# 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 (eg. 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 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 1500xg for 10 min and subsequently frozen and stored at $-80$ 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 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 analysed 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 2x 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 prevalence of celiac disease autoimmunity was 8.2% among them (12 out of 147). There were no differences in age or gender distribution between the IgA nephropathy patients with or without celiac disease autoimmunity (Table 3). In comparison of the prevalence of co-morbidities, there was a trend showing that patients with celiac disease autoimmunity had higher prevalence of hypertension than those without autoimmunity (11 [92%] out of 12 vs. 83 [62%] out of 134, P=0.056). However, patients in the celiac disease autoimmunity group did not suffer significantly more from hyperlipidemia or type 2 diabetes (4 [33%] out of 12 vs. 48 [36%] out of 134, P=1.000, and 3 [25%] out of 12 vs. 18 [13%] out of 135, P=0.380, respectively). None of the patients in the present series had type 1 diabetes. At the time of the kidney biopsy, the renal function was inferior in IgA nephropathy patients with celiac disease autoimmunity; creatinine levels were higher and eGFR lower among this patient group (Table 3). After a median follow-up period of 5 to 6 years the same trend still existed showing the difference in renal function between groups divided according

to celiac disease autoimmunity. Nevertheless, the annual change of eGFR and a need for dialysis or transplantation during the follow-up period were not different between the groups (Table 3). Twenty-five percent out of the IgA nephropathy patients with celiac disease autoimmunity died during the follow-up, while the prognosis seemed to be slightly better in the group without celiac autoimmunity (10% died, Table 3). Still, this difference did not reach statistical significance. The causes of death were not known.

## 4. Discussion

This study shows that 5.4% of patients undergoing kidney biopsies have evidence of celiac disease autoimmunity. Such prevalence is approximately three times higher than percentages achieved in serologic celiac disease screening studies in general population [5,19]. Even though the prevalence of clinically diagnosed celiac disease in this patient cohort was slightly higher (1.1%), than that in the Finnish general population (0.7%) [20], the majority of patients with celiac disease autoimmunity had remained undiagnosed before the current study. This finding is consistent with the current knowledge that the association between celiac disease and renal disorders often stays unrecognised by clinicians. Current clinical guidelines do not recommend systematic screening of celiac disease among kidney disease patients [2]. However our findings support this kind of screening.

The current study also confirmed the association between celiac disease and IgA nephropathy, as almost 8% of the IgA nephropathy patients were found to have celiac disease autoimmunity. Similar positive association has been demonstrated also in our previous cohort of 223 IgA nephropathy patients diagnosed in the 1980's [10]. In addition, a large Swedish epidemiologic study with 27 000 celiac disease patients showed that celiac disease patients suffer a 3-fold increased risk of future IgA nephropathy [11]. Still, despite such large celiac disease patient cohort, the number of patients found to have IgA nephropathy was small and eventually only seven cases had these two co-existent disorders [11]. There are also some previous studies showing negative associations between celiac disease and IgA nephropathy [12,21]. The reason for the contradictory findings might be explained by small study groups or the use of immunosuppressive drugs which can lead to negative results in serological screening.

It is well known that celiac disease is detected even among one tenth of the patients with type 1 diabetes [3]. A previous epidemiological study showed an increased risk for end-stage renal disease among patients with celiac disease, and the most common underlying renal disorder causing end-

stage renal disease among celiac disease patients was diabetic nephropathy [22]. The reason for type 1 diabetes being underrepresented in the current study might be that the diagnosis of diabetic nephropathy is usually done clinically and no biopsies are needed [23]. Hence patients suffering from type 1 diabetes and renal problems would not have been included in the study cohort of patients undergoing renal biopsies. Therefore, in the current study the prevalence of celiac disease autoimmunity could be even higher if all patients with diabetic nephropathy would have been included.

