P1-283

CHILDREN WITH HASHIMOTO'S THYROIDITIS HAVE INCREASED INTESTINAL PERMEABILITY: RESULTS OF A PILOT STUDY

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Disclosure

The authors have nothing to disclose.

Introduction

Both genetic predisposition and environmental factors serve as the trigger of Hashimoto's thyroiditis (HT), but the exact mechanisms are still not fully understood. Increased intestinal permeability (IIP) was shown to be a constant and early feature of several autoimmune disorders[1]. Although HT is the most common autoimmune disorder worldwide, the role of IIP in its pathogenesis had received little attention.

Human zonulin regulates intestinal permeability by modulating intracellular tight junctions (TJ)[2]. Zonulin was shown to play a key role in the IIP, when up regulated[3]. Higher zonulin expression was reported in the intestinal tissues of patients with many autoimmune disorders[4]. Increased serum zonulin levels were detected in human subjects during the pre-diabetic stage and preceded the onset of type 1diabetes[4]. On a rat model, zonulin-dependent IIP was shown to precede the onset of type 1 diabetes by 2–3 weeks[3]. Administration of the zonulin inhibitor (AT-1001) to these rats blocked autoantibody formation, zonulin-mediated IIP and reduced the incidence of diabetes[3]. AT-1001 competitively blocks apical zonulin receptor and prevents the opening of TJ[2] .

Objective

To examine the hypothesis that patients with HT have increased intestinal permeability.

Methods

A case-control study on a group of 30 children and adolescents with HT, and age, gender and body mass index (BMI) matched 30 patients with congenital hypothyroidism (CH). Obese patients and patients with acute or other chronic diseases were excluded from the study. Serum zonulin levels, free thyroxine (fT4), thyroid stimulating hormone (TSH), anti-thyroglobulin antibody and anti-thyroid peroxidase antibody were measured. Thyroid ultrasound results were retrieved from the patient's files. Data were presented as the mean ±SDS. Comparisons were made by using Independent Samples t Test or X^2 Test. We used Pearson analysis to determine correlations between zonulin levels and other clinical parameters. We created separate linear regression models to examine the associations of blood zonulin levels in patients with HT and CH. All statistical analyses were conducted with SPSS15.0. Statistical significance was defined as p ≤0.05.

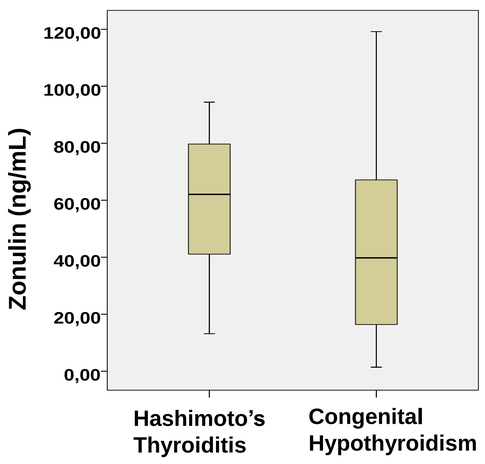

Figure 1. Serum zonulin levels in patients with Hashimoto's thyroiditis and congenital hypothyroidism.

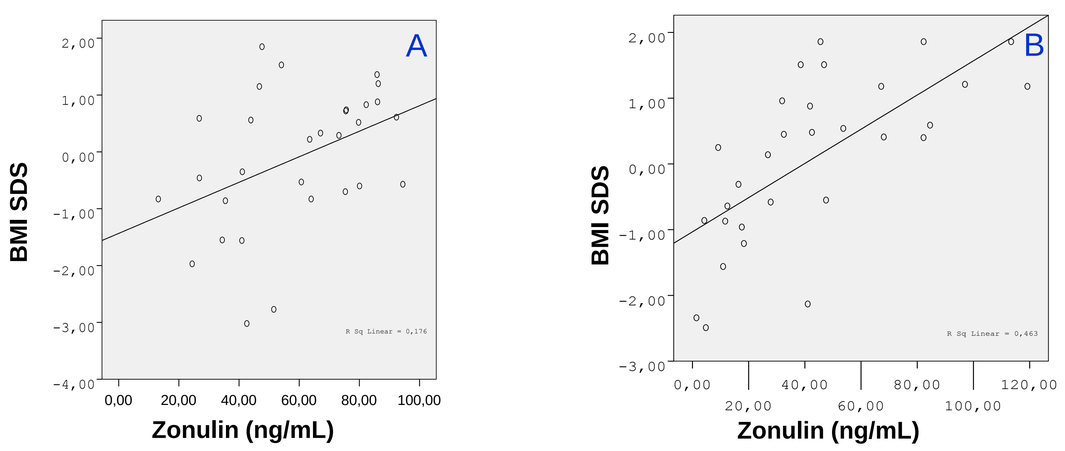

Figure 2. Correlations between zonulin levels and BMI SDS in patients with Hashimoto's thyroiditis (A) and congenital hypothyroidism (B).

