

Dilated Cardiomyopathy and Type 1 Diabetes in a Patient with Celiac Disease

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Abstract

Association of Celiac Disease (CD) with Type I diabetes (T1D) and independently with Dilated Cardiomyopathy (DCM) has been cited in literature multiple times. Although no definitive etiology has been identified in patients with CD that would exacerbate other autoimmune conditions multiple theories have been developed. It has been observed that children with CD and T1D have significant improvement in their glycemic index once adherent to Gluten Free Diet (GFD). Equally interesting, it has been noted that children with CD and DCM have improvement of their cardiac function once adherent to GFD. In fact prevalence of DCM is higher in patients with CD as well as patients whose relatives have positive Celiac serology when compared to general population.

Furthermore, increased incidence of tissue transglutaminase (TTG) in patients with end stage heart failure and no indication for CD with normal small intestine pathology and negative anti endomysial antibodies (EMA) suggests a common mechanism that can lead to different disease manifestations.

We present an adolescent who developed CD after several years of T1D whose condition was further complicated by acute onset DCM. At the initial diagnosis of CD, he showed elevated TTG, EMA, and high serum levels of zonulin, a modulator of intercellular tight junctions that has been recently associated with the pathogenesis of both CD and T1D. With adherence to GFD, his CD serology tests normalized, his glycemic index got better, and his cardiac function improved on consequent evaluations, ultimately avoiding inevitable heart transplantation. Furthermore, repeated serum zonulin levels drawn after one year of GFD have dropped to normal levels coinciding with an overall improvement.

Introduction

- With the increase recognition of Celiac Disease (CD) prevalence more attention has been paid to other associated diseases in hope of unveiling common mechanisms and understand pathophysiology of different clinical interactions
- With elimination of dietary antigens, immune mediated intestinal damage in CD patients is reversed allowing intestinal regeneration and decreasing disease associated morbidity
- Type I diabetes (T1D) and idiopathic dilated cardiomyopathy (DCM) are among many other diseases that are found to have higher prevalence in patients with CD as compared to non celiac population
- Equally important, it has been noted that prevalence of CD is greater in T1D as well as DCM cohorts when compared to general population

Introduction

- Different theories have been cited in literature explaining the beneficial interactions of gluten restricted diet (GFD) in CD patients on other associated conditions such as DCM or T1D
- In patient with DCM and CD strict adherence to GFD has benefited not just their cardiac function as noted with improved echocardiographic parameters and decreased requirement for pharmacologic intervention, but also disappearance of cardiac related antibodies
- Dietary restrictions in patients with CD and T1D did not result in significant reduction of anti islet cell antibodies, however, studies did show mildly improved glycemic control and improved growth parameters in pediatric population

Introduction

- Studies of intestinal permeability in CD patients showed significant improvement in permeability once individuals would adhere to GFD
- Zonulin, a protein shown to have a role in modulating intestinal permeability by disassembling intercellular tight junction integrity has been shown to correlate with celiac disease progression
- Molecular modification of intercellular tight junction integrity is not limited to Celiac disease alone; it has also been observed as an affected region in animal models of dilated cardiomyopathy
- In studying disease progression of T1D, zonulin upregulation has been noted to precede disease onset and potentially trigger immune mediated process through alteration of intestinal permeability

