EXPRESSION OF RECEPTOR FOR ADVANCED GLYCATION END-PRODUCTS AND ITS LIGANDS HMGB1 AND S100A12 IN CHILDREN AND ADOLESCENTS WITH NEW ONSET TYPE 1 DIABETES AND IN PATIENTS WITH LONGER DISEASE DURATION

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INTRODUCTON: Receptor for advanced glycation end-products (RAGE) is a multiligand receptor up-regulated at sites of inflammation, especially in tissues with accelerated advanced glycation end-products formation. It is additionally stimulated by RAGE ligands S100A12 and HMGB1 released from recruited immune cells thus perpetuating inflammatory process with potential role in development of type 1 diabetes as well as in development in diabetes complications. Expression of RAGE molecules and its ligands has not been evaluated in new onset diabetic patients, and data on their role in diabetes development are still scarce

AIM: To assess gene expression for RAGE, S100A12 and HMGB1 in peripheral blood mononuclear cells (PBMC) and plasma concentration of truncated receptor sRAGE and CRP in patients suffering from new onset type 1 diabetes (NT1D), in patients with disease duration of more than five years (T1D) and in healthy controls.

SUBJECTS AND METHODS: We included 35 NT1D patients (47.5% female, age 10.7+/-3.0 years), 36 T1D patients (47.2% female, age 16.3+/-5.6 years), and 36 healthy controls (55.6% female, age 16.2+/-6.9 years). Gene expression for RAGE, S100A12 and HMGB1 was quantified using qPCR, and sRAGE level was measured by ELISA. CRP was measured by routine laboratory method.

RESULTS: The PBMC s100A12 gene expression was significantly lower in NT1D patients compared to controls (p=0.040) and compared to T1D (p=0.002) (Figure 1). HMBG expression was also lower in NT1D when compared to controls (p=0.031) with no difference when compared do T1D (Figure 2). There was no difference between groups neither in RAGE gene expression nor in plasma sRAGE levels (Table 1).
NT1D also showed higher CRP (mg/dL) levels when compared to control group (2,32±4,15 (0,77-3,87) v.s. 0,62±0,95 (0,27-0,96), p=0.023).

		Controls (N=36)	NT1D (N=35)	T1D (N=36)
RAGE (AU)	Median (IQR)	0,2 (0,0-0,5)	0,2 (0,0-0,6)	0,1 (0,0-0,2)
	Mean±SD (95% CI)	0,31±0,44 (0,18-0,44)	0,60±0,90 (0,29-0,91)	0,42±0,83 (0,01-0,83)
S100A12 (AU)	Median (IQR)	2,2 (1,5-3,2)	1,1 (0,5-1,7)	2,2 (1,2-3,3)
	Mean±SD (95% CI)	2,62±1,80 (2,01-3,23)	1,22±0,81 (0,94-1,51)	3,07±3,10 (2,02-4,12)
HMGB-1 (AU)	Median (IQR)	1,2 (0,8-1,1)	0,6 (0,2-1,2)	0,7 (0,4-1,0)
	Mean±SD (95% CI)	1,19±0,66 (0,97-1,42)	0,73±0,63 (0,51-0,95)	3,07±3,10 (2,02-4,12)
sRAGE (ng/ml)	Median (IQR)	1,0 (0,8-1,2)	1,0 (0,7-1,5)	0,9 (0,7-1,2)
	Mean±SD (95% CI)	1,09±0,57 (0,90-1,28)	1,13±0,49 (0,95-1,31)	0,95±0,41 (0,81-1,09)

AU – arbitrary units; IQR – interquartile range; CI – confidence interval; NT1D – new onset type 1 tiabetes; T1D – type 1 diabetes with disease duration of more than five years

Table 1.

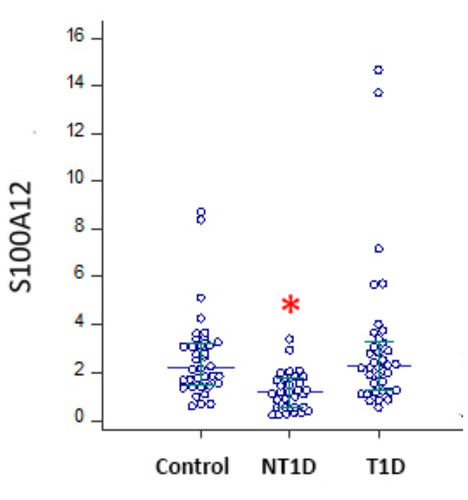

Figure1.

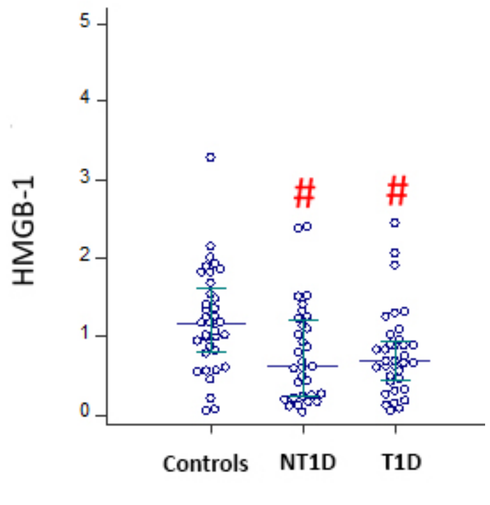

Figure 2.

CONCLUSION: Our findings might support the role of s100A12 and HMGB1 in type 1 diabetes development. However, we expected increased expression of this molecules in the setting of enhanced inflammation as suggested by higher CRP levels. We speculate that s100A12 and HMGB1 expression might be restricted to sites of inflammation harvesting PBMC expressing these genes from peripheral blood. Comparison between gene and protein expression in peripheral blood as well as between circulation and affected tissues should be performed in order to explain contribution of these molecules to development of diabetes.

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