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Correlations between Serum Interleukin-4 with Pro- and Anti-inflammatory Markers in Type 1 and 2 Diabetes: A Comparative Study

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Abstract

Background and objective: Interleukin-4 inhibits the secretion of many inflammatory cytokines and it acts as anti-inflammatory against insulinits that induced by autoimmunity in type-1 diabetes. This cross-sectional study aimed to determine the serum level IL-4 in patients with T1D and T2D, and to look into its relation to other pro-and anti- inflammatory cytokines and glycemic status.

Methods: Patients with a history of type-1 (T1D) (Group I, n=75) and type-2 (T2D) diabetes (Group II, n=75) were recruited from the Center of Diabetes in Erbil. Glycemic indices (included fasting serum glucose, insulin, glycated hemoglobin, c- peptide) and inflammatory-related cytokines (including highly sensitive C-reactive protein [hs-CRP], IL-1β, IL-4, IL-10, Interferon [INF-γ], and tumor necrosis factor [TNF-α]) were measured.

Results: Group II patients showed significant increase of hs-CRP, IL-10, and IL-4, while the serum levels of IL-1β and INF-γ were significantly reduced compared with Group I. Significant inverse correlations between IL-4 with each of the following markers; hs-CRP (r=-0.858), IL-1β(r=-0.890), INF-γ(r=-0.859), IL-10(-0.685), and TNF-α (r=-0.733) with predictive values ranged between 46.9% and 73.8% were observed in the Group II but not in the Group I. Non-significant correlation between IL-4 and glycemic indices were observed in Group I and II.

Conclusion: We conclude that determination of IL-4 can help to discriminate between autoimmune-from inflammatory markers that are associated with diabetes, and can serve as a predictor cytokine in T2D.

Keywords: Interleukin-4; Diabetes mellitus; Inflammatory markers; Glycemic status.

Introduction

Interleukin-4 (IL-4) is a cytokine that produced by the activated TH-2 cells and natural killer cells. It is an immune regulator that regulates the humoral and adaptive immunity by regulating the proliferation of the T-and B-cells, and it plays a role in the differentiation of the TH-0 cells.[1] It reduces the inflammatory process via its effect against macrophages, producing interleukin-10 (IL-10) and reducing the levels of Interferon-γ. In experimental animal model, IL-4 stimulates the production of adipocytes proinflammatory, and inhibits anti-inflammatory markers release.[2] In vitro study, IL-4 does not involve in the activation of insulin signaling, but it restores the insulin sensitivity in the adiposetissue.[3] In non-obese type-1 diabetes (T1D) experimental model, IL-4 acts as anti- inflammatory against insulinits that induced by autoimmunity.[4] Previous studies demonstrated that IL-4 inhibits the secretion of many inflammatory cytokines including tumor necrosis factor (TNF-α), IL-1β, and IL-6.[5]

High plasma IL-4 level is observed in obese type-2 diabetes (T2D) while in non-obese T2D, the plasma level of IL-4 is within the normal reference values.[6] Some authors believed that IL-4 involved in the pathogenesis of T2D.[7]

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Serum level of IL-4 is inversely related to the level of serum autoantibodies in T1D, and it is within normal reference value in absence of autoantibodies.[8] The rational of this study is the TH-2 cell-producing IL-4 can alter the production of other cytokines or change the glycemic status in T1D or T2D. Therefore, this study aimed to determine the serum level IL-4 in patients with T1D and T2D, and to assess its relation to other pro-and anti-inflammatory cytokines and glycemic status.

Methods

Participants

This cross-sectional study was conducted in the Department of Microbiology-Immunology in the College of Health Sciences at Hawler Medical University in Erbil- Iraq from 1st April 2018 to 31st August 2018. Each patient signed a consent prior to the admission to the study. The study was conducted according to the ethical guidelines constructed by the Institutional Scientific Committee by which the treatment or using device should not be harmful to the patient and the patient is free to decline from the study or to refuse for study admission. The patients were recruited from the Center of Diabetes in Erbil-Iraq. Eligible patients were both genders of whatever age in respect to the type of diabetes. The criteria for inclusion are known cases of T1D (with positive autoantibodies tests including islet cell antibodies and glutamic acid decarboxylase-67 autoantibodies), and T2D with negative autoantibodies tests. The exclusion criteria were clinical complications of diabetes, liver or kidney disease, and patients were using anti-inflammatory or hormonal therapy within 2 weeks of enrollment into the study. The sample size of each group was calculated by using margin of errors (α= 0.05, β = 0.2), two tails and 95% confidence interval. One hundred and fifty patients who met the inclusion criteria were distributed into the two groups: Group I (T1D, n=75) and Group II T2D, (n=75).

