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PGY1 Medicine

IRB Proposal

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**Selective IgA deficiency and celiac disease: IgG deamidated gliadin peptide antibody for diagnosis and monitoring dietary compliance**

## A. Study Purpose and Rationale:

Selective immunoglobulin A (IgA) deficiency is the most common primary immunoglobulin deficiency in the general population (1). Prevalence depends on ethnic background, but in the United States the prevalence of IgA deficiency is estimated to be from 1:223 to 1:1000 in community studies and from 1:400 to 1:3000 in healthy blood donors (1,2). In patients with celiac disease (CD) the prevalence of IgA deficiency has been found to be much higher than that of the general population, occurring in 1:39 to 1:43 patients with CD (3,4).

The gold standard for diagnosing celiac disease is small bowel biopsy, however, it is also common to screen for celiac disease with antibody testing, especially when there is a low pre-test probability. In patients with normal IgA levels, measuring tissue transglutaminase (TTG) IGA antibodies is the preferred screening test (5). In patients with biopsy proven CD and normal IgA levels, gluten intake can also be monitored via TTG IgA antibody levels(6). Antibody levels should revert to negative in patients who are compliant with a GFD, correlating with histological improvement.

However, in patients with IgA deficiency testing for IgA antibodies cannot be used. Our recent research looked at IgA deficiency and partial deficiency in CD. Although patients with total IgA deficiency did not produce IgA celiac antibodies, the majority of patients with partial IgA deficiency did produce IgA antibodies, and could therefore be diagnosed and monitored in the same way as the non-IgA deficient patients. We then explored the possibility of looking at TTG IgG levels at time of diagnosis in the IgA deficient patients but found the sensitivity of this test to be only 76%. We also looked at following TTG IgG levels as a marker of dietary compliance and disease resolution, but found this test to be unreliable, as antibodies levels often remained elevated despite histological improvement (50% of patients had persistently positive TTG IgG antibodies on a gluten free diet).

The deamidated gliadin peptide (DGP) antibody test is a newer antibody test that has recently become available. Deamidation of gliadin peptides by TTG results in a negatively charged peptide with enhanced binding capacity to HLADQ2 or 8 and results in an enhanced T-cell response (7). Antibody response is also enhanced by the deamidation process (8). A recent meta-analysis was conducted to compare the performance of the deamidated gliadin peptide test with TTG (5). Sensitivity for DGP IgA was 87.7 (95% CI, 85.6-89.9) and for TTG IgA was 93% (95% CI, 91.2-94.5). Specificity for DGP IgA was 94.1 (95% CI, 92.5-95.5) and for TTG IgA was 96.5 (95% CI, 95.2-97.5). They concluded that although both tests performed well, DPG IgA was slightly outperformed by TTG IgA in terms of sensitivity. However, they did note that

most studies analyzed had methodological flaws, especially ascertainment bias. This meta-analysis also did not look at antibody testing in monitoring dietary compliance.

Another recent study that prospectively followed children at high risk of developing CD showed that DGP antibodies can precede the appearance of TTG IgA antibodies and resolved sooner, indicating that DGP antibodies may be better in earlier diagnosis of CD and in monitoring compliance (9).

Only one study evaluated TTG IgG and DGP IgG in patients with selective IgA deficiency. It looked at 20 patients with CD and IgA deficiency and 113 controls and found that TTG IgG sensitivity of several different testing kits ranged from 75 to 95%. The sensitivity of DGP IgG was found to be 87% (10).

In this study we propose to look more closely at DGP IgG antibodies in the IgA deficient patient population, both in terms of sensitivity at diagnosis and reliability in following this antibody to assess for compliance with a gluten free diet.

**B. Study design and statistical procedures:**

This will be a single center retrospective study of the 1819 patients (1501 adults and 318 children) with CD at the Celiac Disease Center at Columbia University, all of whom have consented to be listed in our computerized celiac database and to have their medical records/data utilized for the purpose of CD research.

Total serum IgA levels are routinely measured in all of our CD patients. Patients will be determined to be IgA deficient if they have undetectable levels of total serum IgA (<6.67). Those patients who have total serum IgA levels that are detectable, but below the lower limit of normal (between 6.67 and 70) will be considered to be partially IgA deficient.

For the IgA deficient patients we will look more closely at the method of diagnosis, including which antibodies were tested and were positive at the time of diagnosis, as well as follow up biopsies and serologies after starting a GFD. Patients will be considered to have a positive biopsy if histology demonstrated partial villous atrophy (Marsh 3A) or subtotal/total villous atrophy (Marsh 3B/C).

As DGP testing was not available at the time of diagnosis for the patients currently listed in our database, we will need to analyze the banked blood of the IgA deficient patients at the time of diagnosis to check for DGP IgG. We can use these results and the results of the biopsy at the time of diagnosis (gold standard) to determine the sensitivity of the DGP IgG test in our patients. We can also check banked follow-up serum to evaluate the DGP IgG antibody response to a gluten free diet and correlate this response with histological response on follow up biopsy if available. Any new patients seen in our center with IgA deficiency and possible CD can be. followed prospectively.

Based on the data from the recent meta-analysis (5) and Villalta study (10) we will assume that the sensitivity of the DGP IgG test is around 87%. We would consider a sensitivity above 70% to be a significant result (given that the sensitivity we calculated in our IgA deficient patient population for TTG IgG at time of diagnosis was about 75%). Power analysis using the chi

square test reveals that for 80% power , testing at p=0.05 we would need a sample size of about 103 to determine an effect that is to be considered significant.

In regards to following serologies to monitor dietary compliance, we assume that we can expect 90% of patients to have DGP antibody levels revert to negative on a gluten free diet. A significant effect would be >50%, (about 50% of patients in our prior study had TTG IgG levels that reverted to normal on a gluten free diet). Power analysis using the chi square test reveals that for 80% power , testing at p=0.05 we would need a sample size of about 25 to determine an effect that is to be considered significant.

We currently have 26 patients in our database who are IgA deficient, which would give us adequate power for the second part of this study (monitoring serologies to monitor dietary compliance), however not enough for determining the sensitivity of the DGP IgG test at diagnosis. To obtain adequate power with this portion of the study it could be possible to collaborate with the celiac disease centers of other institutions.

**C. Study Procedures**

Non-applicable

**D. Study Drugs**

Non-applicable

**E. Medical Devices**

Non-applicable

**F. Questionnaire**

Non-applicable

**G. Study Subjects**

All patients with CD and IgA deficiency in our celiac disease database.

**H. Recruitment of Subjects**

All patients seen at the celiac disease center are asked if they are willing to consent to be part of the celiac disease database where their medical record would be available for use in celiac disease research.

## I. Confidentiality of Study Data

Patient information is kept in the celiac database with only MRNs as identifiers. This database is password protected/ All information is available only to the research assistants and investigators.

## J. Potential Conflicts of Interest

There are no potential conflicts of interest

## K. Location of the Study

Columbia Celiac Disease Center

## L. Potential risks

No potential risks associated with this study.

## M. Potential benefits

No direct benefit to the study participants. The study may benefit future patients with CD and IgA deficiency by improving diagnosis and management of patients with this diseases.

## N. Alternative therapies

Non-applicable

## P. Cost to subjects

Non-applicable

## References:


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