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The Gut Protein Zonulin is Increased in Patients with Type 1 Diabetes and Their First Degree Relatives

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Background: The trigger of the autoimmune destruction of pancreatic beta cells in Type 1 diabetes is unclear. One theory is that antigens absorbed through the gut may be involved. A gut protein, zonulin, has been described that opens the tight junctions and enables absorption of particles from the gut. Zonulin has been found to be increased in the serum of patients with Celiac Disease and in a rat model of Type 1 diabetes.

Objective: The objective of this study is to determine if zonulin may be linked to the pathogenesis of Type 1 diabetes in humans.

Design/Methods: After obtaining informed consent, blood was obtained from children with Type 1 diabetes, parents, siblings, and non-diabetic controls. Zonulin was measured in the serum of children with Type 1 diabetes (n=28), their first degree relatives (adults n=24, children n=4), and non-diabetic controls (adults n=68, children n=79) by sandwich ELISA.

Results: In controls children, mean zonulin was 2.1 pg/mg protein (S.D. 3.6); in children with Type 1 diabetes 12.2 pg/ml (S.D. 11.6), $p < 0.0001$. In adult controls, mean zonulin was 4.6 pg/mg protein (S.D. 10.4); in adult relatives 13.5 pg/mg protein (S.D. 11.7), $p < 0.0001$. Zonulin was higher in adult controls than pediatric controls ($p = 0.03$) and relatives were slightly higher than diabetics, but not significant ($p = 0.54$). Four % of adult controls and 13% of adult relatives had zonulins greater than 25 pg/mg protein (mean + 2 S.D. of controls). Five % of pediatric controls, 75% of pediatric relatives, and 50 % of children with diabetes had zonulins greater than 9 pg/mg protein (mean + 2 S.D. of controls). There was no relationship of age of onset of diabetes or number of years since diagnosis to zonulin level.

Conclusions: Zonulin is significantly increased in children with Type 1 diabetes and their first degree relatives compared to non-diabetic controls. These data suggest that zonulin-dependent gut leakiness is a necessary (but not sufficient) predisposing factor to develop Type 1 diabetes in genetically susceptible individuals. Studies of gut permeability (lactulose and mannitol test) are planned to compare subjects with elevated versus low zonulin to controls. The finding of increased zonulin in children with Type 1 diabetes and patients with Celiac Disease may explain the association between these two conditions, and perhaps may be a causative link for other associated autoimmune diseases,