Clinical data and measurements

Consultants of endocrinology examined each patient and the researchers obtained the characteristic features of the participants. The glycemic status of each patient was assessed by measuring the fasting serum glucose, insulin, glycated hemoglobin (HBA1c%) and c-peptide. Islet cell and glutamic acid decarboxylase-67 autoantibodies

Results

Table 1 show that fasting serum glucose and glycated hemoglobin values were significantly higher in Group I compared with Group II. Significant low levels of fasting serum insulin and c-peptide observed in Group I, which reduced to 0.11 and 0.24 of the mean values of Group II, respectively (Table 1).

Table 1 Serum levels of glycemic status measurements

Determinants	Group I (n=75)	Group II (n=75)	*P*-value
Fasting Serum Glucose (mg/dl)	303.4±12.5	274.6±13.5	<0.001
Glycated hemoglobin (%)	9.5±1.1	8.2±1.0	<0.001
Fasting Serum Insulin (mU/L)	1.9±0.4	16.1±2.7	<0.001
c-peptide (ng/ml)	1.1±0.4	4.5±1.2	<0.001
Islet cell antibodies (U/ml)	1.26±0.18	0.88±0.14	<0.001
Glutamic acid decarboxylase antibodies (U/ml)	22.3±3.3	10.9±1.3	<0.001

The results are expressed as mean ±SD. *P* value was calculated by using two-tailed, two independent samples t-test. GroupI: Type 1 diabetes, Group II: type 2 diabetes.

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Serum levels of autoantibodies were significantly higher in Group I compared with Group II. Group II patients showed significant increase of serum hs-CRP, Il-10 and Il-4 levels, while the serum levels of IL-1β and INF-γ were significantly reduced compared with Group I (Table 2).

Serum level of TNF-α showed a non-significant difference between Groups and II. Figure 1 and Table 3 show significant inverse correlations between IL-4 and each of the following markers; hs-CRP, IL-1β, INF-γ, IL-10 and TNF-α in T2D, where as these correlations do not reach to significant levels in T1D (Figure 2).

The calculated prediction values that derived from the relationship between IL-4 and other markers in T2D are; 73.3%, 65.5%, 73.8%, 46.9%, and 53.7% for hs-CRP, IL-1β, INF- γ, IL-10 and TNF-α, respectively.

Table 2 Serum levels of pro-and anti-inflammatory markers

Inflammatory markers and cytokines	Group I (n=75)	Group II (n=75)	*P*-value
High sensitivity C-reactive protein (mg/L)	1.8±0.5	2.7±0.8	<0.001
Interleukin-1β (pg/ml)	115.4±8.8	100.5±22.1	<0.001
Tumor necrosis factor-α (pg/ml)	139.8±22.8	129.8±44.3	0.085
Interferon-γ (pg/ml)	28.3±2.1	26.9±4.4	0.015
Interleukin1 0 (pg/ml)	45.1±10.0	98.8±33.9	<0.001
Interleukin 4 (pg/ml)	20.1±2.8	30.62±10.65	<0.001

The results are expressed as mean ±SD. *P* was value calculated by using two-tailed, two independent samples t-test. Group I: Type 1 diabetes, Group II: Type 2 diabetes.

Table 3 Correlation between interleukin-4 with the inflammatory (high sensitivity C- reactive protein, interleukin-1β, interferon-γ, tumor necrosis factor-α) and anti- inflammatory (interleukin-10) markers in patients with type-1 (Group I) and type-2 diabetes (Group II)

Variables	Group I (n=75)					Group II (n=75)				
	R	R2	β	F	P	R	R2	β	F	P
hs-CRP	0.023	0.001	0.004	0.039	0.845	-0.858	0.736	-0.065	240.0	<0.001
	0.001	0.000	1.000	0.000	0.990	-0.871	0.759	1.027	229.6	<0.001
IL-1β	0.020	0.000	0.060	0.029	0.865	-0.809	0.655	-1.677	138.7	<0.001
	0.017	0.000	1.000	0.022	0.882	-0.838	0.702	1.017	172.0	<0.001
INF-γ	0.042	0.002	0.031	0.128	0.722	-0.859	0.738	-0.356	205.8	<0.001
	0.035	0.001	0.999	0.088	0.767	-0.872	0.761	1.014	231.9	<0.001
TNF-α	0.129	0.017	0.994	1.230	0.271	-0.733	0.537	-3.048	84.6	0.001
	0.134	0.018	0.992	1.325	0.253	-0.758	0.574	1.029	98.5	0.001
IL-10	0.140	0.020	-0.479	1.459	0.231	-0.685	0.469	-2.178	64.5	0.001
	0.153	0.023	1.011	1.746	0.190	-0.727	0.529	1.023	82.0	0.001

