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Original article

Refractory celiac disease and EATL patients show severe malnutrition and malabsorption at diagnosis

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SUMMARY

Background & aims: Refractory celiac disease type II (RCDII) and EATL (Enteropathy Associated T-cell Lymphoma) are (pre)malignant complications of celiac disease (CD). Data on malnutrition and intestinal absorption is lacking in these patients. Therefore, the aim of the study is to comprehensively assess nutritional status and intestinal absorption capacity of patients with RCDII and EATL, compared with data of newly diagnosed CD patients.

Methods: Observational study in tertiary care setting in RCDII (n = 24, 63.8 ± 8.2 y), EATL (n = 25, 62.3 ± 5.7 y) and CD patients (n = 43, 45.6 ± 14.8 y). At diagnosis, anthropometry (BMI, unintentional weight loss, fat-free mass index (FFMI), handgrip strength (HGS), nutritional intake, fecal losses and Resting Energy Expenditure (REE)) were assessed.

Results: Low BMI (<18.5) was more often observed in RCDII patients than in CD or EATL patients (in 33%, 12% and 12%, respectively, p = 0.029). EATL patients more frequently had unintentional weight loss (>10%) than CD or RCDII patients (in 58%, 19% and 39% of patients, respectively; p = 0.005/0.082). Energy malabsorption (<85%) was detected in 44% and 33% of RCDII and EATL patients, vs 21.6% in CD (NS). Fecal energy losses were higher in RCDII than in CD patients (589 ± 451 vs 277 ± 137 kcal/d, p = 0.017). REE was underestimated by predicted-REE with>10% in 60% of RCDII, 89% of EATL, and 38% of CD patients (p = 0.006). Low FFMI and HGS were detected in one third and two thirds of all patients, respectively.

Conclusions: The nutritional status of patients with RCDII and EATL is inferior compared with untreated naïve CD patients at presentation. Both malabsorption as well as hypermetabolism contribute to malnutrition.

1. Introduction

Celiac disease (CD) is defined as an immune-mediated chronic enteropathy, caused by an irreversible intolerance for gluten in individuals who are genetically susceptible. Its prevalence has been estimated to be 0.5%–1% [1]. Histopathological characteristics comprise a variable degree of villous atrophy, crypt hyperplasia and intra-epithelial lymphocytosis, primarily in duodenum and jejunum [2,3]. The only accepted treatment is a strict and lifelong adherence to a gluten free diet (GFD), which interrupts the immune response triggered by gluten.

Most patients improve clinically within several weeks to months after instigation of a GFD [4]. In a substantial number of patients mucosal recovery is delayed and may last until 2 years after initiation of a strict diet [5–8]. A small minority of patients

Abbreviations: BMI, Body Mass Index; CD, celiac disease; EATL, enteropathy associated t-cell lymphoma; EMA, anti-endomysial antibodies; FCarbohydrate, fecal carbohydrate content; FEnergy, fecal energy loss; FFat, fecal fat content; FFM(I), fat-free mass (index); FNitrogen, fecal nitrogen content; FProtein, fecal protein content; FWW, fecal wet weight; GFD, gluten free diet; H&B, Harris and Benedict; HGS, handgrip strength; HLA, human leukocyte antigen; IEL, intraepithelial lymphocyte; RCD, refractory celiac disease; REE, Resting Energy Expenditure; TEE, Total Energy Expenditure; TEI, total dietary energy intake; tTG, anti-transglutaminase antibodies.

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(approximately 0.5–1% of adulthood diagnosed CD [5]) fails to improve clinically upon a strict GFD for over 12 months (primary resistance) or shows a relapse (secondary resistance). The most common cause for refractoriness to a GFD is unintentional contamination with gluten [8] or an (associated) disorder of the small bowel resembling CD. When dietary adherence is meticulously evaluated by a skilled dietician and other reasons for villous atrophy have been ruled out, patients are diagnosed with refractory CD (RCD). RCD is subdivided into 2 types based on the non-presence (type I) or presence (type II) of abnormal intraepithelial lymphocytes (IELs) referred to as aberrant lymphocytes [9], the cut-off for RCDII being >20% [10]. These 2 groups differ fundamentally since RCDII, in contrast to RCDI, may be considered as a low-grade lymphoma that may develop into a (destructive) enteropathy-associated-T-cell lymphoma (EATL) with an excessive mortality [11]. Untreated, 60–80% of RCDII patients develop an EATL within 5 years. However, EATL may also develop in association with uncomplicated (secondary EATL) or unknown CD (primary EATL).

Symptoms in uncomplicated active CD patients may include diarrhea, abdominal pain, fatigue, malaise, deficiencies and weight loss, although clinical signs may also be succinct or even absent. Based on clinical presentation, RCDII and EATL patients show overlapping characteristics with 'active' or untreated CD; ongoing weight loss, diarrhea and fatty stools are usual and refractory to dietetic treatment, thus, adherence to a strict GFD [12,13]. Unsuitably, literature regarding other nutritional parameters and energy expenditure in both RCDII and EATL is lacking.

