

Resolution of metabolic syndrome after following a gluten free diet in an adult woman diagnosed with celiac disease

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and no significant changes in diet were documented apart from the GFD. The present case study is the first reported description of an association between CD and metabolic syndrome, and invites investigation of the metabolic changes induced by gluten in celiac patients.

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Key words: Celiac disease; Metabolic syndrome; Gluten-free diet

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Abstract

Adult celiac disease (CD) presents with very diverse symptoms that are clearly different from those typically seen in pediatric patients, including ferropenic anemia, dyspepsia, endocrine alterations and elevated transaminase concentration. We present the case of a 51-year-old overweight woman with altered basal blood glucose, hypercholesterolemia, hypertriglyceridemia and persisting elevated transaminase levels, who showed all the symptoms for a diagnosis of metabolic syndrome. Because she presented iron deficiency anemia, she was referred to the gastroenterology department and subsequently diagnosed with celiac disease after duodenal biopsies and detection of a compatible HLA haplotype. Gluten-free diet (GFD) was prescribed and after 6 mo the patient showed resolution of laboratory abnormalities (including recovering anemia and iron reserves, normalization of altered lipid and liver function parameters and decrease of glucose blood levels). No changes in weight or waist circumference were observed

INTRODUCTION

Celiac disease (CD) is a systemic disorder characterized by enteropathy secondary to an altered immune response induced and maintained by exposure to gluten in the diet. CD is observed in genetically susceptible individuals and is one of the main causes of malabsorption in Europe^[1]. The pathogenesis of the disease includes the activation of cytotoxic T lymphocytes in the lamina propria of the duodenum, together with the production of autoantibodies, giving rise to duodenal mucosal lesions of variable intensity as well as manifestations in other organs^[2]. Approximately 1% of the world population is affected, and many patients go undiagnosed for years. Over half of all new cases are diag-

Table 1 Laboratory test parameters of the patient before and after 6 mo following a gluten free diet

Test parameter	Normal value	Before GFD	After GFD
Glucose	70-110 mg/dL	124.00	92.00
Cholesterol	140-200 mg/dL	338.00	212.00
Triglycerides	45-150 mg/dL	229.00	52.00
CRP	0-0.5 mg/dL	2.00	0.60
AP	40-105 IU/L	50.00	52.00
AST	10-40 IU/L	88.00	17.00
ALT	10-40 IU/L	82.00	18.00
GGT	10-40 IU/L	372.00	24.00
Hemoglobin	12-16 g/dL	10.80	12.60
MCV	80-100 fL	85.40	95.30
Ferritin	30-284 ng/mL	12.00	27.00
Vit. B12	197-866 pg/mL	598.00	817.00
FA	3-17.5 ng/mL	14.30	14.90
25OH-Vit. D ³	>40 ng/mL	23.00	39.00
TSH	0.27-4.24 µIU/mL	3.24	2.60
Free T4	0.93-1.78 ng/dL	1.01	1.05

GFD: Gluten free diet; CRP: C-reactive protein; AP: Alkaline phosphatase; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; GGT: Gamma-glutamyl transpeptidase; MCV: Mean corpuscular volume; AF: Folic acid; 25OH-Vit. D³: calcidiol; TSH: thyroid stimulating hormone; Free T4: Free thyroxine.

nosed in adults^[3]. Indeed, CD can by no means be considered as a childhood disease, and it has been estimated that 20% of all patients are over the age of 60 at the time of the diagnosis^[4]. Adult CD manifests with very diverse symptoms that are clearly different from those typically seen in pediatric patients. Particular symptoms include iron deficiency anemia, dyspepsia, endocrine alterations (particularly of the thyroid gland), neuropsychiatric manifestations, osteoporosis and infertility. At the time of diagnosis, over half of all celiac patients present with chronic constipation rather than diarrhea. As a result of this varied range of symptoms, the estimated delay in diagnosing the adult disease is 11 years from the onset of symptoms^[2]. This makes it necessary to maintain an active search for new cases, since it has been estimated that there are 2-7 undetected cases for every known patient with the disease^[4]. As can be seen from the case described below, CD is also able to simulate disorders characteristic of metabolic syndrome, resulting in delayed diagnosis and treatment of the disease. In this context, effective treatment consists of a gluten free diet (GFD).