The results were analyzed by linear (above) and logistic (below) regression test. R: correlation factor, R^2:prediction proportion, β:regression coefficient, F:calculated value by ANOVA, P: probability. hs-CRP: high sensitivity C-reactive protein, IL: interleukin, INF: interferon, and TNF: tumor necrosis factor.

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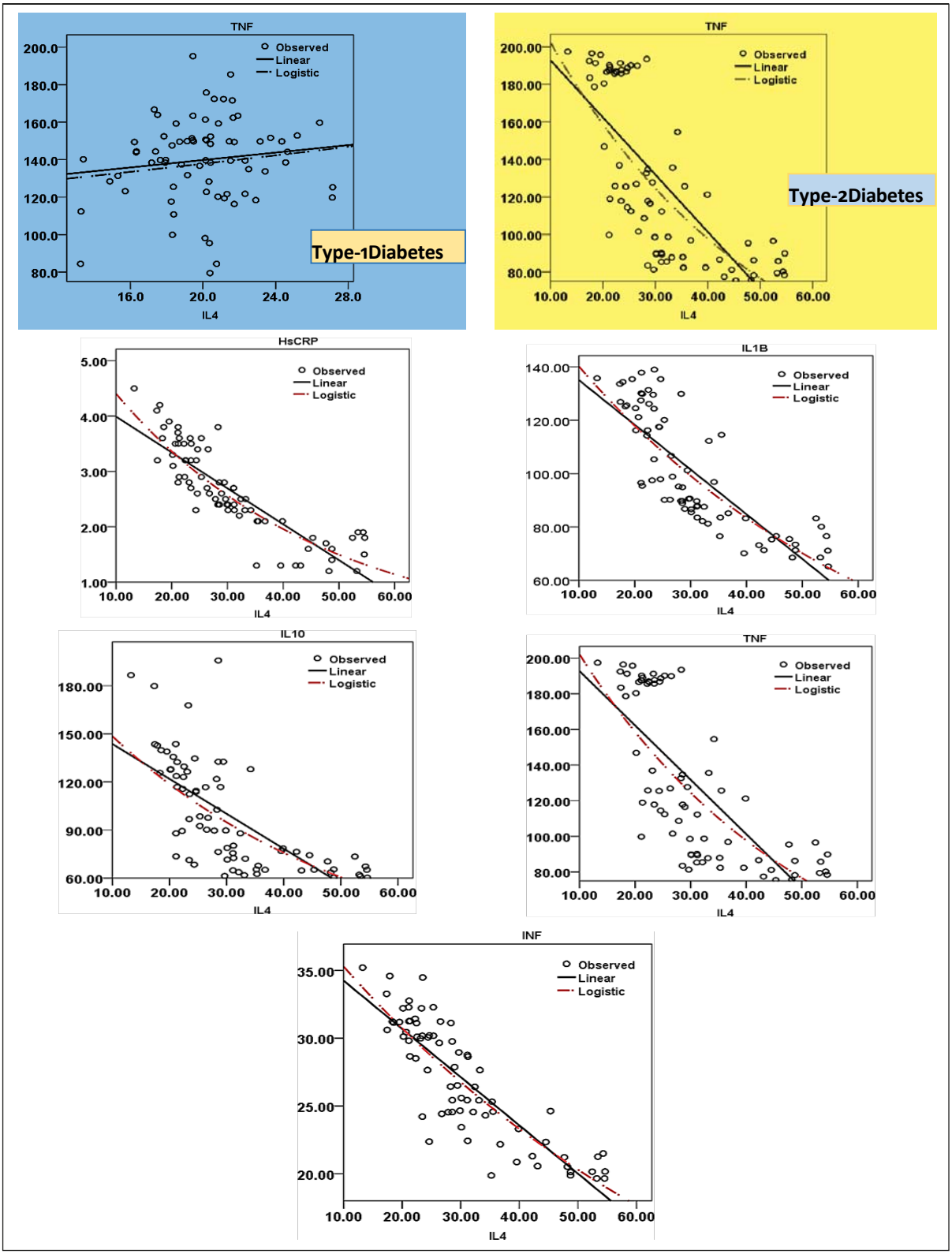

