan population with similar medical and demographic characteristics including duration of diabetes, sex, age and socio-economical status (Table 1). Information about lipid levels, proteinuria, estimate of glomerular filtration rate (GFR) and drug therapy of patients are also listed in Table 1. The ethical approval of this study was granted by the Ethical Committee of Rafsanjan University of Medical Sciences.

2.2. Assays

Fasting blood sugar, urine albumin level, blood pressure and clinical presentations were assessed three times during a period of 6 months for each patient and also control group. The bias factors such as infections, allergic conditions and smoking were eliminated from the study. IL-17A and IFN-γ serum levels were detected using ELISA (eBioscience, ESP) in both groups just immediately after blood collection. Assays were performed as manufacturer’s guidance. The sensitivity of kit was 2 pg/ml and inter- and intra-assay assessments of reliability of the kit were conducted.

2.3. Statistical analysis

The differences in variables were analyzed by Student’s t-tests, as appropriate. The P values of less than 0.05 were considered significant.

3. Results

Results of our study showed that the mean IFN-γ serum level was 22.79 ± 2.70, 16.09 ± 2.04 and 4.03 ± 1.00 pg/ml in type-2 diabetic patients without nephropathy, with nephropathy and control group, respectively (Fig. 1).

The values of IL-17A for the same groups were 13.70 ± 2.34, 0.94 ± 0.29 and 4.43 ± 0.54 pg/ml (Fig. 2). Our results demonstrated that the mean serum level of IFN-γ was higher in both diabetic groups compared to the control. The serum level of IL-17A was also higher in diabetic patients without nephropathy, while it was lower in nephropathic type-2 diabetic patients. Our results also showed that inter- and intra-assays were CV < 14% and CV < 0.03%, respectively.

Our results also showed that, there were no significant difference between groups regarding the mean age (P = 0.85), gender (P = 0.9), duration of diabetes (P = 0.1) and socio-economical status of the participants (P = 0.90) (Table 1). The results of current study showed that proteinuria was significantly increased (P = 0.002) and estimated GFR was decreased (P ≤ 0.001) in nephropathic patients compared to non-nephropathic subjects (Table 1).

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<th>Table 1 – Demographic, socio-economic conditions and laboratory characteristics of diabetic patient and controls.</th>
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* Significant difference in proteinuria (P < 0.002, t-test, case vs. control). Data are shown as mean ± SE.

# Significant difference in estimated GFR (P < 0.001, t-test, case vs. control). Data are shown as mean ± SE.

activation of regulatory T cells [20].
In this study, the patient and control groups were matched for duration of diabetes, sex, age, monthly income and level of education. Our findings indicated a significant difference between IFN-γ serum level in type-2 diabetic patients without nephropathy, nephropathic diabetic patients and control. Moreover, contrary to the lower serum level of IL-17A in patients with nephropathies, this value was higher in the other group of patients compared to control. To our knowledge this is the first study which was performed to evaluate the serum level of IL-17A and IFN-γ in these patients. However in a study, Tsiavou et al. showed a decreased intracellular IFN-γ in T lymphocyte of type-2 diabetic patients [6] but Mavridis et al. indicated that the serum level of IFN-γ was increased in insulin-treated patients with type-2 diabetes in comparison to sulfonylurea-treated patients [22]. Investigators also showed that the serum levels of inflammatory cytokines like IL-6, IL-18 and TNF-α are increased in type-2 diabetic patients with nephropathy [11,23]. The increased serum level of IFN-γ related chemokine, IP-10 has been also demonstrated in nephropathic patients [24]. In this study, we also found that the serum level of IFN-γ was increased in both nephropathic and non-nephropathic type-2 diabetic patients. Therefore, it can be concluded that IFN-γ is likely involved in the pathogenesis of type-2 diabetes and its nephropathic complications. Finally, it can perhaps be concluded that the severity of type-2 diabetes is related to the serum level of IFN-γ. On the other hand, Miljkovic et al. suggested that T cell-derived IL-17 might be involved in NO-dependent damage of beta cells in mouse streptozotocin model of diabetes [25]. Mensah-Brown et al. also reported that interleukin-23/interleukin-17 pro-inflammatory axis are involved in the induction of diabetes in animal models [26]. Investigators also showed that IL-17A is increased in obese women (which is a risk factor for diabetes) [27]. Our results also showed that IL-17A was markedly increased in type-2 diabetic patients without nephropathy. Based on our study and results from similar works, it can be inferred that IL-17A plays an important role in the etiology and pathogenesis of type-2 diabetes. Previous studies demonstrated that IL-17A is an important cytokine which contributes in autoimmune diseases [25,27]; thus, enhancement of IL-17A in non-nephropathic diabetic patient may represent the autoimmunity pattern of this disease. Overall, based on the results of the current study on evaluation of the serum level of these two pro-inflammatory cytokines in nephropathic and non-nephropathic type-2 diabetic patients contemporary, we can perhaps conclude that nephropathic complications in this type of diabetes is not related to immune factors because non-nephropathic patients also showed elevated serum level of IFN-γ; thus, it seems that the enhancement of IFN-γ level maybe more related to the diabetes than nephropathies. Our data also showed that nephropathic complications of type-2 diabetics may not be associated with IL-17A, hence, the authors of this article suggest that nephropathic disorders of type-2 diabetes can probably not be considered as autoimmune disorder and other etiological factors such as physiological and pathological conditions may involved in this complication. On the other hand, Matsumoto and Kannmatsuse reported that urinary excretion of IL-17A in nephropathic patients was increased [13]. Our results also showed that proteinuria was increased and estimated GFR was decreased in nephropathic type-2 diabetic patients, hence, it can be probably concluded that
most of the IL-17A from serum was excreted to urinary in these patients. In order to answer to the question of why serum levels of IL-17A are decreased in patients with nephropathy whereas interferon-gamma levels are increased, authors of this article suggest that other researchers evaluate serum and urinary level of IL-17A, simultaneously, in nephropathic type 2 diabetic patients.

Finally nephropathic complications of type-2 diabetes are very complex that are associated with several environmental and genetic factors which these aspects of the disease should be examined in further studies.

Conflict of interest

There are no conflicts of interest.

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R E F E R E N C E S


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