It is notable that patients having celiac disease autoimmunity were found to have more severe kidney disease defined by the significantly higher levels of creatinine and lower eGFR among this patient group. Creatinine values were higher already at the time of kidney biopsy but also after the follow-up period. However, renal diseases were not found to proceed more rapidly among IgA nephropathy patients with celiac disease autoimmunity than those without it. Furthermore, there was a trend showing a higher number of deaths among IgA nephropathy patients with celiac disease autoimmunity, but probably due to relatively short follow-up period and small study group size we could not show any statistically significant differences in final outcomes. The clinical course of IgA nephropathy is variable. Estimates of renal survival are often biased because of differences in renal biopsy indications in different centers [24]. In a previous Finnish material, progressive course was observed in 18% of IgA nephropathy patients during a median follow-up time of 10 years [25]. Hence a median follow-up period of 5-7 years might be too short to show the clinical worsening of the disease.

Biological mechanisms underlying the positive association between celiac disease autoimmunity and more severe kidney disease have yet to be established. Increased intestinal mucosal permeability has been described in IgA nephropathy as well as in advanced chronic kidney diseases in general [26,27]. A defective intestinal mucosal barrier may allow increased absorption of dietary antigens and bacterial toxins. This may lead to activation of mucosal immune system and antigen access to the

systemic circulation [26-30]. Elevated levels of circulating endotoxin have been associated with more severe renal impairment, systemic inflammation, oxidative stress and markers of cardiac injury as well as reduced survival [31]. Small bowel mucosal inflammation and increased permeability are characteristic hallmarks of celiac disease. It could be hypothesized that co-existent celiac disease in patients having renal diseases may lead to more leaky intestinal mucosal barrier and therefore predispose to amplified systemic inflammation and more advanced kidney disease.

We have previously reported that despite normal morphology, ongoing inflammation and stress are present in the small bowel of patients with IgA nephropathy [32,33]. We found increased number of T cells, increased expression of epithelial HLA-DR antigen and GroEL stress protein [32] as well as increased mucosal cyclooxygenase 2 (COX-2) expression [33] in IgA nephropathy. Our findings also suggested that subepithelial fibroblasts are involved in gut the mucosal inflammatory process in IgA nephropathy [33]. These results support the association between the gut and IgA nephropathy.

There are many important strengths in this study. The renal biopsies and serum samples were collected prospectively. The study was conducted in one center where the biopsy indications, clinicians and pathologists were same during the whole recruitment period. Hence the data on kidney biopsies was uniform. On the other hand, the follow-up data of this study was retrospective. We were able to study the clinical outcome and prognosis of patients having IgA nephropathy and celiac disease autoimmunity, however, the other specific subgroups of kidney diseases were too small to investigate these issues. In this study we wanted to focus on the immunologic reactivity and celiac disease autoimmunity, not only on the biopsy-proven celiac disease, and hence the small bowel biopsy was not conducted to patients having positive tTGA levels. This kind of approach has also been applied in recent epidemiological studies where celiac disease autoimmunity defined by tTGA-positivity has been linked to clinical outcomes and prognosis of celiac disease [34,35]. Even if we applied highly sensitive and specific tTGA-test in this study, it is possible that some cases with low positive antibody values might not express celiac disease autoimmunity. In some occasions these

antibodies can also be found in patients without celiac disease but having other conditions such as chronic liver disease or autoimmune disorders [36]. However, tTGA positivity with normal small bowel villous morphology may not always be a false positive finding, but a sign of early developing celiac disease [37], and thus tTGA positivity may represent earlier stage of the disease with less impact on small intestine. Additional endomysial antibody (EmA) testing and small bowel biopsies might have given some further information on small bowel morphology. However, both EmA- and endoscopic testing have their own limitations (e.g. human variation in EmA and biopsy interpretation, endoscopic sample cutoff differences, and testing is labor-intensive) [2]. In this study we applied more objective ELISA-based testing on disease process, and we focused on sero-epidemiology related to celiac disease autoimmunity and not only on celiac disease and enteropathy per se. Antibodies to gliadin were not measured due to lower specificity than tTGA [38]. Causes of deaths could not be extracted from the patient records, and in this study we did not have access to National Statistics death register. Still, as absolute number of deaths remained low in the study cohorts, we would not be able to draw any firm conclusions about individual causes of deaths. Furthermore, we had no possibility to evaluate the effect of gluten-free diet on the progression of renal diseases. Interestingly, IgA nephropathy has been reported to improve on a low-antigenic diet lacking gluten [13,14]. Besides, one previously conducted study with mice showed a beneficial impact of gluten-free diet for the renal function [39]. For showing the influence of gluten-free diet on clinical IgA nephropathy, a large randomised study is urgently needed.

