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Serum IL-1, IL-2, TNFα and INFγ Levels of Patients with Type 1 Diabetes Mellitus and their Siblings

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ABSTRACT

Type 1 diabetes mellitus (DM) develops as a result of autoimmune destruction of the pancreatic beta-cells. The aim of this study was to explore possible associations between serum levels of cytokines, IL-1, IL-2, TNFα and INFγ and metabolic parameters in children with type 1 DM and their non-diabetic siblings to determine whether these cytokines could be indicators of disordered immune regulation. The study population consisted of 41 children with type 1 DM, 32 non-diabetic siblings, and 28 healthy controls. Children with DM were divided into three subgroups: 1) newly diagnosed patients with diabetic ketoacidosis (ND + DKA), 2) newly diagnosed patients without DKA' (ND - DKA), and 3) previously diagnosed patients (PD). The highest serum IL-1α level was found in the ND - DKA group, which was significant compared to both the ND + DKA ($p < 0.05$) and the siblings (S) ($p < 0.005$). IL-2 levels were similar among all groups. The highest TNFα level was observed in the ND + DKA group, which was significant against the ND - DKA ($p < 0.05$), PD ($p < 0.001$), S ($p < 0.05$), and control (C) ($p < 0.005$) groups. TNFα concentration in the PD group was significantly lower than those of S ($p < 0.005$) and C ($p < 0.001$) groups. The ND - DKA group had the highest INFγ and this was statistically significant when compared with the S ($p < 0.005$) and C ($p < 0.05$) groups. Both the newly diabetics and all diabetics as a group had statistically significantly higher INFγ levels than both the S ($p < 0.01$ for both) and C ($p < 0.05$ for both) groups. In the diabetics as a whole group, TNFα showed correlations with INFγ ($r = 0.370$, $p < 0.05$). IL-1 showed correlation with TNFα ($r = 0.368$, $p < 0.05$) INFγ ($r = 0.796$, $p < 0.001$) and IL-2 ($r = 0.862$, $p < 0.001$) in the all diabetics group. IL-2 was correlated with TNFα ($r = 0.320$, $p < 0.05$) and INFγ ($r = 0.754$, $p < 0.01$) in the all diabetics group. In conclusion, our results suggest that proinflammatory cytokines TNFα, INFγ, IL-1α and IL-2 may play important roles alone or in combination in the pathogenesis of type 1 diabetes mellitus.

KEY WORDS

TNFα, INFγ, IL-1α, IL-2, type 1 diabetes mellitus, siblings

INTRODUCTION

Type 1 diabetes mellitus (DM) develops as a result of autoimmune destruction of the pancreatic beta-cells. According to the present understanding of the autoimmune process, T helper (Th)-1 cells and the cytokines produced by them (type 1 cytokines: interleukin-2 [IL-2], interferon [INF]-γ, and tumor necrosis factor [TNF]-β) become dominant over Th-2 cells which are known to be responsible for immune regulation, and their associated cytokines, IL-4 and IL-10. Increased Th-1 and related cytokines lead to the activation of an autoimmune inflammatory process that eventually results in destruction of the pancreatic β-cells, also called insulitis. Type 1 cytokines activate cytotoxic cells, proinflammatory cytokines (IL-1, TNFα) and free oxygen radical producing macrophages,

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which are extremely toxic to the β-cells. In addition, IL-1, TNFα and INFγ exert β-cell cytotoxicity by inducing the formation of free oxygen radicals, nitric oxide (NO) and peroxynitrite within the β-cells themselves[1].

The purpose of this study was to explore possible associations between serum levels of cytokines, IL-1, IL-2, TNFα and INFγ, and metabolic parameters in children with type 1 DM and their non-diabetic siblings to determine whether these cytokines could be indicators of disordered immune regulation.

CHILDREN AND METHODS

The study population consisted of 41 children (21 girls and 20 boys) with type 1 DM, who have been cared for in our clinic, their 32 non-diabetic siblings, and 28 healthy controls. There were no differences in age or sex distribution between the groups. The patient group had a mean age of 8.5 ± 3-6 years (range 1-14.8 years). This group was divided into three subgroups:

1. Newly diagnosed patients with diabetic ketoacidosis (ND + DKA): ten girls and seven boys with a mean age of 7.7 ± 4.1 years (range 1.5-13.6 years);
2. Newly diagnosed patients without DKA (ND - DKA): six girls and five boys with a mean age of 8.8 ± 3.5 years (range 1-12.9 years);
3. Previously diagnosed patients group (PD) with a mean disease duration of 2.9 ± 2.6 years (range 4 months-7.5 years): five girls and eight boys with a mean age of 9.4 ± 3.1 years (range 1-14.8 years).

