

# Association of cardiomyopathy and celiac disease: an almost diffuse but still less know entity. A review

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## Abstract

**Introduction:** This study is a systematic revision of scientific articles regarding the epidemiological, clinical and therapeutic aspects of cardiomyopathy associated with celiac disease.

**Material and methods:** 1193 adult cases of cardiomyopathy and 15890 clinically healthy control subjects have been scrutinized.

**Results:** The prevalence of celiac disease in cardiomyopathy patients was found higher vs control (3.36 vs. 0.425%,  $P=0.004$ ). The risk of association was 2-3 times higher than expected. Mean age a 42 years ejection fraction was 25%. A gluten free diet induced an improvement in cardiac performance.

**Conclusions:** In patients with cardiomyopathy may be the real risk of a concomitant celiac disease. The study protocol is not able to provide inferences on the cause-effect relationship existing between two diseases. Gluten free diet can improve cardiac performance in patients with this association. In patients with cardiomyopathy, an appropriate screening of celiac disease should be routinely performed.

**Key words:** dilatative cardiomyopathy, celiac disease, association, gluten free diet effect, prevalence.

## Introduction

Celiac disease (CD) is an inflammatory pathology of the small bowel, due to gluten intolerance, developed by genetically susceptible individuals. It induces malabsorption related to villous atrophy. Malabsorption syndrome is characterized by: diarrhoea, steatorrhea and weight loss. Minor or apparently unrelated symptoms are also: upper abdominal complaints, iron-deficiency anaemia, osteopenic bone disease, amenorrhoea, infertility, epilepsy, dermatitis herpetiformis, hypertransaminasaemia, lymphoproliferative diseases, etc. [1-3]. CD is often asymptomatic and in some cases can be associated with autoimmune diseases such as insulin-dependent diabetes, thyroiditis, and rheumatoid arthritis [4].

In 1999, a study was published demonstrating increased prevalence of CD also in patients with idiopathic dilated cardiomyopathy (CM) compared to the general adult population [5]. In the last few years, other "case report" and "case-control" studies have been published, in Europe and South America, confirming the increased prevalence of CD also in other forms of CM, with a different percentage [6-16]. Genetic [8], immunological

[12, 13] and/or inflammatory [11] hypotheses about the pathogenesis of this association have been postulated, but at the moment exhaustive conclusions are not available.

Some authors underline mutual negative interaction between the two diseases during clinical evolution of CM. CM patients may suffer from tardive malabsorption, caused by a stasis of intestinal venous blood flow. CD patients, in turn, because of their villous atrophy, show absorptive intestinal dysfunction with a deficiency of some dietary micronutrients, such as iron, copper, zinc, calcium, potassium, selenium and carnitine, that are fundamental for myocardial contraction and electrical cardiac excitation. In addition, CD patients may show malabsorption also for cardiovascular drugs [17], a circumstance that in CM patients may potentially contribute to making cardiac disease more severe. The gluten-free diet (GFD) seems to improve cardiac performance [6-7, 11, 12, 15, 18], confirming this last hypothesis.

A review of the literature could clarify some epidemiological and clinical aspects of the association. The aims of this study are: 1) to elaborate a statistical analysis of CD prevalence in CM vs. the common population, 2) to identify the clinical aspects of this association, 3) to identify and quantify the clinical effects of a GFD on the cardiac performance in such patients.

## Material and methods

The literature review was performed via MEDLINE and Cochrane databases, choosing arbitrarily January 1966 as the starting date, and including January 2007. [Since the conclusion of this systematic review of the 'ad hoc' literature, another study has been published on this topic by Glover BM, et al. Therefore, its bibliographic citation is reported at the end of the References section as a supernumerary article [19] not included in this review]. Search terms included: cardiomyopathy, dilated cardiomyopathy, celiac/coeliac disease, prevalence of celiac disease. The oldest citation detected for adult cases was dated 1986.

As mentioned in the outset, the analytical approach was as follows.