Since the pathophysiology and etiology of malnutrition are complex, it appears inappropriate to assess nutritional status and its possible determinants (e.g. malabsorption and increased metabolism) on the basis of a single parameter, ignoring/neglecting temporal weight loss, Body Mass Index (BMI), body composition, functional indices, intestinal absorption and basal metabolism. Therefore, the aim of this study was to perform a comprehensive assessment of the nutritional status and energy balance of patients with RCDII and EATL and to compare these results with newly diagnosed, naive CD patients.

2. Materials and methods

This observational cross sectional study was performed in recently diagnosed, naive CD, RCDII and EATL patients. Nutritional status was determined according to three independent variables: 1) current BMI and percentage of weight loss (unintentionally) during the 6 months prior to diagnosis; 2) body composition and 3) a parameter of functionality being handgrip strength (HGS). Energy balance was determined evaluating nutritional intake, fecal losses and Resting Energy Expenditure (REE). Energy balance (kcal/d) was calculated as the difference between energy intake and 'total energy use', the latter being calculated as Total Energy Expenditure (TEE) plus fecal energy loss. All measurements were performed in one routinely medical appointment by an experienced dietician.

2.1. Patients

During the period 2005–2013, all consecutively diagnosed adult RCDII or EATL patients from the outpatient clinic of the VU University Medical Centre, Amsterdam, the Netherlands, were enrolled. Besides, newly diagnosed (naïve) CD patients were concurrently and consecutively recruited. Patients either consumed a normal or standard Dutch western and gluten containing diet (newly diagnosed CD and primary EATL patients) or a GFD for at least 12 months prior to diagnosis (RCDII patients and EATL patients secondary to a former diagnosis of CD or RCDII).

2.2. Diagnosis of CD, RCDII and EATL

Anti-endomysial (EMA) and anti-transglutaminase antibodies (tTG), i.e. the CD associated antibodies, were determined. In addition, HLA-genotyping was determined, to analyze the incidence of DQ_2 and DQ_8 haplotypes as a requirement for a conclusive diagnosis. Duodenal biopsy specimens were gathered to define the grade of histological impairment as classified by Marsh [14] (modified by Rostami [15,16]), the gold standard method of diagnosis of CD.

CD diagnosis relied on the demonstration of partial or complete villous atrophy (Marsh IIIA-C), and the detection of CD-related antibodies and the presence of CD-related genotypes. In the CD patient group, patients with low grade histopathological abnormalities (Marsh I or II, i.e. lymphocytic enteritis with crypt hyperplasia) could only and exceptionally be included in case of family screening, together with presence of gluten-dependent disorders, in combination with elevated CD associated antibodies and HLA-DQ_2 or HLA-DQ_8 haplotype.

The RCDII diagnosis was based on recurring or persisting clinical symptoms and villous atrophy of the small intestine (Marsh IIIA-C) which remained or reoccurred in spite of a strict GFD for over a year and at the exclusion of other villous atrophy causes. Furthermore, the clinically endorsed cut-off value of over 20% aberrant IELs (perceived by flow cytometric analysis) was used to diagnose RCDII [10]. The EATL diagnosis was based on the criteria according to the WHO Classification of Tumors of Hematopoietic and Lymphoid Tissues. Diagnosis was confirmed histologically by our expert pathologist. Primary EATL was defined as diagnosis of EATL in patients without a preceding CD history or when diagnosis of both EATL and CD were made at the same time or with a maximal six-months-interval. Inconclusive or negative serology was not an exclusion criteria in all patients groups, when patients met the villous atrophy and CD-related genotype criteria.

The study protocol was approved by the Medical Ethics Committee of the VU University Medical Centre Amsterdam, The Netherlands. All patients provided informed consent.

2.3. Nutritional status

2.3.1. BMI and weight loss

Patient characteristics, demographic data and anthropometric data were collected directly after diagnosis and before dietary treatment to either initiate a GFD (CD patients) or nutritional support (RCD or EATL patients). Nutritional status parameters included body weight (in kg, measured on a digital electronic scale (with an accuracy of 0.1 kg), and self-reported body height (m) and weight loss (involuntary in kg) in the past one month and in the past six months. Patients were classified into three BMI cohorts (based on the World Health Organization's definition (2000)): BMI up to 18.5 kg/m^2 (underweight), 18.5–25.0 kg/m^2 (normal weight) and over 25 kg/m^2 (overweight, or 'obese' when BMI exceeded 30 kg/m^2). Patients were classified as 'malnourished' in case of unintentional loss of body weight of more than 10% in the past six months or more than 5% loss of body weight in the month previous to diagnosis. Patients were classified as having 'risk of malnutrition' in case of 5%–10% loss of bodyw eight (unintentionally) in the six months prior to diagnosis. Overall patients were classified as having a 'normal nutritional status' when BMI exceeded 18.5 and no weight loss (<10% in past six months or <5% in one month) occurred.

2.3.2. Body composition

Body composition was measured using (the 50 KHz data of) a multiple frequency bioelectrical impedance analyzer (Hydra ECF/