CASE REPORT

A 51-year-old woman was referred to the endocrinologist due to hypercholesterolemia. Her history reflected depressive syndrome treated with duloxetine, chronic constipation and dyspepsia, for which rabeprazole had been prescribed (20 mg/d). Body weight was 75 kg, with a body mass index (BMI) of 28.22 kg/m², and a waist circumference (WC) of 93 cm. The laboratory tests revealed normocytic anemia, altered basal blood glucose, hypercholesterolemia, hypertriglyceridemia and elevated transaminase levels-the latter having been detected in earlier tests (Table 1). On the basis of these findings,

written instructions were provided for hyperlipidemia control without caloric restrictions and the patient was referred to the Department of Gastroenterology where studies were made to establish the origin of the altered liver biochemical profile, the anemia and symptoms of dyspepsia. The serology findings for hepatotropic viruses proved negative, and the iron and copper metabolic results were normal. There was no alpha-1-antitrypsin deficit, and no thyroid gland alterations were detected. The immunoglobulins were within normal limits, and the non-organ specific antibody titers proved negative. The tissue anti-transglutaminase IgA levels were within the normal range (1.1 IU/mL), and the hepatobiliary ultrasound findings were normal. Gastroscopy and colonoscopy likewise revealed no alterations, and multiple biopsies were obtained from the gastric antrum and second portion of the duodenum. The histological study revealed a dense intraepithelial lymphocyte infiltration in the duodenal mucosa (> 40%, mostly CD3+/CD8+ after immunohistochemical staining), consistent with lymphocytic enteritis or grade 1 of the classification developed by Marsh for CD^[5]. The gastric mucosa was normal, with no evidence of *Helicobacter pylori*. A genetic study, made at this point, confirmed the presence of HLA-DQ2, a risk genotype for CD. As a result, CD was diagnosed and specific management was started in the form of GFD.

Six months later, the patient had correctly followed the prescribed GFD, but claimed to have failed to adhere to the low-fat recommendations, due to the restrictions to which she was already subjected. A diet questionnaire was administered by qualified personnel, identifying no changes in total intake or in macronutrient distribution. The patient consumed hardly any manufactured products, refined sugars or fried foods before starting GFD and, as a result, there were no significant changes following introduction of the latter diet. No proprietary and independent cause of CD was identified which could explain the laboratory test changes. The patient's constipation and mood state had improved. A slight weight loss was observed (73 kg, BMI 27.5 kg/m²), with no significant changes in WC as measured by the same observer (92 cm). The laboratory tests showed resolution of the anemia and recovery of her iron reserves, with normalization of the transaminase levels and a decrease in cholesterol and triglycerides (37% and 77%, respectively) (Table 1), indicating that the metabolic disorders were practically resolved.

DISCUSSION

The present case study is the first description of an association between CD and metabolic syndrome, with reversion following the prescription of a GFD, together with complete resolution of ferropenic anemia and elevated transaminase levels. The clinical characteristics of the patient (altered lipid and liver function parameters) were consistent with metabolic syndrome, a condition which following its initial description by Reaven in 1988^[6] has received nume-

rous definitions in seeking a central reference parameter (e.g. insulin resistance or abdominal obesity) capable of confirming its existence as a single clinical entity. However, the many definitions and lack of uniformity have led even Reaven to deny the existence of metabolic syndrome as a distinct clinical entity, thereby stressing the importance of treating rather than of defining the condition. The present case shows how adult CD can present as metabolic syndrome according to any of its definitions^[7], despite the fact that CD is presently not included in the differential diagnosis of hyperlipidemia and has not been given importance in the context of metabolic syndrome.