Figure 1 Correlations between interleukin-4 with the inflammatory (high sensitivity C-reactive protein, interleukin-1β, interferon-γ, tumor necrosis factor-α) and anti- inflammatory (interleukin-10) markers in patients with type-2 diabetes (Group II)

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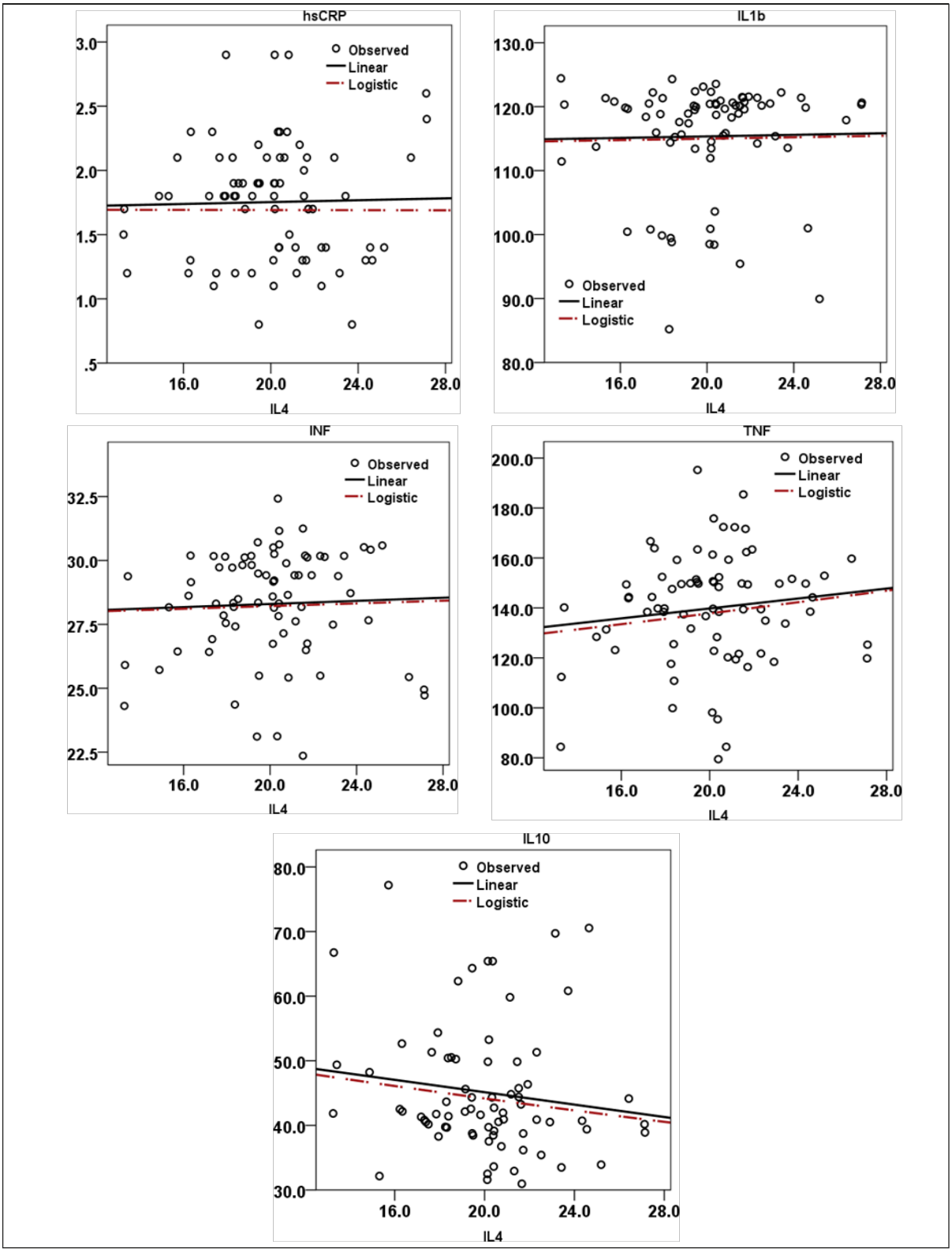

Figure 2 Correlations between interleukin-4 with the inflammatory (high sensitivity C-reactive protein, interleukin-1β, interferon-γ, tumor necrosis factor-α) and anti- inflammatory (interleukin-10) markers in patients with type-1 (Group I).

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Table 4 shows that IL-4 level does not correlate with fasting serum glucose, glycated hemoglobin, c-peptide and insulin in T1D and T2D.

