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Impact of standardized duodenal biopsy sampling on the diagnosis of ultrashort celiac disease

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Ultrashort celiac disease (UCD), characterized by villous atrophy confined exclusively to the duodenal bulb, represents a distinct phenotype within the spectrum of celiac disease (CD). Although its existence is supported by the literature (1,2), its diagnosis remains challenging due to both the histologic particularities of the bulb and insufficient adherence to biopsy protocols recommended by clinical guidelines (3). In this context, we consider it relevant to share the findings from our patient series, which provide evidence regarding the distinctive features of UCD and the impact of adequate duodenal biopsy sampling on its diagnosis.

In our series of 728 adult patients, the prevalence of UCD was 4.5%, compared with 73.7% for conventional celiac disease (CCD), defined by positive IgA anti–tissue transglutaminase antibodies and intestinal damage ≥ Marsh 2 in the second portion of the duodenum. Patients with UCD presented symptoms similar to those observed in CCD; however, several differences were identified (Table 1): they were younger and had a lower frequency of extraintestinal manifestations—particularly iron deficiency or iron-deficiency anemia—lower titers of IgA anti–tissue transglutaminase antibodies, and a lower prevalence of the HLA-DQ2.5 haplotype, in line with previously published data (1,2). These findings suggest that UCD may represent a less aggressive or incipient

form of CD, a hypothesis that requires confirmation in longitudinal studies.

One of the most relevant aspects of our study was the evaluation of the impact of duodenal bulb biopsies. After the implementation of standardized biopsy protocols at our center in 2015, the proportion of endoscopies including duodenal bulb biopsies increased from 36.2% to 90.1%, resulting in a significant increase—more than sevenfold—in the diagnosis of UCD (0.7% vs 5.4%, p = 0.017). These results, consistent with findings from a systematic review and meta-analysis addressing the role of duodenal bulb biopsies in adult CD (4), reinforce the importance of strict adherence to national and international recommendations, highlighting the diagnostic value of these samples despite their interpretative difficulties (5).

Overall, our results support the existence of UCD as a CD subtype with distinctive epidemiologic, clinical, serologic, and genetic features, and underscore the need to standardize endoscopic procedures and strengthen the training of professionals involved in CD diagnosis to avoid underdiagnosis of this entity.

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Table 1. Characteristics of patients with conventional celiac disease (CCD) and ultrashort celiac disease (UCD)

	CCD n = 537	**UCD n = 33**	**p-value**
Women (n (%))	413 (76,9)	28 (84,8)	0,32
Age at onset			
Mean ± SE (range)	37,6 ± 0,6 (18-86)	34,0 ± 1,9 (19-72)	
Median (IQR)	34 (28-44)	32 (26,5-39,5)	0,41
Clinical manifestations (n (%))			
Digestive			0,77
Asymptomatic	103 (19,2)	7 (21,2)	
Classic	194 (36,1)	10 (30,3)	
Non-classic	240 (44,7)	16 (48,5)	
Dyspepsia/Abdominal bloating and flatulence	237 (47,5)	15 (46,9)	
Extraintestinal	386 (71,9)	20 (60,6)	0,17
Iron-deficiency anemia	207 (38,5)	4 (12,1)	**<0,001**
Osteopenia/osteoporosis	138 (25,7)	8 (24,2)	
Hypertransaminasemia	63 (11,7)	1 (3)	
Neurologic manifestations	25 (4,7)	3 (9,1)	
Dermatitis herpetiformis	26 (4,8)	1 (3)	
IgA anti-tissue transglutaminase (tTG-IgA)*			
	N = 326	N = 29	
Mean ± SE (range) (U/ml)	1592,6 ± 184,8 (15,2-25000)	166,2 ± 72,1 (0,5-1926,3)	
Median (IQR)	250 (126,8-1512,1)	51,9 (24,2-116,8)*	**<0,001**

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HLA genetics			
DQ2.5	330 (87,1)	19 (73,1)	**0,046**
DQ8	31 (8,2)	4 (15,4)	0,27
DQ2.2	17 (4,5)	3 (11,5)	0,13
DQ7.5	1 (0,3)	0	

*Quantification by chemiluminescence using the BioPlex® system. Reference value ≥ 15 U/mL, established according to manufacturer recommendations and validated by the laboratory.