Association of CD with other immune mediated conditions

Two philosophies

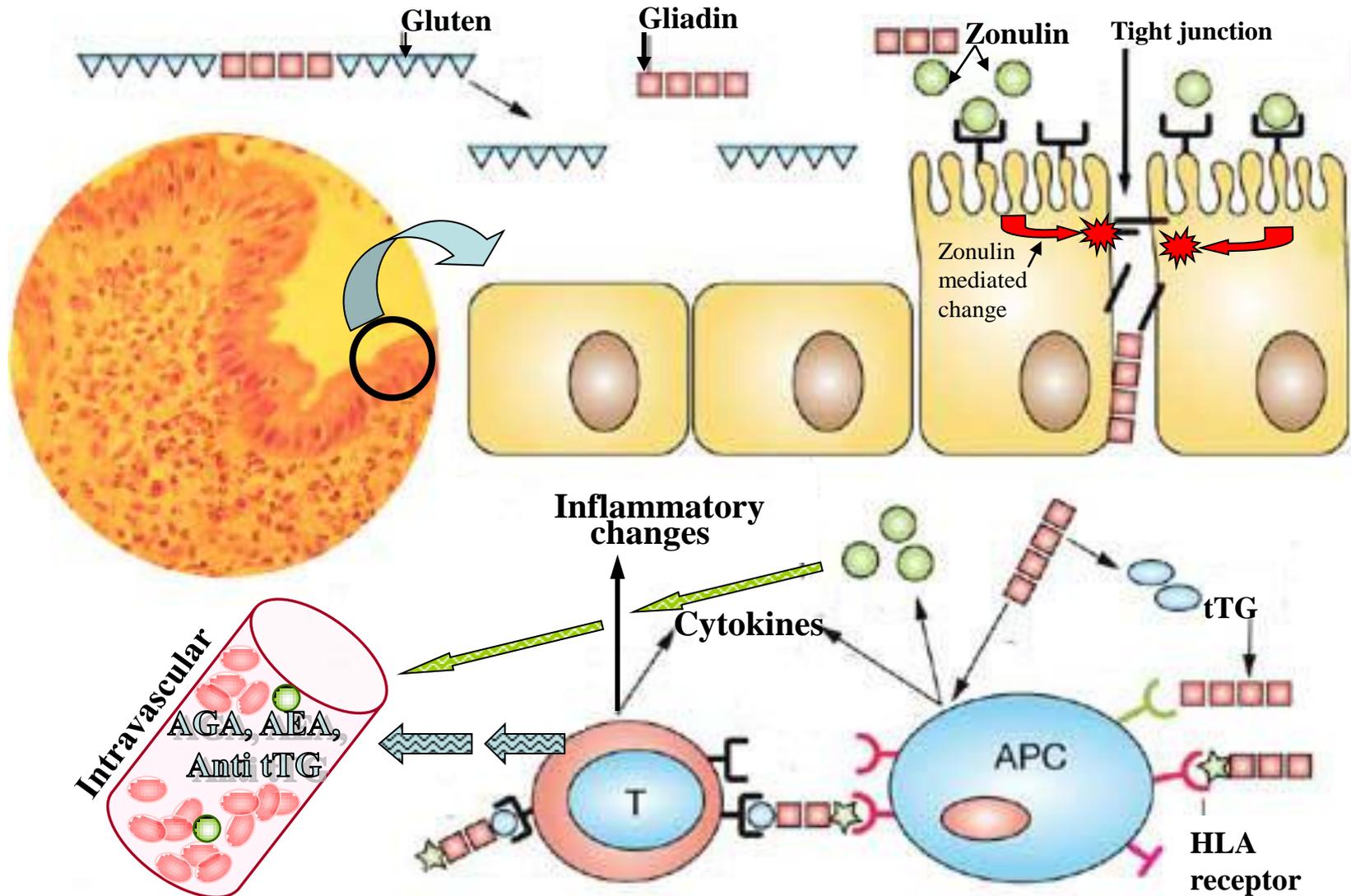
Linkage disequilibrium

- ❑ Aggregation of genes associated with CD are located close to genes implicated in manifestation of other immune mediated conditions
- ❑ Multiple genes travel together

Co-morbidity secondary to untreated CD

- ❑ Immune mediated response triggered by gliadin ingestion increases synthesis of zonulin
- ❑ Zonulin alters intercellular tight junctions leading to increased intercellular permeability
- ❑ Variety of different antigens enter submucosal environment and trigger innate immunity

The Continuous Stimulation by Gluten is Necessary to Perpetuate the Autoimmune Process in Celiac Disease and Alter Intestinal Permeability



