Serum Anti-Endomysial and Anti-Tissue Transglutaminase for Screening of Celiac Disease

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Celiac disease is a human leukocyte antigen-DQ2 (or DQ8)-associated autoimmune disorder of the human small intestine [1] that is induced by dietary exposure to wheat gliadin, barley hordein, rye secalin and possibly oat avenins [2]. The disease is characterized by small intestinal mucosal damage with loss of absorptive villi and hyperplasia of the crypts that can lead to malabsorption [3]. In addition to nutrient deficiencies and growth failure, prolonged untreated celiac disease is associated with an increased risk of malignancy, especially intestinal T cell lymphoma [4]. Celiac disease is associated with various endocrine disorders, such as juvenile diabetes mellitus [5], thyroid disease and Addison's disease [6], as well as with autoimmune diseases, e.g., autoimmune thrombocytopenia [7]. It was found that the relation between celiac disease and autoimmune diseases is directly correlated to the duration of gluten exposure [7]. In addition, celiac disease is associated with dermatitis herpetiformis [8], Down syndrome, sarcoidosis and selective immunoglobulin A deficiency [7].

The revised criteria of the European Society for Pediatric Gastroenterology, Hepatology and Nutrition for the diagnosis of celiac disease [9] include a distinct pattern of abnormalities in the small intestinal biopsy and elevated serologic markers when the patient is eating an adequate amount of gluten, and a full clinical remission after gluten is withdrawn from the diet, with concomitant decrease in the level of the serologic markers.

Clearly there was a need for a simple, sensitive and specific non-invasive screening test for celiac disease [10]. In 1979 Signer et al. [11] reported that serum antibodies to gliadin constitute a possible diagnostic tool. Since then, antigliadin antibodies of isotypes IgA and IgG, anti-endomysial antibodies of isotype IgA and anti-tissue transglutaminase antibodies of isotype IgA were used as screening tests for celiac disease [12–16]. While the sensitivity of anti-endomysial and anti-tissue transglutaminase antibodies were close to 100% [12–16], the sensitivity of antigliadin IgA and IgG was 89%. The specificity of anti-endomysial was 100% while anti-TTG was 97%. Antigliadin IgA was 96% and antigliadin IgG 78% [16]. However, the most important predictive value was seen by anti-endomysial antibodies – 97%, whereas it was considerably lower for anti-TTG and antigliadin IgA and IgG antibodies [16].

A recent study [17] demonstrated that anti-TTG enzyme-linked immunoabsorbent assay has a high frequency of false negative and false positive results. However, because the test is both simple and fast, it was suggested that it be used in large screening programs for celiac disease [17]. It was also suggested that after an initial positive anti-TTG test, an anti-endomysial antibody test should be performed provided that IgA deficiency is excluded [16,17]. Nevertheless, assessment of the small intestinal mucosal morphology is still mandatory as the ultimate requirement for the diagnosis of celiac disease [9].

The anti-endomysial antibody test has significant technical drawbacks. The use of the immunofluorescence method is not easy to interpret due to large inter-observer variability. The antigen is taken from monkey esophageal tissue and the procedure is time-consuming [18].

In this issue of *IMAJ*, Shamir and co-workers [19] evaluated a new anti-endomysial ELISA test to replace the immunofluorescent technique and compared it to the anti-transglutaminase test. The new anti-endomysial ELISA test is based on endomysium antigens purified by affinity chromatography from primate liver. The findings by Shamir et al. [19] reveal a high correlation between the level of the new test and the level of the human TTG antibodies. This study, despite its small sample size, is very important as it offers the possibility of using a simple, easy to interpret and effective screening test for the diagnosis of celiac disease.

The quest for improvement of the current tests for determination of anti-endomysial antibodies and anti-TTG antibodies uses at least three methods based on different principles – all detecting autoantibodies against the same antigen [20]. Radio-immunoprecipitation assay using recombinant TTG was compared first to commercial enzyme immunoassay using guinea pig TTG (ELISA) as well as indirect immunofluorescence for detection of anti-endomysial antibodies [20]. The results demonstrated a very high sensitivity and specificity for the radio-immunoprecipitation when compared to the other methods [20]. The advantage of the radio-immunoprecipitation method can be explained by the use of human recombinant TTG and the possible increased capacity of the method to detect low titers of autoantibodies.

IG = immunoglobulin
TTG = tissue transglutaminase

ELISA = enzyme-linked immunosorbent assay

Another important question is how to diagnose IgA-deficient patients suffering from celiac disease. An evaluation of anti-endomysial antibodies of isotype IgG1 [21] revealed a group of IgA-deficient patients with negative anti-endomysial antibodies of isotype IgA that has antibodies to isotype IgG-1 [21].

Overall, an improved anti-endomysial or anti-TTG of isotypes IgA and IgG might provide us with an ultimate tool to screen populations for celiac disease. Recent studies indicate that the prevalence of celiac disease in Western Europe is 1:85–300 [22,23]. We therefore recommend that a screening test for celiac disease be conducted in the population of Israel to avoid the unwarranted clinical outcomes, autoimmune diseases, and malignancy associated with undiagnosed celiac disease.

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