An Additional Piece in the Israeli Celiac Disease Puzzle

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In the present issue of *IMAJ*, Israeli et al. [1] explore the prevalence of celiac disease in 850 healthy military recruits screened in 2003 by serology and confirmed by intestinal biopsies. The overt CD prevalence, prior to recruitment, was 0.12%. The serologic prevalence was 1.1% and the pathology-based prevalence 0.7%. The authors should be congratulated for undertaking such a task since crucial information on the incidence and prevalence of this frequent autoimmune disease in Israel is lacking. Nevertheless, several controversial aspects arise from the study and will be discussed below.

The prevalence of a disease is the proportion of the affected subjects at a specific time. Prevalence studies should be based on a random sample of the population in the electoral roll or selected by postcodes using the method of population in proportion to size. Unfortunately, most prevalence studies on CD were conducted on sera from selected groups such as blood donors, school-age children, outpatient clinics, or military personnel or recruits as in the present study. This selectivity induces bias to the true prevalence of CD. Table 1 summarizes the studies of CD prevalence done in Israel on selected populations. The table illuminates the bias of comparing the prevalence in selected populations as shown by the wide variation in the prevalence of CD.

In addition to selecting the population to be screened is the dilemma – what serologic test to use. In the last few years the armamentarium of tests expanded considerably. The old anti-gliadin antibody [5] was replaced by the more recent anti-endomysial and anti-tissue transglutaminase [6,7]. The latest to enter the race for the serologic diagnosis or future screening of CD are the new anti-deaminated gliadin peptide and the tTG-neo-epitope. The most commonly used antibody for population screening is immunoglobulinA-EmA and IgA-tTG and only the future will show if newer antibodies like deaminated gliadin peptide or the neo-epitope of tTG will perform better. A major step forward is the replacement of the cumbersome, operator-dependent immunofluorescent EmA by the simpler, standardized, less costly and reliable EmA measured by the enzyme-linked immunosorbent assay technique [6].

Reliance on serum IgA-EmA as the only screening antibody has led to the underestimation of the true prevalence of CD, and adding IgA-tTG improves the results [8,9]. On the other hand, confirmation with EmA is advised when tTG is performed as a first-level screening for suspected celiac disease [10]. In our screening of blood donors, we concluded that the disparity between the various serologic markers suggests that using one serologic marker is insufficient for establishing the true prevalence of CD [4].

The emergence of CD-specific antibodies of the IgG type – namely IgG-EmA, IgG-tTG, IgG anti-deaminated gliadin-analogous fusion peptides [11], celiac G+ antibodies [12], and IgG tTG-neo-epitope [13] – as separate kits or as part of a multiplex immunoassay [14] brings hope to the problem of diagnosing CD in IgA-deficient patients. In fact, IgA deficiency occurs in 1:400 in the general population but 1:40 of celiac patients, increasing the diagnostic importance of this subpopulation. In a recent cost-effectiveness analysis, Dorn et al. [15] concluded that routinely screening for IgA deficiency in order to avoid a false-negative diagnosis is quite costly. It is possible that the screening method of the future will include a multiplex kit with two IgA and two IgG-based, reliable, celiac-specific antibodies, thus avoiding routine total IgA determination.

The issue of mass screening for CD is highly controversial and the reader is referred to the summary of the pro and cons in the September 2009 issue of the

CD = celiac disease

EmA = anti-endomysial antibodies
Ig = immunoglobulin
tTG = anti-tissue transglutaminase

Table. Studies of CD prevalence in Israel on selected populations

Reference	Pathologic confirmation	Overall prevalence (%)	Serologic prevalence (%)	Population	No. screened
1	6\6	0.7	1.1	Military recruits	850
2			1.486	Military personnel	538
3	1\1	0.48	0.48	Normal controls	210
4	10\30	0.6	3.8	Blood donors	1571

British Medical Journal [16,17]. However, we recently learned that 90% of CD is being missed [18], positive serologic results are often not confirmed histologically [19], undiagnosed CD is associated with a nearly fourfold increase in mortality [20], and many of the patients identified by screening do not ultimately benefit from being screened [21]. Clearly, we need a large-scale screening to detect the true prevalence of CD in the population and a centralized national registration system to establish a data bank of CD. The most reliable detecting antibodies and the preferred technique should be established before large-scale screening. Due to the low compliance – for multiple reasons – with a gluten-free diet, new therapeutic strategies to treat CD should be developed [22].