### Prevalence of CD in CM and its risk of occurrence

Five observational "case-control" studies [1-5] were found. Student's t test, one-way ANOVA, chi-square test or exact Fisher test, when appropriate, were applied in single studies and overall. Statistical significance was assigned to the value  $P \leq 0.05$ . Additionally, the data of each case-control study were analyzed for relative risk (RR) and odds ratio (OR) – with their 95% CL – in order to assess the overall risk of CD and CM association, using the Mantel-Haenszel-Peto method.

### Clinical features of patients with the association of CM and CD

The clinical data of the forty-six patients – thirty-one patients from "case-control" studies [5-10] plus fifteen patients from "case report" studies, short reports or letters to the Editor [12-15, 17] – were considered in order to describe the clinical features of CM associated with CD.

### Effects of a GFD on cardiac performance in patients with the association of CM and CD

Ejection fraction, Lown class (LC) and ventricular arrhythmias index were evaluated before and during a GFD in sixteen patients. The significance of the differences was evaluated by means of Student's t test, one-way ANOVA and Friedman test [5-7, 12-15, 17, 18].

## Results

### Prevalence of CD in CM and its risk of occurrence

As shown in Table I, an increased prevalence of CD in patients with CM was detected in all the recorded studies. Such a higher prevalence was found to be highly statistically significant ( $t=3.961$ ,  $P=0.004$ ), suggesting that the finding of CD in CM patients may have a high probability of being a clinical event of non-casual association.

In order to confirm such an inference, a chi-square test for the absolute occurrences was performed.

As shown in Table II, a highly statistically significant overall chi-square value was detected ( $\chi^2=81.51$ ,  $P<0.001$ ), reinforcing the statistical conviction that the association of CD and CM may be clinically probable.

In order to corroborate the idea that there could be a real objective risk of encountering CD in CM patients, a statistical evaluation RR and OR – with their 95% CL – was performed.

Both the indices were found to be consistently above the value of 1 (overall RR=7.24, 95% CL=4.70-11.17, overall OR=7.41, 95% CL=4.65-11.76), suggesting that there is a real objective risk for a CM patient to be contemporarily affected by CD.

### Clinical features in patients with the association of CM and CD

Mean age and male/female ratio in CM patients (available data in 42/46 patients) were respectively  $42 \pm 18$  years and 1.2/1. Mean age in CD patients of case-control studies was  $46 \pm 4.93$ .

Dilative CM was present in 27/46 (58.7%) patients, myocarditis in 9/46 (19.6%), ischaemic CM in 5/46 (10.7%), valvular CM in 1/46 (2.1%), other forms of CM in 4/46 (8.7%). Mean ejection fraction

**Table I.** Prevalence of coeliac disease (CD) in patients with cardiomyopathy (CM) from a systematic review of the literature. Studies reported in accordance with their date of publication

Authors and references	Year of publication	Prevalence of CD in CM [%]	Prevalence of CD in general population [%]
Curione et al. [5]	1999	5.70	0.55*
Prati et al. [6]	2002	1.90	0.35
Frustaci et al. [7]	2002	4.40	0.30
Not et al. [8]	2003	2.10	0.80
De Bem et al. [9]#	2006	2.70	0.125
<b>Overall studies</b>	<b>1999-2006</b>	<b>mean =3.36±1.64</b>	<b>mean =0.425±0.26</b>

\*Control data from Corazza GR, et al. The smaller size of the "celiac iceberg" in adults. *Scand J Gastroenterol* 1977; 32: 917-9

#Data of two studies related to Center West region (Gandolfi L, Pratesi R, Cordoba JC, et al. Prevalence of celiac disease among blood donors in Brazil. *Am J Gastroenterol* 2000; 95: 579-80) and to Southern region of Brazil (Nisihara RM, Utiyama SR, Kotze LM, et al. Serologic investigation of celiac disease in southern area from Brazil. *Arq Gastroenterol* 2005, as cited in reference 9), have been summarized

