*International Journal of Celiac Disease, 2015, Vol. 3, No. 1, 28-30*
Available online at http://pubs.sciepub.com/ijcd/3/1/6

DOI:10.12691/ijcd-3-1-6

# Celiac Disease: Intestinal, Heart and Skin Interconnections

**Aaron Lerner[1,*], Torsten Matthias[2]**

[1]Pediatric Gastroenterology and Nutrition Unit, Carmel Medical Center, B, Rappaport School of Medicine, Technion-Israel institute of Technology, Haifa, Israel
[2]Aesku.Kipp Institute, Wendelsheim, Germany
*Corresponding author: aaronlerner1948@gmail.com

*Received January 13, 2015; Revised January 15, 2015; Accepted January 17, 2015*

**Abstract** The first description of celiac disease associated with dilated cardiomyopathy and pellagra in the same person, brings multiple interesting aspects to discuss. Celiac disease is prevalent in cardiac failure and vice versa, multiple cardiac manifestations exist in celiac disease. Pathophysiologically, autoimmune, nutritional, infectious and thrombophilic pathways can be involved. In some cases the cardiomyopathy respond to gluten free diet. Multiple cutaneous manifestations, including pellagra like rash, were described in CD. Autoimmune mechanisms and much more, (e.g. nutrient deficiencies) might aggravate the skin manifestation. The present editorial highlights the cardiac-cutaneous-intestinal cross talks in celiac disease in order to increase the awareness of the physician community to speed up celiac disease diagnosis in those extraintestinal manifestations.

***Keywords:*** *celiac disease, cardiomyopathy, pellagra, skin, heart, nutritional deficiencies*

**Cite This Article:** Aaron Lerner, and Torsten Matthias, "Celiac Disease: Intestinal, Heart and Skin Interconnections." *International Journal of Celiac Disease*, vol. 3, no. 1 (2015): 28-30. doi: 10.12691/ijcd-3-1-6.

## 1. Introduction

Celiac disease (CD) is an autoimmune inflammatory disorder of the small intestine, triggered by the ingestion of prolamins contained in wheat, barley, rye or oat in genetically susceptible individuals. It has been shown that the classic intestinal clinical picture of malnutrition, chronic diarrhea and nutritional deficiencies are disappearing and extraintestinal presentations are emerging. Skin, cardiological, endocrine, skeletal, hepatic, hematological, thrombophilic, gynecological, fertility, dental and behavioral abnormalities are often described [1,2,3,4,5].

All these extraintestinal presentations make the diagnosis of the disease more difficult and the reliance on the typical symptomatology more remote. These are some of the reasons why serological screening and diagnosis of CD have achieved prime importance and the high-risk CD populations were expanded to other conditions andto extraintestinal target organs symptomatologies [6,7].

Cardiomyopathy represents a diverse and heterogeneous group of disorders affecting the myocardium and ultimately resulting in cardiac dysfunction. The prevalence of heart failure is high (5 million symptomatic patients in the United States) and increasing. Cardiomyopathy is the leading cause of hospitalization in patients older than 65 years of age, resulting in enormous healthcare expenditure and lost productivity. Dilated cardiomyopathy (DCM) is the most commonly seen type of cardiomyopathy. Ischemic cardiomyopathy accounts for about half of these patients, but in several large clinical trials the prevalence of potentially reversible non-ischemic cardiomyopathy is also significant, ranging from 20% to 50%. [8] Regarding the etiology, genetic causes, endocrine disorders, collagen vascular diseases, drugs, congenital metabolic abnormalities, muscular dystrophies, structural heart diseases, acute or chronic myocarditis and toxins can be presented.

Considered now as a vitamin deficiency state, pellagra has been linked to a chronic lack of niacin (vitamin B3 or nicotinic acid), an important constituent of coenzyme I and coenzyme II. Its clinical map is believed to include the classic 3 Ds: Dermatitis, Dementia and Diarrhea. The order of appearance and severity of these three sub-syndromes varies and some may not show at all.

In the present issue, Ben Ghorbel et al describe a young male presented with acute chest pains, myocardial infarction and dilated cardiomyopathy that 3 years later developed face and hands skin eruption, glossitis, photosensitivity and diarrhea. Based on positive CD associated serology and subtotal mucosal atrophy, the diagnosis of CD was established. Despite the fact that vitamin B3 and tryptophan were not measured, the clinical diagnosis of pellagra was done. It is the first description of CD, cardiomyopathy and pellagra in the same person, however, only associative linkscan be established, but not cause and effect relationships. Unfortunately, the patient was not diagnosed biochemically as pellagra and died before gluten free diet was initiated.