Case presentation

- Patient presented to celiac clinic at the age of 17 with a 10 year history of T1D and a recent serologic and endoscopic diagnosis of celiac disease. His initial gastroenterological evaluation was prompted because of chronic iron deficiency anemia resistant to oral and intravenous therapy and a first degree family history of colon cancer.
- Esophagogastroduodenoscopy (EGD) was significant for atrophic changes in the duodenum with intraepithelial lymphocytes strongly suggestive of celiac disease

Case timeline

Family History:

- Healthy siblings
- Colon CA (Father)
- Diabetes (MGM)

Prevalence of T1D in CD patients is 5.4% vs 1.5% control

Diagnosis of Celiac disease
EMA+, tTG-109, Histo +
Zonulin-2.4

Prevalence of CD among DCM is estimated at 5.7% vs 0.4% in the general population

Dilated cardiomyopathy
EF 15-20%
Evaluation for Heart transplant

Improved cardiac function
↑ Exercise tolerance, tTG-30
Zonulin-0.3

Anemia

Gluten free diet

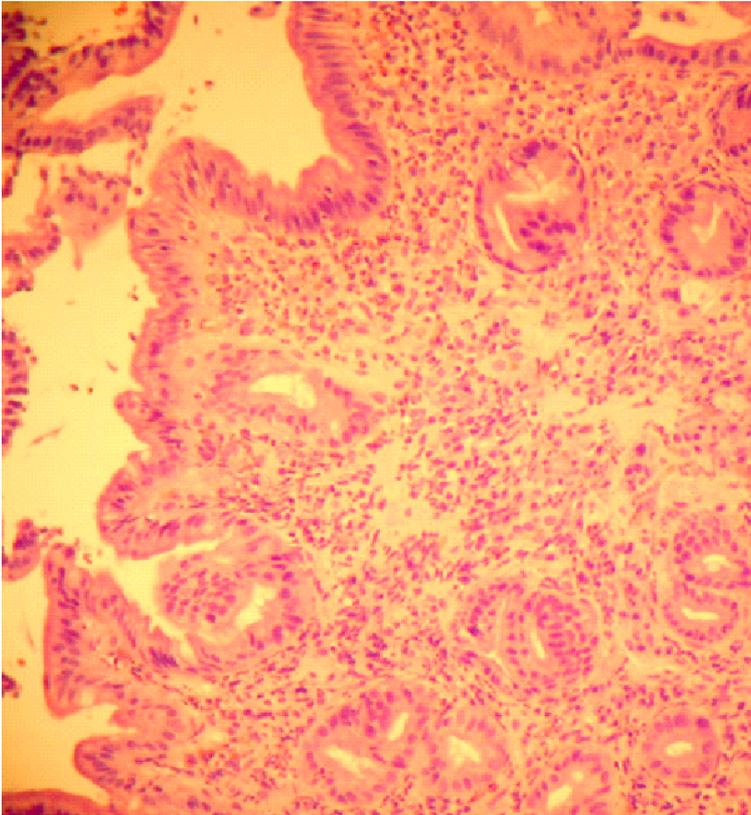
Type 1 Diabetes

10 Age in years 15 16 18 19

Case presentation

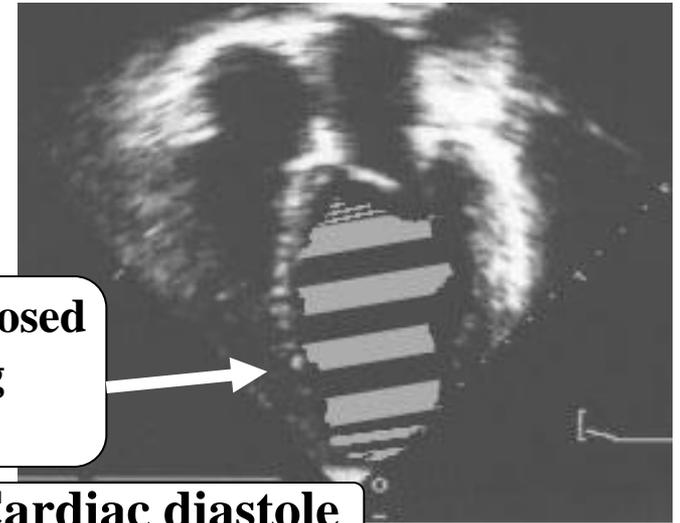
- Blood work at initial evaluation for CD
 - Tissue transglutaminase (TTG) >100
 - Serum **zonulin** -2.4 (Normal range 0 - 0.6)
- Dilated Cardiomyopathy (DCM)
 - Diagnosed within several weeks of CD diagnosis
 - Left ventricular ejection fraction of 15-20%
 - Global myocardial hypokinesis
 - Initiated evaluation for cardiac transplantation
- Despite poor prognostic factors regarding his cardiomyopathy, his deterioration subsides and he improved with initiation of GFD and pharmacotherapy
 - No longer candidate for cardiac transplantation

Histology and echocardiography findings



**Blunted Duodenal Mucosa with
Intraepithelial lymphocytes**

**Superimposed
LV during
systole**



