Analysis of Vitamin D Levels in Patients with Celiac Disease and Co-Existing Autoimmune Disorders

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1. Study Purpose and Rationale

Celiac Disease is an autoimmune disorder that is characterized by intolerance to gluten, which is the major storage protein of wheat, rye and barley[1,2,3]. It can present in both children and adults, but the clinical manifestations of the disease vary according to age group. Infants and young children can present with diarrhea, abdominal distention, and failure to thrive, while older children and adolescents typically present with extra-intestinal manifestations, such as short stature, neurological symptoms, or anemia[1,13]. Adults who present with celiac disease can often present with diarrhea, abdominal pain, or discomfort. However, 'silent' presentations of celiac disease, including iron deficiency anemia and osteoporosis, can occur in adult patients.

The diagnostic approach for celiac disease includes serological testing and small intestinal mucosal biopsy[3]. Typically, serological testing for IgA antibodies is completed in patients with unexplained bloating, chronic diarrhea, laboratory results that suggest malabsorption, or the presence of autoimmune diseases known to be associated with celiac disease[4]. The two most sensitive antibodies to screen for celiac disease are endomysial IgA antibodies and anti-tissue transglutaminase IgA antibodies[4]. However, the gold standard for diagnosis of celiac disease is small intestinal mucosal biopsy[3,4]. The histologic changes that can be seen include villous atrophy, crypt hyperplasia, and mucosal inflammation. In addition, villous atrophy can range from total to partial villous atrophy, causing various clinical presentations and malabsorption[3]. Lastly, celiac disease is present in about 1% of the population, and is commonly present in people of European ancestry, in addition to the Middle East, Asia, South America, and North Africa[4-12].

Celiac disease is also associated with an increased risk of developing other autoimmune diseases. While autoimmune diseases are present in about 3.2% of the general population, with a female predominance, a study of 323 patients with celiac disease found that autoimmune diseases were present in 30.7% of patients, with a female to male ratio of 1:1[14]. Autoimmune disorders commonly seen in patients with celiac disease include insulin-dependent diabetes mellitus, hypothyroidism, primary biliary cirrhosis, systemic lupus erythematosus, rheumatoid arthritis, Sjogren's syndrome, and multiple sclerosis[3,14-16]. In addition, the prevalence of autoimmune disorders in patients with celiac disease increased with increasing age of diagnosis, with 5% in patients less than 2 years old, 17% in patients between 2-10 years old, and 23.6% in patients greater than 10 years old[15].

Outside of the risk of autoimmune disorders, patients with celiac disease often present with nutritional deficiencies as a result of villous atrophy and subsequent malabsorption. Vitamin D is one such nutritional deficiency that has been noted in

patients with celiac disease and which the implications have been observed in the general population. While it is well known that vitamin D is important in bone mineralization and skeletal health, the immune modulating effects of vitamin D have recently been highlighted in the literature. Several large observational studies have shown an increased risk of type 1 diabetes mellitus, multiple sclerosis, metabolic, and neoplastic disease when the levels of vitamin D decrease to below 20 ng per milliliter[17-21]. One condition that has often been connected with low levels of vitamin D is diabetes mellitus[22]. In non-obese diabetic (NOD) mice, vitamin D deficiency increased the incidence and severity of disease[23]. In addition, one study found lower plasma 25-hydroxyvitamin D levels at diagnosis of type 1 diabetes when compared to controls[24]. Although there is evidence that vitamin D deficiency increases the incidence of some autoimmune diseases, most of this data is from observational studies and mouse models of type 1 diabetes, suggesting that while vitamin D has a role in these disease processes, the complete story is not yet fully known[22,25].

In general, patients with celiac disease not only have a higher incidence of autoimmune disorders than the general population, they can also have low levels of vitamin D, usually seen at the time of presentation. In addition, multiple observational and mice studies have shown that vitamin D can modify the immune system and that low levels can increase the risk of developing an autoimmune disorder. As a result, we sought to study whether low vitamin D levels are predictive of concomitant autoimmune disease in a patient population that has celiac disease. Considering that patients with celiac disease have both disease processes, we chose to study whether patients with low vitamin D levels are the ones who will or have developed other autoimmune disorders.