The siblings group (S) consisted of 14 girls and 18 boys with a mean age of 9.0 ± 3.5 years (range 2.5-14.9 years).

The control group (C) consisted of 12 girls and 16 boys aged 9.1 ± 3.7 years (range 2-14.1 years) who were free of any infectious or inflammatory disease at the time of the study.

The following physical parameters were determined in all children: height (cm), weight (kg), body mass index (BMI) (weight [kg]/height [m^2]) and pubertal status by Tanner criteria.

The following metabolic parameters were measured (corresponding methods in parentheses): glucose (automated enzymatic/colorimetric glucose oxidase), hemoglobin A_{1c} (automated chromatographic/photometric), C-peptide (RIA), total lipids (automated Kunkel method), total cholesterol (automated enzymatic/colorimetric method without precipitation), and triglycerides (enzymatic/colorimetric GPO-PAP methods).

Simultaneous venous blood samples for cytokine measurements were drawn in the morning. Sera were kept at -20°C until assays. Serum IL-1α, IL-2, TNFα and INFγ were measured by ELISA, according to the manufacturers' instructions (ChemiKine for INFγ and Cytelisa for the rest). Technical details of the assays according to the manufacturer are as follows: *for IL-1:* sensitivity: 0.80 pg/ml, range of detection: 8-500 pg/ml, cross-reactivity: <0.5% against cytokine standards, intra-assay variability: ±8.3%, interassay variability: ±11.2%; *for IL-2:* sensitivity: 1.10 pg/ml, range of detection: 8-500 pg/ml, cross-reactivity: <0.5% against cytokine standards, intra-assay variability: ±7.0%, interassay variability: ±10.6%; *for TNFα:* sensitivity: 4.8 pg/ml, range of detection: 15.6-1000 pg/ml, cross-reactivity: <0.5% against cytokine standards, intra-assay variability: ±8.3%, interassay variability: ±10.8%; *for INFγ* sensitivity: 0.72 pg/ml, range of detection: 8-500 pg/ml, cross-reactivity: <0.5% against cytokine standards, intra-assay variability: ±8.1%, interassay variability: ±10.6%.

Informed consent was obtained from each child and/or the parents. The study was approved by the ethics committee of our hospital.

The SPPS for Windows release 9.0 program was used for statistical analysis. The Kruskal-Wallis and Mann-Whitney U tests were used for comparisons. Spearman's rank correlation was used to assess the relationship between parameters. p values less than 0.05 were considered significant. Values are shown as means ± standard deviation (SD).

RESULTS

Mean height, weight, BMI, glucose, HbA_{1c}, C-peptide, total lipids, total cholesterol, HDL-cholesterol, LDL-cholesterol, and triglyceride levels

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are shown in Table 1. Table 2 shows IL-1α, IL-2, TNFα, and INFγ concentrations in different groups.

The highest serum IL-1α level was found in the ND - DKA group, which was significant compared to both the ND + DKA ($p < 0.05$) and the S ($p < 0.005$) groups. There were no statistically significant differences between the ND + DKA, PD, and C groups ($p > 0.05$). There were also no significant differences between the group of diabetics as a whole and the S or C groups.

IL-2 levels were similar in all groups. In addition, there were no differences between diabetics as a whole and the S or C groups.

The highest TNFα level was observed in the ND + DKA group, which was significant against the ND - DKA ($p < 0.05$), PD ($p < 0.001$), S ($p < 0.05$), and C ($p < 0.005$) groups. TNFα concentration in the PD group was significantly lower than those of the S ($p < 0.005$) and C ($p < 0.001$) groups. It was higher in the S group compared with the C group, but without statistical significance.