Cardiac diastole



Cardiac systole

Case presentation

- After one year of strict GFD diet
 - significant improvement of celiac serology
 - resolution of chronic anemia
 - Normalization of Hemoglobin A1C
 - Improvement of glycemic control
 - MUGA (Multiple Gated Acquisition Scan) ejection fraction of 36% with significantly improved exercise tolerance
 - complete normalization of serum zonulin levels

Discussion

- We present a unique case of an adolescent with a poorly controlled type 1 diabetes and a newly diagnosed celiac disease who developed an acute onset cardiac failure
- While on gluten containing diet, child was diagnosed with severely dilated cardiomyopathy and placed on a cardiac transplant list
- Management of celiac disease with strict adherence to gluten free diet had a tremendous impact on his concurrent diagnoses of type 1 diabetes and dilated cardiomyopathy
- This is the first case in English literature of a child with celiac disease, type 1 diabetes and a dilated cardiomyopathy where all three entities improved with adherence to gluten free diet

Discussion

- Gluten free diet originally indicated for patients with celiac disease has been shown to benefit other immune mediated conditions that are found to have higher prevalence in celiac disease patients
- There are few cases in literature where either cardiomyopathy or insulin dependent diabetes improved with adherence to gluten free diet in patients with concurrent celiac disease
- Although there are many theories on the possible mechanism of damage in celiac associated conditions, there are no definite studies mapping the relationship between celiac disease and other associated entities
- We propose a theory that altered intestinal permeability contributes to immune mediated disease progression in patients with celiac disease