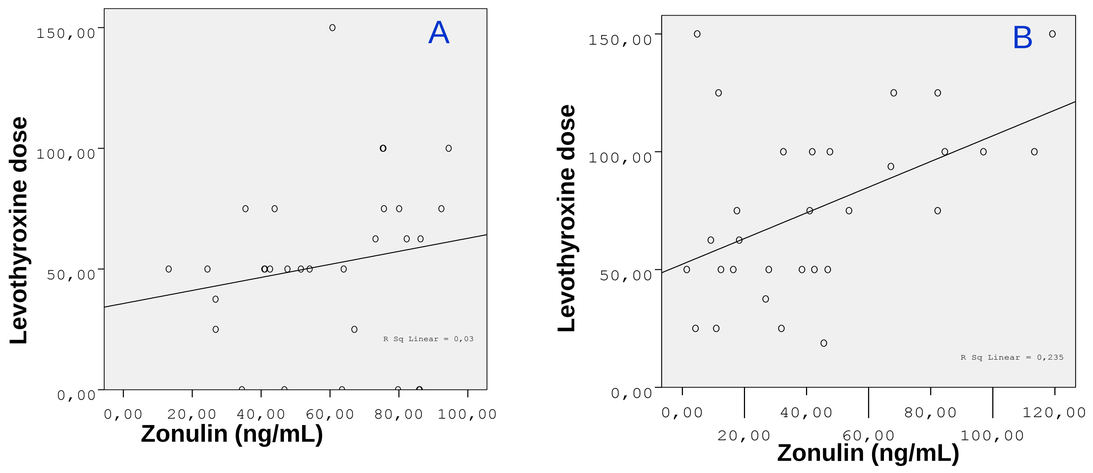

Figure 3. Correlations between zonulin levels and levothyroxine dose (µg/day) in patients with Hashimoto's thyroiditis (A) and congenital hypothyroidism (B).

Results

Patients' Characteristics **are summarised in Table 1.**

Serum zonulin levels were significantly higher in patients with HT than patients with CH (Table 1 and Figure 1).

In patients with HT**, zonulin levels were positively correlated with weight SDS (r= 0.377, p=0.04), BMI SDS (r= 0.419, p=0.02, Figure 2A) and levothyroxine dose (r= 0.463, p=0.02, Figure 3A). No significant correlation between zonulin levels and age, anti-TPO or anti-TG levels were found (r=0.212, p=0.26, r= -0.174, p=0.4 and r= 0.295, p=0.1, respectively).**

In patients with CH**, there were strong positive correlations between zonulin levels and age (r= 0.475, p=0.008), weight SDS (r= 0.532, p=0.002), BMI SDS (r= 0.681, p<0.001, Figure 2B) and levothyroxine dose (r= 0.485, p=0.007, Figure 3B).**

Multiple linear regression

In patients with HT, zonulin level was only associated with levothyroxine dose after adjusting for age, weight, TSH and fT4 levels (R^2=0.36, p=0.05).

When we put the patients with CH in the same regression model, there was no significant association between zonulin level and levothyroxine dose (p=0.4). However, zonulin level was strongly associated with only weight in these patients (R^2=0.62, p<0.001).

Table 1. Comparison of the clinical and laboratory parameters of the patients with Hashimoto's Thyroiditis and with congenital hypothyroidism (All values are means±SDs, except if otherwise stated)

	Hashimoto's Thyroiditis n=30	Congenital Hypothyroidism n=30	P value
Age (years)	12.6±2.7	11.3±3.4	0.11
Gender (F/M)	25/5	22/8	0.35
L-thyroxine dose (µg/day)	64.6±27.5	75.8±37.9	0.22
Weight SDS	-0.32±1.3	0.01±1.1	0.30
Height SDS	-0.40±1.1	-0.20±1.1	0.42
BMI SDS	-0.11±1.2	0.09±1.3	0.54
fT4 (ng/dL)	1.28±0.2	1.45±0.2	**0.004**
TSH (mIU/L)	6.5±5.9	7.7±6.3	0.37
Anti-TPO (IU/mL)	268.2±201	11.4±3	**<0.001**
Anti-TG (IU/mL)	641.4±1076	12.3±3.1	**<0.001**
USG			**<0.001**
Normal	0	12	
Agenesis	0	15	
Heterogeneous	17	3	
Heterogeneous and Pseudo-nodular	13	0	
Zonulin (ng/mL)	59.1±22.9	43.3±32.9	**0.035**

Conclusion

Higher zonulin levels in children and adolescents with HT suggested increased intestinal permeability in these patients. In addition, the association between zonulin levels and levothyroxine dose might imply a relationship between serum zonulin and disease severity.

References

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