The ND - DKA group had the highest INFγ level and this was statistically significant compared with the S ($p < 0.005$) and C ($p < 0.05$) groups. The lowest INFγ level was in the S group. Both the new diabetics and the all diabetics as a group groups had statistically significantly higher INFγ levels than both the S ($p < 0.01$ for both) and C ($p < 0.05$ for both) groups. In the diabetics as a whole group, TNFα showed correlations with INFγ ($r = 0.370$, $p < 0.05$), disease duration ($r = -0.381$, $p < 0.01$), and glucose ($r = 0.409$, $p < 0.01$). It showed no correlations with BMI, lipids, HbA_{1c}, or C-peptide (Tables 2 and 3).

IL-2 showed correlations with TNFα in the ND + DKA ($r = 0.619$, $p < 0.01$), ND - DKA ($r = 0.78$, $p < 0.01$), S ($r = 0.54$, $p < 0.001$), and all diabetics ($r = 0.32$, $p < 0.05$) groups. IL-2 was also correlated with INFγ in the all diabetics ($r = 0.754$, $p < 0.001$) and the ND ($r = 0.842$, $p < 0.001$) groups. IL-1 showed correlations with TNFα in the ND + DKA ($r = 0.575$, $p < 0.05$), ND - DKA ($r = 759$, $p < 0.05$),

TABLE 1

Mean levels of physical and metabolic parameters in all the groups

	ND + DKA group	ND - DKA group	Previously diagnosed group	Siblings group	Control group
Height (cm)	123.8 ± 28.9	124.8 ± 22.9	130.1 ± 20.2	128.8 ± 23.4	129 ± 20.3
Weight (kg)	22.9 ± 13.1	26.4 ± 10.8	29.6 ± 10.2	26.3 ± 12.3	28.4 ± 10.9
Body mass index	13.7 ± 3.2	15.7 ± 2.4	17.1 + 2.1	16.2 ± 3.5	16.4 ± 2.3
Glucose	456 ± 135	281 ± 102	229 ± 115	83 ± 10	89 ± 10
Total lipids	660 ± 237	495 ± 148	548 ± 202	465 ± 151	470 ± 163
Total cholesterol	170.2 ± 47	169.4 ± 44.6	163.2 ± 39.8	157.5 ± 20.8	154.2 ± 30.3
LDL-cholesterol (mg/dl)	96.2 ± 35.7	93.8 ± 23.5	90.3 ± 34	97.1 ± 20.6	91.7 ± 25.7
HDL-cholesterol (mg/dl)	39.2 ± 12.53	46.1 ± 11.9	48.6 ± 24.8	44.8 ± 12.1	44.6 ± 10.1
Triglycerides	176.9 ± 52.4	123.4 ± 105	124 ± 40.6	86.5 ± 40.4	86.6 ± 29.7
HbA_{1c}	12.1 ± 4.4	13.1 ± 6.5	9.7 ± 4.5	5.3 ± 5.6	4.1 ± 1.3
C-peptide	0.75 ± 0.78	0.82 ± 1.06	0.58 ± 0.64	1.39 ± 1.1	2.14 ± 1.49

Results are means ± SD.
See text for definitions of groups.

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TABLE 2

Serum IL-1α, IL-2, TNFα and IFNγ levels

	IL-1α (pg/ml)	IL-2 (pg/ml)	TNFα (pg/ml)	IFNγ (pg/ml)
ND + DKA group (Group 1)	10.54 ± 6.67	19.59 + 21.3	88.2 ± 62.6	46.2 ± 23.8
ND - DKA group (Group 2)	22.6 ± 26.29	63.48 ± 107.2	40.6 ± 52.6	73.01 ± 73.01
Previously diagnosed group (Group 3)	10.9 + 5.65	26.8 ± 39.86	9.21 ± 12.08	37.7 ± 17.7
All new diagnosed group (Group 4)	15.01 ± 17.72	35.8 ± 68.7	70.6 ± 62.6	56.1 ± 48.7
All diabetics (Group 5)	13.35 ± 14.07	32.14 ± 58.2	45.2 ± 57.1	48.4 ± 39.7
Siblings group (Group 6)	11.49 ± 14.2	51.02 ± 81.8	62.2 ± 75.1	29.2 ± 26.7
Control group (Group 7)	14.6 ± 14.8	61.1 ± 93.55	47.7 ± 63.06	34.2 ± 24.4

Results are means ± SD. See text for definitions of groups.

