Celiac disease

Managing IgA-deficient samples in celiac disease testing

Antibody testing to support the diagnosis of celiac disease

Celiac disease is a lifelong condition in which ingesting gluten causes chronic inflammation and damages small intestinal mucosa.[1] Tissue transglutaminase (tTG) is the major autoantigen in celiac disease,[2] and thus, IgA antibodies against tTG are disease-specific serological markers for both celiac disease and dermatitis herpetiformis.[3, 4, 5] IgG antibodies against tTG are less specific but helpful markers in patients with IgA deficiency.[6, 7, 8]

Testing guidelines aim to minimize false negatives

The guidelines established by the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) provide a structured approach for diagnosing celiac disease. According to these guidelines, ESPGHAN advises that assessing total serum IgA along with IgA antibodies against tissue transglutaminase 2 (tTG-IgA) is more advantageous than using other testing combinations. IgG-based testing should be considered only if total IgA is low or undetectable.[8] ESPGHAN advises against using deamidated gliadin peptide antibodies (DGP-IgG/IgA) for initial testing. Patients with positive results should then be referred to a paediatric gastroenterologist/specialist.[8]

In cases where tTG-IgA levels are significantly elevated (10x upper limit of normal; ULN) and confirmed by a second blood sample testing positive for endomysial antibodies (EMA) IgA, a biopsy may be bypassed if agreed upon by the patient's family. Moreover, determination of HLA DQ2 or DQ8 are not obligatory criteria. For cases where tTG-IgA levels are elevated but **not** to the extent mentioned above, biopsies are recommended. In situations where test results conflict with biopsy findings, a re-evaluation of the biopsy may be necessary. Patients showing no or minor histological changes but confirmed autoimmune activity should be closely monitored.[8]

Identifying samples with IgA deficiency is a critical component of the testing process for laboratories performing diagnostic tests.[8]

Selective IgA deficiency, characterized by abnormally low levels of IgA in plasma below 7 mg/dl is relatively common, affecting approximately 1 in 600 individuals in the general population and up to 3% of celiac disease patients.[9,10] Due to the absence or low levels of IgA, some celiac disease patients with this deficiency may yield false-negative results when tested for tTG-IgA alone.[9,10]

Low RU on Phadia instruments suggest IgA deficiency[11]

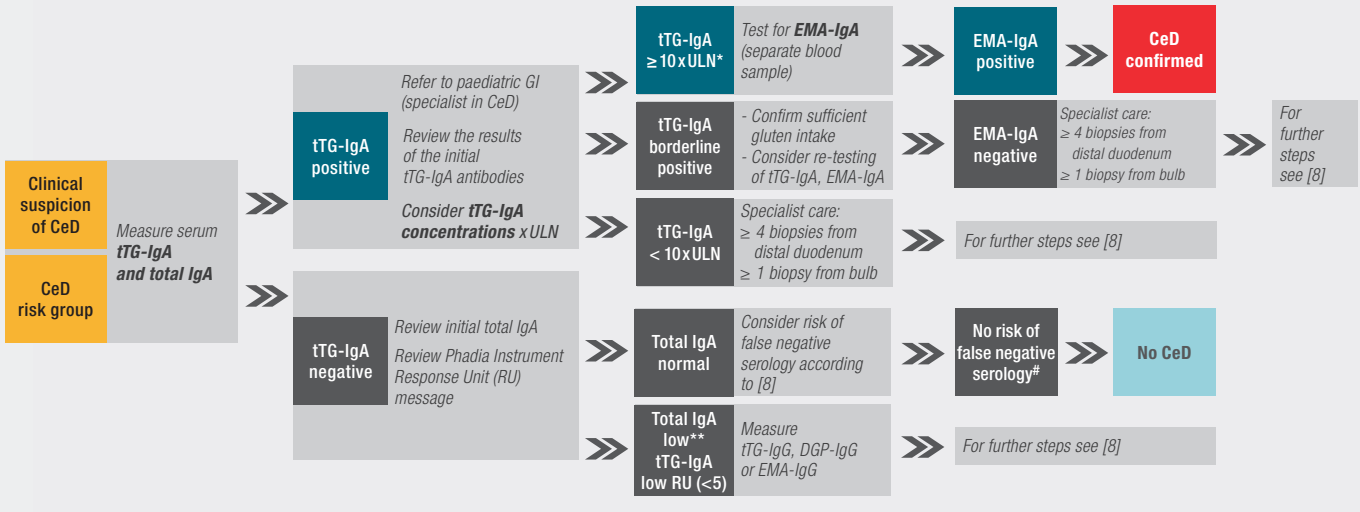
In an internal study examining 17 patients with celiac disease who exhibited deficiency in total IgA, 15 of them demonstrated response unit (RU) values below 5 on the Phadia™ instruments, as indicated in Table 1.[11] This outcome prompted the instrument to generate a "low RU" message, as outlined in the EliA™ Celikey IgA test Directions for Use (DFU) and Phadia™ 250 User Manual.

This indicates that for total IgA-deficient patients with "low RU", tTG-IgG may be measured in the next step (e.g., with the EliA™ Celikey IgG test) to further support a diagnostic decision.[8] Recommendations of the ESPGHAN 2020 guidelines for diagnosing celiac disease call to screen samples for total IgA levels during the complete serology diagnostics to identify IgA-deficient samples.[8] It is recommended to always consider current diagnostic guidelines.[8] The triggered "low RU" message suggests low total IgA values and may be an auxiliary indicator to further test those samples for tTG-IgG.[8] The presence of tTG-IgG is less specific for celiac disease than tTG-IgA but further supports a diagnostic decision.[8] Multiple studies have confirmed that reduced levels of tTG-IgA correspond closely with diminished total IgA levels, thus serving as a reliable predictor of IgA deficiency.[12,13,14] This correlation has been validated with the EliA Celikey IgA test.[13,14]

To learn more, **click here** to read the latest EliA Celikey IgA Well DFU or contact your Thermo Fisher Scientific representative.