Table 4 Correlation between interleukin-4 with the glycemiaindices including fasting serum glucose, glycated hemoglobin (%),c-peptide and insulin in patients with type-1 diabetes (Group I) and type-2 diabetes (Group II)

Variables	Group I (n=70)					Group II (n=70)				
	R	R2	β	F	P	R	R2	β	F	P
FSG	0.024	0.001	0.107	0.042	0.837	0.046	0.002	0.054	0.155	0.695
	0.028	0.001	1.000	0.055	0.814	0.047	0.002	1.000	0.165	0.686
HbA1c	0.049	0.002	-0.018	0.177	0.675	0.186	0.035	0.018	2.612	0.110
	0.048	0.002	1.002	0.167	0.684	0.189	0.036	0.998	2.715	0.104
c-peptide	0.043	0.002	0.006	0.715	0.715	0.082	0.007	0.003	0.493	0.485
	0.054	0.003	0.993	0.647	0.647	0.051	0.003	0.998	0.191	0.663
Insulin	0.086	0.007	-0.014	0.462	0.462	0.078	0.006	0.003	0.442	0.508
	0.109	0.012	1.010	0.352	0.352	0.068	0.005	0.998	0.343	0.560

The results were analyzed by linear (above) and logistic (below) regression test. R: correlation factor, R^2: prediction proportion, β:regression coefficient, F:calculated value by ANOVA, P: probability. FSG: fasting serum glucose, HbA1c: glycated hemoglobin (%).

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Discussion

The results of this study showed the interactions between IL-4 with pro-and anti- inflammatory cytokines are differed which does not relate to the glycemic status of diabetes. The glycemic profile of each group indicates that the patients were uncontrolled diabetic. The diagnosis of T1D is confirmed by detection high values of autoantibodies and low levels of c-peptide and insulin.[9,10]

The serum levels of pro-and anti-inflammatory markers in both groups are higher than the reference values of healthy subjects that demonstrated by others which did not need to measure these cytokines in healthy subjects in this study.[11,12] High sensitivity- C-reactive protein as an independent factor was detected in both GroupI and II which indicates there is low grade inflammation. A significant higher serum level of hs-CRP in Group II indicates that inflammation played a role in the pathogenesis of T2D.[13] Interleukin 1β and interferon-γ levels, as independent inflammatory markers, were significantly higher in T1D compared with T2D. This finding agreed with others who found that IL-1β is a cytokine involved in the destruction of the β-cells and played a role in the pathogenesis of the autoimmunity.[14,15]

High serum level of INF-γin T1D that reported in this study is of clinical importance because the β-pancreatic cells regulate certain substances that limit the self-reactive T cells. A significant high level of the anti-inflammatory markers including IL-4 and IL-10 indicates the body responded to the inflammatory process that occurred in T2D.[16] In this work, we investigate the correlation between IL-4 as dependent anti-inflammatory cytokine with other cytokines and glycemic indices to explore the role of IL-4 in autoimmunity (T1D) and inflammatory process (T2D). Our findings show that production of IL-4 does not correlate with other pro-and anti-inflammatory markers in T1D. This indicates that IL-4 has no specific role against the autoimmunity. Production of IL-4 promotes the differentiation of TH-2 cells,[17] and it hasn't any role in the autoimmunity. Therefore, the serum IL-4 level in the autoimmune diseases approximates the control level, which explained a non-significant correlations with othercytokines.[18]

High significant level of correlations between IL-4 and other cytokines indicate the role of IL-4 in the inflammation rather than autoimmunity. Moreover, an inverse correlations between IL-4 with pro-inflammatory and anti-inflammatory cytokines indicates the immune-regulatory function of IL-4 which characterized by suppressing the overproduction of these cytokine. Determination of IL-4 can be applied to predict the serum levels of pro-and anti- inflammatory cytokines as the prediction values that reported in this study are high. There is no correlation between IL-4 with the glycemicindices in Group I and II. This observation indicates that IL-4 does not act on the pancreatic β-cells. Recent studies showed that IL-4 activates the phosphorylation of the insulin receptor substrate in a complex manner that interferes with cellular apoptosis,[19] but there is no evidence that such activation can change the glycemic status.

Conclusion

We conclude that determination of IL-4 can help to differentiate autoimmunity-from inflammation associated diabetes, and its determination can help to predict the other pro-and anti-inflammatory cytokines in T2D but not in T1D.

Competing interests

The author declares that she has no competing interests.

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