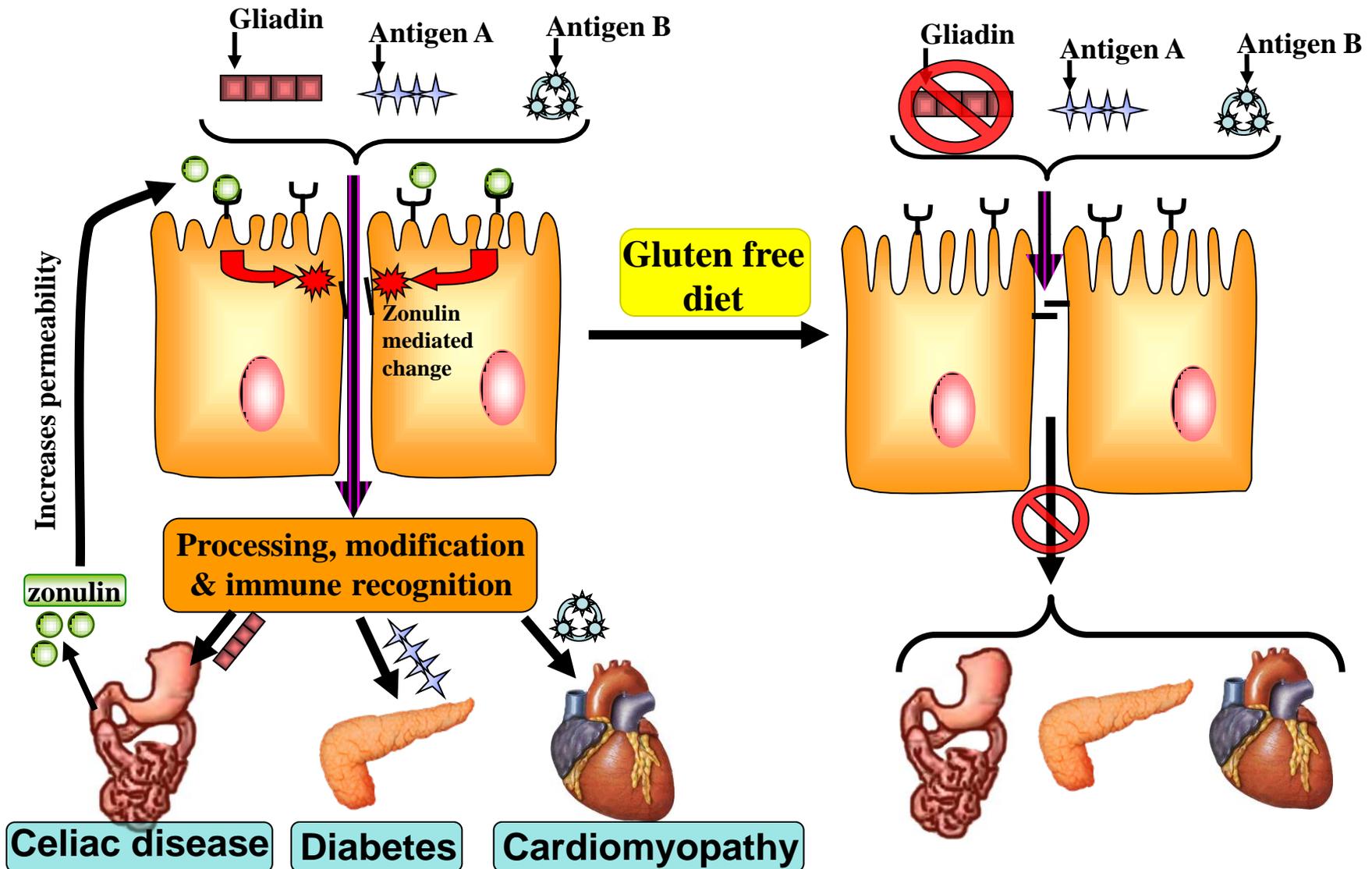
Discussion

- We have observed zonulin, a protein elevated in patients with celiac disease to be an important moderator of a tight junction complexes
- Elevated serum zonulin levels has been found to correlate with increased paracellular permeability of the gastrointestinal mucosa
- Compromised mucosal permeability can potentially allow multiple intraluminal antigens to penetrate mucosal barrier and stimulate immune mediated reactions leading to progression and deterioration of various conditions associated with celiac disease

Discussion

- We have observed very elevated zonulin levels prior to initiation of gluten restricted diet in our patient suggesting that increased mucosal permeability had a negative impact on progression of diabetes and development of cardiomyopathy
- Normalization of serum zonulin levels after one year of adherence to gluten free diet suggests a decrease in intestinal mucosal permeability
- Management of celiac disease with dietary modifications has correlated with clinical improvement of type 1 diabetes and reversal of deteriorating dilated cardiomyopathy in our patient
- We proposed that stabilization of intestinal membrane integrity and decreased permeability to yet unidentified antigens has improved our patient's clinical status of associated T1D and DCM

The Continuous Stimulation by Gluten is Necessary to Perpetuate the Autoimmune Process for multiple immune mediated conditions



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