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Alimentary Tract

Celiac disease or positive tissue transglutaminase antibodies in patients undergoing renal biopsies

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ABSTRACT

Background: An association between celiac disease and renal diseases has been suggested, but the results are controversial.
Aims: To investigate the prevalence of celiac disease autoimmunity among individuals undergoing renal biopsies and to evaluate whether co-existent celiac autoimmunity influences the clinical outcome of the renal disease.
Methods: The prevalence of celiac autoimmunity (previous diagnosis of celiac disease or positive tissue transglutaminase antibodies) was determined in 827 consecutive patients undergoing kidney biopsies due to clinical indications. Up to 15 years' follow-up data on kidney function and co-morbidities were obtained.
Results: Celiac autoimmunity was found in 45 (5.4%) patients. Among the IgA nephropathy patients, 8.2% of had celiac autoimmunity. At the time of kidney biopsy and after a median follow-up of 5 to 6 years, renal function measured by estimated glomerular filtration rate (eGFR) was inferior in IgA nephropathy patients with celiac autoimmunity compared to those without it (P = 0.048 and P = 0.022, respectively).
Conclusion: The prevalence of celiac autoimmunity seems to be high in patients undergoing renal biopsies, especially in patients with IgA nephropathy. Such autoimmunity may be associated with worse renal function in IgA nephropathy. Hence the co-existence of celiac disease should be taken into consideration when treating patients with renal diseases.

1. Introduction

Celiac disease develops from an autoimmune response to dietary gluten, the storage protein of wheat, rye and barley, and it occurs in about 1–2% of the Western population [1]. Typically, the disease is characterized by diarrhea and malabsorption but nowadays many patients have only a mild constellation of symptoms, which often manifest widespread outside the gastrointestinal tract (e.g. dermatitis herpetiformis, infertility, neurological problems, osteoporotic fractures, hepatitis and liver failure) [2,3]. Furthermore, in the majority of cases the condition may be clinically silent and found only by active case-finding in celiac disease risk groups such as patients with type 1 diabetes mellitus and other autoimmune disorders [4]. The heterogeneous clinical picture constitutes a challenge to physicians, and despite the increased awareness of celiac disease the diagnostic delay often exceeds 10 years and even 75–90% of the patients remain undiagnosed [5,6]. The burden of untreated celiac disease can be remarkable for patients and health care system, and additionally predispose patients to different kinds of complications of celiac disease [4,6]. Hence early diagnosis and life-long gluten free diet as a valid treatment are urgently needed [7].

Autoantibodies specific for the enzyme tissue transglutaminase are currently a hallmark of celiac disease. Serological tests are widely used to facilitate preselection of patients for diagnostic endoscopy and small bowel biopsy [3]. An association between

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celiac disease and renal diseases has been suggested using these autoantibodies [8,9]. According to previous studies celiac disease is overrepresented in patients with IgA nephropathy even though the results have remained contradictory [10–12]. Swedish epidemiologic data showed an increased risk of chronic and end-stage renal diseases among patients with celiac disease [8]. Interestingly, certain cases with IgA nephropathy might improve on a low antigenic diet lacking gluten [13,14]. Despite suggested associations between celiac disease and kidney diseases, current clinical guidelines do not consider patients with renal conditions to be at high risk for celiac disease and no systematic screening is recommended [2].

The aim of this study was to investigate the prevalence of celiac disease autoimmunity among patients undergoing kidney biopsies and to determine whether co-existent celiac autoimmunity has any effect on the clinical outcome of the renal disease.