To conclude, the prevalence of celiac disease autoimmunity is increased in patients undergoing kidney biopsy. Such autoimmunity may stay undiagnosed. The link between IgA nephropathy and celiac disease needs to be remembered. Celiac disease may be associated with worse clinical outcome of the renal disease and therefore the co-existence of celiac disease should be taken into consideration when treating patients with renal diseases. The current guidelines, which do not suggest screening of celiac disease among patients with renal problems, may not be valid anymore according to this study.

More studies with longer follow-up are needed to evaluate the connections between celiac disease and renal diseases.

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**Conflict of interest**

The authors have no conflicts of interest to declare.

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**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

**Table 2**

Renal disease according to kidney biopsy finding in patients with and without celiac disease autoimmunity.

| Renal disease according to kidney biopsy[a] | Patients with celiac disease autoimmunity n=45 | | Patients without celiac disease autoimmunity n=767[b] | |
|---|---|---|---|---|
| | n | % | n | % |
| Glomerular diseases | 34 | 76 | 543 | 71 |
| Tubulointerstitial diseases | 4 | 9 | 107 | 14 |
| Vascular diseases | 2 | 4 | 17 | 2 |
| Other | 5 | 11 | 100 | 13 |

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

[b]In 15 patients classification of renal disease was unsuccessful due to insufficient biopsy material

**Table 3**

Clinical data in 147 patients suffering from IgA nephropathy with and without celiac disease autoimmunity.

| | Patients with celiac disease autoimmunity n=12 | | Patients without celiac disease autoimmunity n=135 | | P-value |
|---|---|---|---|---|---|
| *At time of the kidney biopsy* | | | | | |
| Age, median (range), years | 57 | (21-79) | 44 | (17-80) | 0.181 |
| Female, (%) | 3 | (25) | 45 | (33) | 0.751 |
| BMI[b], median (range), kg/m$^2$ | 28 | (25-36) | 27 | (16-47) | 0.436 |
| P-Creatinine[c], median (range), μmol/l | 114 | (78-472) | 93 | (19-1541) | 0.042 |
| eGFR [a, c], median (range), ml/min/1.73 m$^2$ | 76 | (19-117) | 93 | (28-138) | 0.048 |
| Urinary protein excretion rate[d], median (range), g/day | 1.6 | (0.2-4.6) | 1.2 | (0.07-12.9) | 0.684 |
| Hematuria[e], n (%) | | | | | 0.692 |
| Negative | 1 | (8) | 23 | (19) | |
| Positive | 11 | (92) | 101 | (81) | |
| | | | | | |
| *At the latest follow-up* | | | | | |
| Duration of follow-up, median (range), months | 58 | (2-126) | 76 | (0-180) | 0.782 |
| P-Creatitine[f], median (range), μmol/l | 156 | (69-1286) | 96 | (43-1013) | 0.059 |

| | | | | | |
|---|---|---|---|---|---|
| eGFR [a, f], median (range), ml/min/1.73 m$^2$ | 54 | (21-104) | 90 | (10-137) | 0.022 |
| Annual change of eGFR[f], ml/min/1.73 m$^2$ per year | -1 | (-13-34) | -1 | (-189-64) | 0.750 |
| Urinary protein excretion rate[g], median (range), g/day | 0.2 | (0-0.9) | 0.5 | (0-4.5) | 0.472 |
| Hematuria[h], n (%) | | | | | 1.000 |
|   Negative | 6 | (67) | 56 | (70) | |
|   Positive | 3 | (33) | 24 | (30) | |
| Outcome | | | | | |
|   Dialysis after biopsy, n (%) | 1 | (8) | 12 | (9) | 1.000 |
|   Transplantation, n (%) | 0 | (0) | 8 | (6) | 1.000 |
|   Died, n (%) | 3 | (25) | 13 | (10) | 0.126 |

BMI= body mass index, eGFR=estimated glomerular filtration rate

[a] eGFR was calculated by CKD-EPI equation

Variables were available from the following numbers of subjects: [b]68, [c]138, [d]109, [e]136, [f]143, [g]45, [h]89