Algorithm for celiac disease testing

Adapted from: Husby S. et al., JPGN 2020, vol.70, issue 1, 141-456.



*If TGA-IgA is ≥10 x ULN and the family agrees, the no-biopsy diagnosis may be applied if EMA-IgA is positive in a second blood sample

**Low total IgA for age or <0.2 g/L above the age of 3 years

#Risks: low or short duration of gluten intake, immunosuppressive medication, extraintestinal manifestations

Abbreviations: CeD = celiac disease, **IgA/IgG** = Immunglobulin A/G, **DGP** = deamidated gliadin peptide, **EMA** = endomysial antigen, **ULN** = upper limit of normal

Table 1.
IgA-deficient samples analyzed on Phadia instruments with the EliA Celikey IgA test trigger a “low RU” message (mean RU<5).

EliA Celikey IgA test		EliA Celikey IgG test		Indication
Mean RU	EliA U/ml	Mean RU	EliA U/ml	
0	0.0	9175	251.0	
0	0.0	8278	217.8	
0	0.0	6259	152.3	
0	0.0	2881	63.1	
231	0.7	15313	592.1	
8	0.0	2798	61.2	
0	0.0	5771	138.0	
3	0.0	6823	169.5	
0	0.0	3079	67.8	Celiac disease
0	0.0	2408	52.1	
0	0.0	11380	346.5	
1	0.0	10941	325.7	
0	0.0	6549	161.0	
0	0.0	9668	270.5	
0	0.0	12165	372.2	
0	0.0	11869	357.4	
0	0.0	18843	600.0	
20	0.0	194	3.0	
2	0.0	105	1.0	
0	0.0	83	0.5	
0	0.0	87	0.6	Controls*
0	0.0	138	1.9	
1	0.0	74	0.6	
5	0.0	278	4.8	
0	0.0	5	0.0	
282	0.9	190	3.1	Control

* controls suspected to be IgA-deficient

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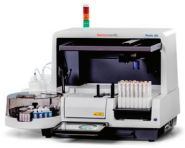

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Technical and ordering information

Product	Article No.	Package size	Interpretation of test results		
			Negative	Equivocal	Positive
EliA™ Celikey IgA Well	14-5517-01	4 x 12	< 7 EliA U/mL	7–10 EliA U/mL	> 10 EliA U/mL
EliA™ Celikey IgG Well	14-5518-01	2 x 12	< 7 EliA U/mL	7–10 EliA U/mL	> 10 EliA U/mL
EliA™ Gliadin^{DP} IgA Well	14-5538-01	4 x 12	< 7 EliA U/mL	7–10 EliA U/mL	> 10 EliA U/mL
EliA™ Gliadin^{DP} IgG Well	14-5539-01	4 x 12	< 7 EliA U/mL	7–10 EliA U/mL	> 10 EliA U/mL

References

1. Mäki M and Collin P. Coeliac disease. Lancet, 1997; 349:1755–1759.
2. Dieterich W, et al. Identification of tissue transglutaminase as the autoantigen of celiac disease. Nature Med, 1997; 3:797–801.
3. Sulkanen S, et al. Tissue transglutaminase autoantibody enzyme-linked immunosorbent assay in detecting celiac disease. Gastroenterology, 1998; 115:1322–1328.
4. Troncone R, et al. IgA antibodies to tissue transglutaminase: An effective diagnostic test for celiac disease. J Pediatr, 1999; 134: 166–171.
5. Rose C, et al. Circulating autoantibodies to tissue transglutaminase differentiate patients with dermatitis herpetiformis from these with linear IgA disease. J Am Acad Dermatol, 1999; 41:957–961.
6. Korponay-Szabó IR, et al. Elevation of IgG antibodies against tissue transglutaminase as a diagnostic tool for coeliac disease in selective IgA deficiency. Gut, 2003; 52:1567–1571.
7. Agardh D, et al. Tissue transglutaminase immunoglobulin isotypes in children with untreated and treated celiac disease. J Pediatr Gastroenterol Nutr, 2003; 36:77–82.
8. Husby S, et al. European Society Paediatric Gastroenterology, Hepatology and Nutrition Guidelines for Diagnosing Coeliac Disease 2020. J Pediatr Gastroenterol Nutr, 2020; 70:141–156.
9. Swain S, et al. The clinical implications of selective IgA deficiency. J Transl Autoimmun, 2019; 2:100025.
10. Mac Lochlainn DJ, et al. Implementation of National Institute for Health and Care Excellence (NICE) guidance to measure immunoglobulin A with al coeliac screens: can an affordable solution be devised? Clin Exp Immunol, 2017; 189:352–358.
11. Thermo Fisher Scientific Internal Study.
12. Shahnaz A, et al. Tissue transglutaminase antibody levels predict IgA deficiency. Arch Dis Child, 2013; 98:873–876.
13. Harrison E, et al. Selective measurement of anti-tTG antibodies in coeliac disease and IgA deficiency: an alternative pathway. Postgrad Med J, 2013; 89:4–7.
14. Löwbeer C and Wallinder H. Undetectable anti-tissue transglutaminase IgA antibody measured with EliA Celikey indicates selective IgA deficiency. Clin Chim Acta, 2010; 411:612.

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