**Table II.** Synoptic results of chi-square ( $\chi^2$ ) test between the occurrence (events) and non-occurrence (non-events) of coeliac disease (CD) in cardiomyopathic patients (experimental group) versus the occurrence (events) and non-occurrence (non-events) of CD in the general population (control group). Data from a systematic review of the literature

Authors and references	Year of publication	Experimental group			Control group			$\chi^2$	P
		event	non event	total	event	non event	total*		
Curione et al. [5]	1999	3	49	52	4	2233	2237	52.09	<0.001 <sup>§</sup>
Prati et al. [6]	2002	12	630	642	34	9686	9720	31.46	<0.001
Frustaci et al. [7]	2002	9	178	187	1	305	306	11.75	<0.001 <sup>§</sup>
Not et al. [8]	2003	5	233	238	16	1984	2000	3.87	<0.064 <sup>§</sup>
De Bem et al. [9]#	2006	2	72	74	2	1625	1627	20.08	<0.010 <sup>§</sup>
<b>Overall</b>	<b>1999-2006</b>	<b>31</b>	<b>1162</b>	<b>1193</b>	<b>57</b>	<b>15833</b>	<b>15890</b>	<b>108.63</b>	<b>&lt;0.001</b>

\*Control data from Corazza GR, et al. The smaller size of the "celiac iceberg" in adults. *Scand J Gastroenterol* 1977; 32: 917-9

#Data of two studies related to Central West region (Gandolfi L, Pratesi R, Cordoba JC, et al. Prevalence of celiac disease among blood donors in Brazil. *Am J Gastroenterol* 2000; 95: 579-80) and to Southern region of Brazil (Nisihara RM, Utiyama SR, Kotze LM, et al. Serologic investigation of celiac disease in southern area from Brazil. *Arq Gastroenterol* 2005, as cited in reference 9), have been summarized

<sup>§</sup>Statistical significance by Fisher's exact test

(EF) was 25.2% (available data in 31/46 patients). NYHA class was III-IV in 22 patients (73.3%) and I-II in 8 (26.7%) patients (available data in 30/46 patients).

**HLA study:** All patients with CM and CD presented DQ2 – DR 3-5-7 except one who was affected by idiopathic dilative CM, presenting DQ8 DR4. In the literature, the prevalence of DR4 in dilated CM and DQ8 in infective myocarditis is reported.

The clinical features were: sideropenic anaemia (refractory to oral iron supplementation), gastritis, recurrent abdominal pain, malabsorption and weight loss. The co-morbidity was given by insulin-dependent diabetes (1 case), thyroiditis (1 case), recurrent abortions (1 case), epilepsy, dermatitis herpetiformis (1 case), hypertransaminasaemia (1 case), lymphoproliferative diseases (2 cases), actin deficit (1 case), paroxysmic haemoglobinuria (1 case), Chagas disease (1 case), arthritis and glomerular nephropathy (1 case).

### Effects of a GFD on cardiac performance in patients with the association of CD and CM

The effects of a GFD on cardiac performance have been investigated in all the 16 reported patients with the association of CD and CM (7 males and 9 females, 5 dilative CM, 9 myocarditis, 1 actin deficiency and 1 with idiopathic dilative CM) who underwent such a dietary treatment.

As shown in Table III, two male patients were found not to present an amelioration in the indices of cardiac performance. The first one, affected by an idiopathic dilative CM, was not compliant; the second one, affected by actin-deficiency-dependent CM, died too early to enable estimation of the GFD effects.