In contrast, the association of CD with endocrine and metabolic alterations has been known for a long time. Type 1 diabetes mellitus classically has been associated with CD, and the possible corrective role of GFD upon the metabolic alterations of the disease has been extensively studied. When both disorders coexist, the introduction of GFD results in fewer hypoglycemic episodes, with no changes in glycosylated haemoglobin values^[8]. A study in type 1 diabetic children diagnosed with CD demonstrated a recovery of normal BMI after following a GFD, together with improvement in glycosylated haemoglobin values as compared with pre-GFD, and with no expected deterioration in glycemic control during puberty^[9]. Furthermore, the beneficial impact of GFD on BMI has been recently demonstrated, since underweight celiac patients gained weight and overweight or obese patients lost weight 2.8 years after starting on a GFD^[10]. A similar effect of GFD upon lipid metabolism therefore should be considered in celiac patients, along with correction of the alterations associated with exposure to gluten in the diet. In fact, diagnosis of CD and its treatment with a GFD has resulted in improvement in the lipoprotein profile, including an increase in HDL and a decrease in the LDL/HDL ratio^[11]. However, contrary results have been also published^[12], although these may be explicable since following a GFD may require a restriction in carbohydrates intake, often leading to increased fat intake^[13]. Depending on the quality of fat this may result in either an increase or decrease of total cholesterol and triglycerides.

Although our case represents a single observation, and larger studies are needed, it does lead us to reflect upon the importance of CD screening. IgA anti-tissue transglutaminase antibodies are considered to be the most useful markers for CD screening, but their diagnostic value in adult patients is limited^[14]. In the case of children it should be noted that the anti-transglutaminase antibody titers correlate with the degree of the duodenal histological lesion, and are very low in children in whom only lymphocytic enteritis is observed. On the other hand, low antibody titres are the most common finding in the adult forms. Thus, it is estimated that their sensitivity which exceeds 90% in the case of childhood CD^[15] is reduced to a mere 15%-30% in screening for CD in adults^[16], for whom a positivity threshold of 2 U/mL is recommended^[17]. This makes it even more necessary to obtain duodenal biopsies and conduct immunohistochemical studies to establish the diagnosis^[18]. This is confirmed by the presence of a risk HLA haplo-

type and particularly by a good clinical and biochemical response to GFD. A strategy based on the genetic evaluation of suspect cases, followed by obtaining duodenal biopsies in individuals confirmed to have risk HLA haplotypes, makes it possible to diagnose three times as many affected cases as when the evaluation is limited to serological testing only^[15]. Different experts in CD agree that because of the difficulty of establishing a diagnosis through other tests, the response to strict GFD for at least 6 mo represents the most definitive diagnostic criterion, particularly when there is an improvement or normalization of the previously altered laboratory test parameters without any associated concomitant medication^[19]. Experts do not recommend the repetition of duodenal biopsies following gluten reintroduction in the case of adults with sufficient diagnostic criteria and a good response to the prescribed treatment^[14].

Our patient was overweight, with an increased waist circumference, mixed hyperlipidemia, altered basal blood glucose and elevated transaminase concentrations. The traditional image of celiac patients, characterized by thin and diarrheic individuals, contrasts with the true situation, since up to 30% of all patients are overweight and 50% suffer constipation^[4], as in our case.

The way in which the malabsorption alterations or immune disorders associated to CD can bring about these metabolic changes is not clear. However, the association between transaminase elevation and CD is well known, and is seen in 60% of all patients with classical clinical manifestations of the disease, as well as in 40% of atypical presentations^[4]. In fact, 10% of all blood transaminase studies result in the diagnosis of CD^[14]. In general, as in obesity, hypertransaminasemia in CD is due to non-alcoholic steatohepatitis and reverts following the introduction of GFD. If no reversion is observed, then the presence of primary biliary cirrhosis, sclerosing cholangitis or autoimmune hepatitis must be excluded, as these are autoimmune conditions that are also associated to CD.

The changes in lipid profile observed in our patient following the introduction of GFD could also be explained by the dietary modifications imposed by GFD itself, a generally healthier and without precooked foods, rather than by the particular absence of gluten. However, the dietary questionnaire revealed no significant changes in diet in this sense. Likewise, the discrete changes in body weight and waist circumference do not, in isolation, seem to explain these important reductions in lipid levels, which in clinical practice are only achieved with drugs. Our patient did not actually reduce her carbohydrate intake, as is normally the case in celiac patients, where increased fat intake is usually observed when gluten-containing flour and cereals are replaced with others lacking gluten. This factor can therefore be taken to have no crucial impact upon correction of the altered basal blood glucose levels and hypertriglyceridemia. Thus, the effects of the absence of gluten upon lipid metabolism remain as the only plausible explanation and, although it must be remembered that ours is an isolated case, the findings do

invite us to investigate the metabolic changes induced by gluten in coeliac patients.

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