2. Study Design and Statistical Procedure

1. *Study Design*

This study will be a retrospective cross-sectional study analyzing vitamin D levels in patients with celiac disease. All patients were evaluated at The Celiac Disease Center at NYP/CUMC and have consented to allow their private health information (PHI) to be used and studied in a celiac disease database.

Initially, we will determine whether patients in the celiac database have had a vitamin D level drawn either at the time of diagnosis or within 6 months of being diagnosed with celiac disease. 25-hydroxyvitamin D, a metabolite of vitamin D made in the liver, will be used to determine a patient's vitamin D status[26]. Once the patients with vitamin D levels have been identified, they will then be stratified into three groups: those with levels <20 ng/mL (vitamin D deficient), those with levels between 20-30 ng/mL (vitamin D insufficient), and those with levels >30 ng/mL (normal).

In addition, among all three patient groups, we will identify those patients who are concurrently diagnosed with an autoimmune disease, including Sjogrens disease, autoimmune neuropathy, vitiligo, psoriasis, autoimmune thyroid disorders (Graves

Disease and Hashimotos), Addison's disease, rheumatoid arthritis, multiple sclerosis, and Type 1 diabetes mellitus (T1DM). The aim of the study is to identify whether patients with low vitamin D levels are more likely to develop an autoimmune disease or have an autoimmune disease at the time of diagnosis.

2. *Statistical Procedure*

Baseline characteristics, vitamin D levels, and concurrent autoimmune diseases will be evaluated in all patients enrolled in the celiac disease database.

Currently, there are about 1500 patients enrolled in the celiac disease database, and we have predicted that about 50% of those patients (n=750) would have vitamin D levels drawn either at the time of diagnosis or within 6 months of diagnosis. Among those patients with vitamin D levels drawn, we have estimated that about 30% of them (n=250) would also have an autoimmune disease. This 30% is obtained from previous studies that have shown that 30% of patients with celiac disease also have an autoimmune disease[14]. Among the patients with an autoimmune disease (n=250), we have predicted that about 50% of them would be vitamin D deficient (n=125).

Among the patient group that does not have an autoimmune disease (n=500), current data estimates that about 50% of the population would be vitamin D insufficient/deficient if normal is defined as >30 ng/mL[26,] leaving a total of 250 patients that would have no autoimmune disease and normal vitamin D levels. In addition, we have hypothesized that about 20% of our study population with no autoimmune disease would be vitamin D deficient (n=100).

The chi-square test for proportions was used to determine an 80% power at $p<0.05$. Initially, we have chosen to only use the two extreme values of vitamin D (those <20 ng/mL and those >30 ng/mL) for our calculations. By doing this, we would have 350 patients without an autoimmune disease (group 1), and have determined that the smallest and largest proportions to determine a difference in group 2 would be .19 and .43.

3. Study Procedures

There will be no additional study procedures outside of those in which patients have already received prior to being enrolled in this study.

4. Study Drugs or Devices

There will be no drugs or devices that will be involved in this study.

5. Study Questionnaires:

There will be no questionnaires or surveys distributed to patients in the study.

6. Study Subjects

Inclusion Criteria	Exclusion Criteria
• ≥ 18 years old • Biopsy Proven Celiac Disease • Vitamin D (25-hydroxyvitamin D) drawn at the time of Celiac Disease diagnosis or within 6 months of diagnosis	• No vitamin D levels • Levels drawn > 6 months from diagnosis • No biopsy proving Celiac Disease

7. Recruitment

Participants in this study will have already consented to the use of their PHI for research purposes. There will be no active recruitment of patients for this study.

8. Confidentiality of Study Data:

The collection of sensitive information about subjects will be limited to the amount necessary to achieve the aims of the research, so that no unneeded sensitive information will be collected. Computer-based files will only be made available to personnel involved in the study through the use of access privileges, passwords, and encryption. Whenever feasible, patient identifiers will be removed from study-related information. Lastly, precautions are in place to ensure the data is secure by using passwords and encryption because the research involves a patient database.

9. Potential Risks:

There are no potential risks identified in this study.

10. Potential Benefits

The potential benefit of this study is the potential finding that low vitamin D levels can be seen in patients with autoimmune diseases. This information could potentially help to predict which patients might eventually develop another autoimmune disease.

11. Alternatives

Non-participation in the study is an option. Patient's can opt out of being included in the Celiac Disease database if they choose to.

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