

Background

Interleukin-15 and -6 play a role in an inflammation, autoimmune, infectious and cancerous processes. Their increased concentrations were observed in psoriasis, asthma, multiple sclerosis and type 2 diabetes. However, the role of IL-15 and IL-6 in autoimmune diabetes (AD) pathogenesis is still unknown.

The aim of our study was to assay circulating IL-15 and IL-6 levels in newly diagnosed AD patients, their first degree relatives and healthy controls in comparison to the presence of anti-islet antibodies and insulin resistance.

Material and methods

The group studied consisted of 54 patients with AD (28 with LADA and 26 with T1D) and 70 first degree relatives and 60 controls.

- IL-6, IL-15 and anti-islet antibodies (GADA, IAA, IA-2A) concentrations - ELISA method
- HOMAIR (Homeostatic Model Assessment of Insulin Resistance) was calculated according to the formula: fasting insulinemia (mU/ml) x fasting plasma glucose (mmol/l) / 22.5.
- eGDR (estimated glucose disposal rate) was calculated according to the equation: $eGDR = 24.31 - (12.22 \times \text{waist-to-hip ratio}) - (3.29 \times \text{Hypertension}) - (0.57 \times \text{HbA1c})$ in $\text{mg/kg}^{-1}/\text{min}^{-1}$
- Statistical analysis was performed using STATISTICA 10.0 software (Statsoft, Tulsa, USA)

Results

Clinical and biochemical characteristics of the studied groups

	Autoimmune diabetes (AD)	First degree relatives (FDR)	Control group (CG)	p value AD vs CG	p value AD vs FDR	p value FDR vs CG
N	54	70	60			
Age (years)	34.5 (18-55)	33.0 (18-60)	38.5 (18-60)	0.2	0.7	0.6
BMI (kg/m ²)	22.5 (17-36)	21.9 (17-3.5)	22.7 (18-36.3)	0.7	0.3	0.7
GADA (U/ml)	111.8 (20.2-1879.7)	0.8 (0.6-218.7)	0.7 (0.5-0.9)	< 0.001	< 0.001	0.01
IAA (U/ml)	3.6 (1.3-9.3)	3.1 (4.4-17.2)	0.2 (0.1-3.6)	< 0.001	0.3	< 0.001
IA-2A (U/ml)	6.5 (4.8-4000)	0.6 (0.6-0.9)	0.6 (0.4-0.7)	< 0.001	< 0.001	0.3
HOMAIR	2.4 (0.3-17.5)	1.04 (0.3-2.9)	0.7 (0.5-1.9)	< 0.001	< 0.001	0.02
IL-15(pg/ml)	1.7 (0.2-7.0)	0.4 (0.2-9.1)	0.2 (0.2-3.6)	< 0.001	0.02	0.02
eGDR (mg/kg/min)	6.5 (0.7-11.7)	11.4 (7.0-13.9)	12.4 (6.7-13.4)	< 0.001	< 0.001	0.004
IL-6 (pg/ml)	1.0 (0.3-9.4)	0.7 (0.2-3.3)	0.1 (0.01-4.7)	< 0.001	0.01	0.6

Clinical and biochemical characteristics of the subgroups with T1D and LADA

	Type 1 diabetes (T1D)	LADA	p value
N	26	28	
Age (years)	25.0 (18-34)	39 (35-55)	< 0.001
BMI (kg/m ²)	22.1 (17-33.2)	23.5 (16.9-36)	0.3
GADA (U/ml)	109.4 (20-3971.1)	139 (20.2-18792)	0.4
IAA (U/ml)	2.7 (1.3-7.6)	2.6 (1.3-9.3)	0.3
IA-2A (U/ml)	14.1 (4.9-4000)	5.6 (4.8-4000)	0.01
eGDR (mg/kg/min)	6.7 (2.6-11.7)	6.2 (-0.7-10.28)	1.00
HOMAIR	2.9 (0.5-7.3)	3.2 (0.5-8.5)	0.2
IL-15 (pg/ml)	1.5 (0.2-4.0)	3.8 (1.7-7.0)	< 0.001
IL-6 (pg/ml)	25.0 (18-34)	39 (35-55)	< 0.001

Clinical and biochemical characteristics of the subgroups of relatives

	Relatives Ab (+)	Relatives Ab (-)	p value
N	31	39	
Age (years)	33.0 (18 - 65)	30.0 (18 - 65)	0.2
BMI (kg/m ²)	22.4 (14.8 - 32.2)	20.3 (13.2 - 36.5)	0.2
eGDR (mg/kg/min)	11.5 (7.0-13.9)	11.2 (7.1-13.8)	0.3
HOMAIR	3.9 (0.5-7.3)	2.1 (0.2-8.8)	0.02
IL-15 (pg/ml)	1.7 (0.8-7.2)	0.2 (0.2-0.6)	< 0.001
IL-6 (pg/ml)	1.4 (0.3-4.6)	0.3 (0.1-1.3)	< 0.001

-in the subgroup of Ab (+) relatives we observed a significantly higher concentrations of IL-15, IL-6 and HOMAIR in comparison to the healthy controls (0.2 [0.2-3.6] pg/ml, p<0.001 and 0.1 [0.005-4.7] pg/ml, p<0.001, 2.9 [0.5-7.3] vs 0.7 [0.5-1.9], p<0.001, respectively)

- in the patients with LADA we found significantly higher concentrations of IL-15 and markedly lower eGDR values in comparison to the Ab(+) relatives (3.8 [1.7-7.0] pg/ml vs 1.7 [0.8-7.2] pg/ml, p<0.001 and 6.2 [0.7-10.2] mg/kg/min vs 11.5 [7.0-13.9] mg/kg/min, p<0.001, respectively)

- the values of eGDR were also lower in the patients with T1D (6.7 [2.6-11.7] pg/ml) than in the relatives with positive autoantibodies (p<0.001)

- IL-6 concentrations and HOMAIR did not differ between the groups with LADA or T1D and the relatives with positive antibodies.

Correlations: only in the LADA group serum IL-15 concentrations negatively correlated with eGDR ($r = -0.436$, $p = 0.02$)

HOMAIR positively correlated with IL-15 concentrations in the LADA ($r = 0.5072$, $p < 0.001$) and T1D group ($r = 0.4209$, $p < 0.001$).

Conclusions

- Significantly higher IL-15, IL-6 concentrations, HOMAIR and markedly lower eGDR in newly diagnosed AD patients and relatives with positive anti-islet antibodies might suggest the role of these proinflammatory cytokines and insulin resistance in the pathogenesis of autoimmune diabetes.
- IL-15 and IL-6 might be used as biomarkers of the risk of autoimmune diabetes development, in particular IL-15 for LADA.
- Both type of method of IR measurement seem to be equally useful for calculate insulin resistance in autoimmune diabetes.

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