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References

1. Israeli E, Hershcovici T, Grotto I, Rouach Z, Branski D, Goldin E. Prevalence of celiac disease in an adult Jewish population in Israel. *IMAJ Isr Med Assoc J* 2010; 12: 00-00.
2. Yagil Y, Goldenberg I, Arnon R, Ezra V, Ashkenazi I. Serologic testing for celiac disease in young adults – a cost-effect analysis. *Dig Dis Sci* 2005; 50: 796-805.
3. Shamaly H, Mahameed A, Sharony A, Shamir R. Infertility and celiac disease: do we need more than one serological marker? *Acta Obstet Gynecol Scand* 2004; 83: 1184-8.
4. Shamir R, Lerner A, Shinar E, et al. The use of a single serological marker underestimates the prevalence of celiac disease in Israel: a study of blood donors. *Am J Gastroenterol* 2002; 97: 38-43.
5. Lerner A, Lebenthal E. The controversy of antigluten antibody (AGA) as a diagnostic tool in celiac disease [Editorial]. *J Pediatr Gastroenterol Nutr* 1991; 12: 407-09.
6. Shamir R, Eliakim R, Lahat N, Sobel E, Lerner A. ELISA assay of anti-endomysial antibodies in the diagnosis of celiac disease: comparison with immunofluorescence assay of anti-endomysial antibodies and tissue transglutaminase antibodies. *IMAJ Isr Med Assoc J* 2002; 4: 594-6.
7. Reif S, Lerner A. Tissue transglutaminase – the key player in celiac disease: a review. *Autoimmun Rev* 2004; 3: 40-5.
8. Dickey W, Hughes DF, Mcmillan SA. Reliance on serum endomysial antibody testing underestimates the true prevalence of celiac disease by one fifth. *Scand J Gastroenterol* 2000; 35: 181-3.
9. Tesei N, Sugai E, Vazquez H, et al. Antibodies to human recombinant tissue transglutaminase may detect coeliac disease patients undiagnosed by endomysial antibodies. *Aliment Pharmacol Ther* 2003; 17: 1415-23.
10. Weiss B, Bujanover Y, Avidan B, Fradkin A, Weintraub I, Shainberg B. Positive tissue transglutaminase antibodies with negative endomysial antibodies: low rate of celiac disease. *IMAJ Isr Med Assoc J* 2004; 6: 9-12.
11. Prause C, Richter T, Koletzko S, et al. New developments in serodiagnosis of childhood celiac disease: assay of antibodies against deaminated gliadins. *Ann NY Acad Sci* 2009; 1173: 28-35.
12. Bansal AK, Lindemann MJ, Ramsperger V, Kumar V. Celiac G+ antibody assay for the detection of autoantibodies in celiac disease. *Ann NY Acad Sci* 2009; 1173: 36-40.
13. Matthias T, Pfeiffer S, Selmi C, Eric Gershwin M. Diagnostic challenges in celiac disease and the role of the tissue transglutaminase-neo-epitope. *Clin Rev Allergy Immunol* 2009; 38: 298-301.
14. Rashtak S, Ettore MW, Homburger HA, Murray JA. Combination testing for antibodies in the diagnosis of coeliac disease: comparison of multiplex immunoassay and ELISA methods. *Aliment Pharmacol Ther* 2008; 28: 805-13.
15. Dorn SD, Matchar DB. Cost-effectiveness analysis of strategies for diagnosing celiac disease. *Dig Dis Sci* 2008; 53: 680-8.
16. Fasano A. Should we screen for celiac disease? Yes. *BMJ* 2009; 339: b3592.
17. Evans K, McAllister R, Sanders DS. Should we screen for celiac disease? No. *BMJ* 2009; 339: b3674.
18. Ravikumara M, Nootigattu VK, Sandhu BK. Ninety percent of celiac disease is being missed. *J Pediatr Gastroenterol Nutr* 2007; 45: 497-9.
19. Evans KE, Malloy AR, Gorard DA. Changing patterns of coeliac disease requests. *Aliment Pharmacol Ther* 2009; 29: 1137-42.
20. Rubio-Tapia A, Kyle RA, Kaplan EL, et al. Increased prevalence and mortality in undiagnosed celiac disease. *Gastroenterolgy* 2009; 137: 88-93.
21. Shamir R, Yehezkely-Schildkraut V, Hartman C, Eliakim R. Population screening for celiac disease: follow up of patients identified by positive serology. *J Gastroenterol Hepatol* 2006; 22: 532-5.
22. Lerner A. New therapeutic strategies for celiac disease. *Autoimmune Rev* 2009; 9: 144-7.