p values for comparison of IL-1α, TNFα and INFγ among groups were as follows:

for IL-1α	*for TNFα*	*for IFNγ*
group 1-2 p = 0.024	group 1-2 p = 0.024	group 1-6 p = 0.005
group 2-6 p = 0.003	group 1-3 p = 0.0001	group 2-6 p = 0.004
	group 1-6 p = 0.03	group 2-7 p = 0.019
	group 1-7 p = 0.002	group 3-6 p = 0.034
	group 3-4 p = 0.0001	group 4-6 p = 0.0001
	group 3-6 p = 0.002	group 4-7 p = 0.014
	group 3-7 p = 0.0001	group 5-6 p = 0.001
		group 5-7 p = 0.038

TABLE 3

Correlations of TNFα with other parameters

	LDL	IFN-γ	HbA1c	Disease duration	Glucose
ND + DKA group	r = -0.524 p <0.05				
ND - DKA group		r = 0.435 p <0.01			
Siblings			r = 0.435 p <0.01		
All diabetics		r = 0.370 p <0.05		r = -0.381 p <0.005	r = 0.409 p <0.005

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TABLE 4

Correlations of IL-2 with other parameters

	TNFα	IFNγ
ND + DKA group	r = 0.619 p <0.01	
ND - DKA group	r = 0.78 p <0.01	r = 0.900 p <0.001
Siblings	r = 0.540 p <0.01	
All new diagnosed group		r = 0.842 p <0.001
All diabetics	r = 0.320 p <0.05	r = 0.754 p <0.001

PD (r = 0.525, p <0.05), S (r = 0.394, p <0.05), and all diabetics (r = 0.368, p <0.05) groups. IL-1 also correlated with INFγ (r = 0.796, p <0.001) and IL-2 (r = 0.862, p <0.001) in the all diabetics group. IL-1 had negative correlations with HbA_{1c} (r = -0.459, p <0.05) and BMI (r = -0.544, p<0.05) in the PD group (Tables 4 and 5).

DISCUSSION

Type 1 DM is an autoimmune disease resulting from T-cell-mediated islet cell destruction. Autoreactive T cell lymphocytes are the most important effector cells. They cause apoptosis in the pancreatic islet cells[2,3]. CD+8 T cells play a role in the beginning of the beta-cell destruction while CD+4 T cells are the final effectors[2,4]. In addition, it has been reported that macrophages are involved as effector cells by releasing cytotoxic mediators[5]. Recent studies have focused on the roles of proinflammatory cytokines in many autoimmune diseases. IL-1, TNFα, INFγ, and INFβ have been held responsible for islet cell destruction and dysfunction[3,6-9].

Studies in NOD mice and BB rats, which are animal models for human type 1 DM, have shown that cytokines released from islet-associated T lymphocytes, macrophages, and the islet cells themselves cause injury and destruction in the beta-cells thorough a direct cytotoxic effect with apoptosis, increasing the expression of adhesion molecules and MHC proteins on the surface of islet cells, and a decrease in insulin secretion[1-5,10-12]. In addition, it has been shown that patients with type 1 DM have

TABLE 5

Correlations of IL-1α with other parameters

	TNFα	IL-2	IFNγ	HbA_{1c}	BMI
ND + DKA group	r = 0.575 p <0.05	r = 0.718 p <0.001			
ND - DKA group	r = 0.759 p <0.05		r = 0.930 p <0.001		
Previously diagnosed group	r = 0.525 p <0.05			r = -0.459 p <0.05	r = -0.544 p <0.05
Siblings	r = 0.394 p <0.05				
All new diagnosed group		r = 0.946 p <0.001	r = 0.858 p <0.001		
All diabetics	r = 0.368 p <0.05	r = 0.862 p <0.001	r = 0.796 p <0.001		

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increased concentrations of these cytokines in their sera[5,7,8,13-17].

The role played by TNFα in the pathogenesis of type 1 DM is still unclear. In this study, we found significantly elevated levels of this cytokine in the ND + DKA group when compared with the ND - DKA ($p < 0.05$), PD ($p < 0.001$), S ($p < 0.05$), and C ($p < 0.005$) groups. On the other hand, TNFα levels in the PD group were significantly lower than those of the S ($p < 0.005$) and C ($p < 0.001$) groups. These findings are consistent with many previous studies[13,15]. However, there have been studies reporting no difference in serum TNFα concentrations between the patients with type 1 DM and controls[7,16]. Vitali *et al.* reported low levels of TNFα in the siblings of patients with type 1 DM as well[18]. On the contrary, we found higher, albeit statistically insignificant, TNFα concentrations in our siblings group. Elevated concentrations of this cytokine may be important in the pathogenesis of this disease. We have not yet observed any new incidence of DM in the sibling group, but only a short time has elapsed since beginning this study.