2. Subjects and methods

2.1. Patients and study design

The study cohort consisted of 827 individual patients to whom a kidney biopsy was performed consecutively at Tampere University Hospital, Finland, during the years 2000–2012. The kidney biopsy specimens were taken and processed by standard methods, as earlier described [15]. The referral letters and the pathology reports of the kidney samples were re-read and structurally categorized. Firstly, the kidney biopsy indications were classified to seven groups as follows: diffuse nephritic syndrome (hematuria and the daily urinary excretion of more than 1.5 g of protein), focal nephritic syndrome (hematuria and the daily urinary excretion of less than 1.5 g of protein), nephrotic syndrome (the daily urinary excretion of more than 3.5 g of protein without hematuria), proteinuria (the daily urinary excretion of protein 0.3–3.5 g without hematuria), hematuria (the daily urinary excretion of protein less than 0.3 g), renal insufficiency (elevated creatinine levels) or any other indication. Secondly, the four groups were formed based on the histopathological findings of the kidney biopsy specimens: glomerular diseases, tubulointerstitial diseases, vascular diseases, and other findings. Blood samples were taken at the day of kidney biopsy, serum was separated by centrifugation at $1500 \times g$ for 10 min and subsequently frozen and stored at $-80\,^{\circ}C$ until analyzed for IgA-class tissue transglutaminase antibodies (tTGA). The patients with available blood samples were included in the current study. The clinical histories of patients were collected systematically from the medical records of Tampere University Hospital during 2014–2015. The study population was divided into two groups according to presence or absence of celiac disease autoimmunity, which was defined as having previous celiac disease diagnosis or positive tTGA.

2.2. Serological tests

Serum IgA-class tTGA were investigated by enzyme-linked immunosorbent assay (ELISA) according to manufacturers' instruction (Celikey®, Phadia, GmbH, Freiburg, Germany). All analyses were carried out blind to the knowledge of the clinical information. Values higher than 3.0 U were regarded as positive [16,17].

2.3. Clinical data

The medical files were systematically analyzed by the same investigator. Data on previous diagnoses of celiac disease as well as type 1 and 2 diabetes mellitus, hypertension and hyperlipidemia were collected. Weight and height values were recorded at the time of kidney biopsy and body mass indexes (BMIs) calculated as weight/height^2 (kg/m^2). Plasma creatinine, daily urinary protein excretion and data of hematuria were gathered from medical records at the time of biopsy and at the latest follow-up. The values of urine dipstick test showing hematuria were dichotomized as negative (values 0 or +) or positive (values ++ or +++). Estimated glomerular filtration rate (eGFR) was defined using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation [18]. Annual change of eGFR was determined by dividing the differences between baseline and end eGFR values by number of follow-up years. Furthermore, data on need for renal dialysis or renal transplant as well as mortality during the follow-up period was recorded.

2.4. Statistical methods

Quantitative data was expressed as medians and ranges. Statistical differences were evaluated by using Mann–Whitney test, Chi-square test, independent t-test or Fisher's test. A P value less than 0.05 was considered statistically significant. All statistical testing was performed using SPSS version 17.0 (SPSS Inc., Chicago, IL, USA).

2.5. Ethical consideration

The study protocol was approved by the Ethical Committee of Tampere University Hospital. All subjects gave written informed consent at the time of kidney biopsy.

3. Results

Altogether 827 patients who underwent renal biopsies during 2000–2012, were enrolled in the analyses (38% female, median age 59 years, range 16–85 years). Forty-five (5.4%) out of the 827 patients were found to have celiac disease autoimmunity; nine (1.1%) had previously diagnosed celiac disease (56% female, median age 59 years, range 35–76 years) and additional 36 subjects had elevated serum tTGA level (31% female, median age 60 years, range 21–83 years). Twelve tTGA-positive subjects had antibody values higher than 2× upper normal limit (range 7.6–87.0 U), 24 had lower positive values (range 3.1–5.4 U). The indications for kidney biopsies and the biopsy findings were not significantly different between patients with or without celiac disease autoimmunity (P = 0.328 and P = 0.580, respectively; Tables 1 and 2). Glomerular disease was the most common finding in both groups.

When analyzing the available data of patients having the most common glomerulonephritis, IgA nephropathy, separately, the

Table 1
Indications for kidney biopsies in patients with and without celiac disease autoimmunity.

Indications for kidney biopsies[a]	Patients with celiac disease autoimmunity n = 45		Patients without celiac disease autoimmunity n = 782	
	n	%	n	%
Focal nephritic syndrome	13	29	140	18
Renal failure	11	24	190	24
Diffuse nephritic syndrome	9	20	171	22
Nephrotic syndrome	8	18	116	15
Proteinuria	4	9	117	15
Hematuria	0	0	34	4
Other causes	0	0	14	2

[a] Difference between patients with and without celiac disease autoimmunity was not significant.

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