The present editorial will expand on the association between the above mention: celiac disease, cardiomyopathy and cutaneous eruptions, described by Ben Ghorbel et al. [9] and their pathophysiological interactions

## 2. Dilated Cardiomyopathy and CD

The association of the 2 conditions is well described [10,11,12]. The prevalence of CD in patients with sporadic or inherited DCM is substantially higher than in controls. Taking in account that 1% of the western population has CD, the percentage of DCM in the CD patients is around 5.0-6.75%.The largest Sweden patient register survey found that CD patients are at increased risk of idiopathic dilated cardiomyopathy with a hazard ratio of 1.73; 95% confidence interval, 1.00-3.00. [13] Regarding shared etiology between the two conditions, the autoimmune common trait, thatshares genes and the nutritional deficiencies are coming up. By having an autoimmune disease, CD patients are prone to develop additional autoimmune conditions during life, autoimmune myocarditis or cardiomyopathy, are some of them. [14] The recent expansion of the genome-wide association studies and exome sequencing technique sun revealed multiple shared mutations between the autoimmune diseases. It is possible that some of the 32 mutations identified in hereditary cardiomyopathies are shared with more than 40 non-HLA loci identified in CD. [15,16] Being a malabsorptive state, multiple nutritional deficiencies can be expected in CD [17,18]. Some of them like: hypocalcaemia, hypokalemia, carnitine, selenium, thiamine, zink, coenzyme Q10, taurine, vitamin E and C, riboflavin, pyridoxine and creatine were described in cardiomyopathy or associated with heart performance [19,20,21]. Unfortunately, those nutritional parameters weren't checked in the case presented. It is conceivable that a person with "impaired general condition with moderate asthenia and weight loss" and chronic diarrhea with subtotal intestinal atrophy, will have multiple nutritional deficiencies, that might have affected his cardiac performance.

Several pathophysiological pathways can be suggested, relying heart pathology to CD: 1. Autoimmunogenesis shared between multiple autoimmune diseases [14], 2. Nutrient deficiencies, as mentioned above [22,23,24], 3. Autoantibodies against actin and myosin exist in CD and DCM and were postulated to participate in the damage to the target organs of both conditions [25,26,27]. In fact, impairment of protein trafficking by direct interaction of gliadin peptides with actin and actin-deficient cardiomyopathy coexisting with celiac disease, reinforce the interrelationship [28,29]. 4. Hypercoagulability and thrombophilic autoantibodies like anticardiolipin and others are shared by both conditions [30,31,32,33]. Can hypercoagulability be an additional factor aggravating intestinal and cardiac pathology? 5. Finally, Infections are considered as environmental etiologies for the two conditions. [34] Myocardial microabscesses detected by endomyocardial biopsy in a patient with dilated cardiomyopathy and celiac disease hint for the infectious avenue [35].

## 3. Pellagra and CD

The two diseases can be connected in two aspects. 58% of pellagra patients were shown to have malabsorption and many had intestinal pathology on biopsies [36,37]. Alternatively, Pellagra was described in CD [38]. The skin manifestations in pellagra might have some additional etiologies, since multiple nutrient deficiencies are at the origin of the cutaneous manifestations in CD. The following nutritional deficiencies inducing skin rashes, were describe in CD: Zinc, Iron, Vitamin A, E, B12, niacin, folate, selenium and essential fatty acids [39,40].

## 4. Does a Gluten Free Diet Ameliorate Cardiac and Skin Manifestations Associated with CD?

It goes without saying that the nutritional manifestations due to the malabsorptive state of CD improve on strict elimination of wheat, Barley, rye and oat. In severe deficiencies the deficient nutrient should be supplemented. A more challenging aspect is the reversibility of the cardiomyopathy on gluten avoidance. No large scaled studies exist in the literature on the subject, but there are some case presentations reporting complete or partial recovery or progression avoidance of the cardiomyopathy linked to CD [41,42,43,44].

## 5. The Take Home Messages for the Clinicians

Speed up CD diagnosis in face of cardiomyopathy and look for associated autoimmune antibodies and nutritional deficiencies.

Speed up CD diagnosis in face of pellagra –like skin manifestations and look for additional CD nutritional deficiencies associated with cutaneous manifestations.

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