The other 14 patients (5 males and 9 females) were found to show an improved cardiac performance. Ten of them were seen to show a significant increase of EF (from 29.6 to 52.5%;

**Table III.** Effects of gluten-free diet (GFD) on cardiac performance in 14/16 cardiomyopathic patients showing the association of different cardiomyopathies with coeliac disease

Authors and references	Patient age and sex	Type of cardiomyopathy	Ejection fraction [%] before GFD	Ejection fraction [%] after GFD	Lown class before GFD	Lown class after GFD
Makhdoom [12]	49/F	DCM	30	65	–	
Curione [5]	40/M	DCM	38	42	–	–
	32/M	DCM	25	30		–
Frustaci [7]	14/F	myocarditis	–	–	III	I
	36/M	myocarditis	27	48	–	–
	16/F	myocarditis	36	54	–	–
	38/F	myocarditis	–	–	IV	I
	32/M	myocarditis	17	46	–	
	16/F	myocarditis	–	–	III	I
	35/F	myocarditis	–	–	IV	I
	22/F	myocarditis	21	56	–	
24/F	myocarditis	32	54		–	
Goel [15]	70/M	DCM	40	65	–	
Namendys [16]	28/F	unknown	30	65	–	–
<b>Overall</b>	<b>32.2/5M-9F</b>		<b>mean =29.6±7.35</b>	<b>mean =52.5±11.37</b>		

DCM – dilatative cardiomyopathy

paired Student’s t test:  $t=6.306$ ,  $P<0.001$ ; one-way ANOVA:  $F=27.41$ ,  $P<0.001$ ; Friedman test:  $\chi^2=10.00$ ,  $P<0.002$ ). The other four cases were found to exhibit a significant reduction of LC (Friedman test:  $\chi^2=4.00$ ,  $P=0.046$ ), a sign of reduced bioelectrical instability.

### Discussion

In the US, the incidence of CM (prevalently in a dilatative form) is 400,000 cases per year and the population of CM patients is about 2.5 million. Assuming the prevalence of CD in the general population to be about 1%, no more than 1% of CM patients should be affected by CD, for a contingent no greater than 25,000 individuals (1% of CM patients).

The systematic revision made in this study has, however, clarified that the prevalence and the risk of CD in patients with CM are both higher than expected. With a prevalence 2-3 times higher than in the general population, one can assume that the relatively frequent finding of CD in CM patients is a phenomenon that deserves to be epidemiologically, immunologically, genetically and clinically investigated as a non-casual association, being estimated to be present in about 50,000-75,000 individuals (2-3% of CM patients) in the US. The higher prevalence of CD in CM might be a feature of a non-fortuitous real objective

association that, for unknown reasons, can assume clinical relevance.

Few data are at the moment available to characterize anthropometric and clinical features in patients affected by the association versus patients with isolated CM. Dilatative type of CM seems to be the most frequent, EF is low and all NYHA classes are represented. Definitive conclusions on these matters are not possible at present because some pending biases in inclusion criteria, different in each study, are present. Nevertheless, signs, symptoms, HLA pattern and co-morbidity shown by patients affected by CM associated with CD are those more frequently described in isolated CD. This last finding could help to find patients with CM at high risk of association with CD.

In the literature, there is agreement on the efficacy of treatment of CD with a GFD. Patients have shown beneficial effects on cardiac performance and on arrhythmic risk. The GFD can contrast, via better intestinal absorption of micronutrients and cardiovascular drugs, the negative natural history of CM, and it may be a clinical intercurrent strategy.

In conclusion, CM patients have a significant objective risk (two-three times higher than expected) to be concomitantly affected by CD. Many CM patients may suffer from undiagnosed CD and therefore they do not observe a GFD, proven useful to improve the clinical course of CM.

This study is not structured to give a response to the nexus of causality, if any, that exists between CM and CD. Nevertheless, from the data obtained, it can be supposed that CD in CM patients may be the expression of a true association, instead of a casual association. Obviously, the final response to such an associative hypothesis needs to be ascertained by 'ad hoc' immunological and genetic investigations.

This last observation, in our opinion, may represent a further significant clinical message for physicians to perform screening of CD in all patients affected by CM. Such screening is absolutely unavoidable when the CM patient shows clinical signs of intestinal malabsorption.

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