When the patients with DM in this study were taken as a whole, we found a positive correlation between TNFα and plasma glucose, and a negative correlation with disease duration. Studies in NOD mice have shown that the production of TNFα increased, and the administration of anti-TNFα prevented DM[3,17]. TNFα has also been shown *in vitro* to increase NO production and to cause apoptosis in islet cells[3]. Our results as well as those of the studies cited above suggest a role for TNFα especially in the early stages of the development of type 1 DM.

We found significantly higher levels of INFγ in the ND group than in the S ($p < 0.01$) and C ($p < 0.05$) groups. In addition, the diabetics as a whole group had higher levels of this cytokine than the S ($p < 0.01$) and C ($p < 0.05$) groups. Thai *et al.* reported similar findings[14]. It has also been reported that the production of INFγ in islet cells of NOD mice was increased, and that beta-cell destruction could be diminished by decreasing INFγ production[19]. In another study, INFγ was reported to increase beta-cell apoptosis in synergy with TNFα[3]. Herold *et al.* demonstrated the prevention of DM by using monoclonal antibodies against INFγ in the streptozocin-induced DM model[20]. In addition, islet cell ICAM-1 expression was reported to be increased by INFγ alone or in combination with TNFα[10]. In the present study, we found a positive correlation between INFγ and TNFα ($r = 0.370$, $p < 0.05$). These findings suggest that INFγ may play a role in the pathogenesis of type 1 DM.

The exact role of IL-1α in the development of type 1 DM is unknown. In this study, we did not observe a significant difference in IL-1α levels from that of the control group. However, there were positive correlations between IL-1α and TNFα in the all diabetics group and sibling group ($r = 0.368$, $p < 0.05$ and $r = 0.394$, $p < 0.05$, respectively). In addition, IL-1α showed correlations with INFγ ($r = 0.796$, $p < 0.001$) and IL-2 ($r = 0.862$, $p < 0.001$) in the all diabetics group. Yamada *et al.* reported that IL-1α, in synergy with INFγ, induces Fas-mediated apoptosis in mouse islet cells[21]. Vassiladis *et al.* suggested that IL-1α might play a role in the development of type 1 DM[22]. Although we did not find higher levels of IL-1α in the diabetic group, its correlations with the other cytokines suggest a possible synergistic role in the pathogenesis of DM.

In this study, IL-2 levels in the patients were not different from those of healthy controls. This result is consistent with that of Cavallo *et al.*[13]. In experimental studies, Burstein *et al.*[23] found no involvement of this cytokine in the development of DM, while Hayashi *et al.*[24] showed that anti-IL-2 antibody had a preventative effect. On the other hand, hyperglycemia was found to decrease IL-2 production[25]. In the present study, we did not observe such a negative correlation. We found positive correlations between IL-2 and TNFα in the all diabetics ($r = 0.320$, $p < 0.05$) and the S ($r = 0.540$, $p < 0.001$) groups. In addition, IL-2 was correlated with INFγ in the all diabetics ($r = 0.754$, $p < 0.01$) and ND ($r = 0.842$, $p < 0.001$) groups. These findings suggest that IL-2 may contribute to the development of DM in association with other cytokines.

Changes in cytokine levels are not specific to type 1 DM or other autoimmune disorders. Confounding factors, such as infections, hyperglycemia or acidosis, may influence their levels. None of the children in our study had any infections or other inflammatory conditions at the time of the study.

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Regarding acidosis and hyperglycemia, the findings in the literature are controversial. These factors have been found to increase[25] or decrease[6] levels of certain cytokines or to have no effect[16].

In conclusion, our results suggest that pro-inflammatory cytokines TNFα, INFγ, IL-1α and IL-2 may play important roles alone or in combination in the pathogenesis of type 1 DM. Elevated serum levels of TNFα and INFγ may be indicators of immune dysregulation.

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