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Glycemic control and microvascular complications in adults with type 1 diabetes and long-lasting treated celiac disease: A case-control study

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ABSTRACT

Aims: To investigate whether in type 1 diabetes (T1DM) patients the concomitance of long-lasting celiac disease (CD) treated with a gluten free diet (GFD) impacts glycaemic control and the prevalence/severity of microvascular complications.

Methods: A case-control, observational study was performed in 34 patients with T1DM and GFD-treated CD and 66 patients with T1DM alone matched for age, gender, and T1DM duration. Anthropometric parameters, glucose control ($HbA1_c$), status of chronic complications and concomitant autoimmune diseases were evaluated.

Results: $HbA1_c$ level was similar in T1DM + CD and T1DM alone (7.8 ± 1.0 vs 7.7 ± 1.1%, $P = 0.57$); insulin requirement was significantly higher in T1DM + CD compared with T1DM ($P = 0.04$). There were no differences in systolic blood pressure while diastolic blood pressure was significantly lower in T1DM + CD ($P = 0.003$). The prevalence/severity of microvascular complications was similar between the two groups. Glomerular filtration rate (eGFR) was significantly lower in T1DM + CD (100 ± 20 vs 110 ± 16 ml/min/1.73 m^2, $P = 0.007$).

Conclusions: In patients with T1DM, the co-occurrence of long-term GFD-treated CD neither worsens glycemic control nor negatively impacts chronic microvascular complications. However, patients with T1DM + CD have lower eGFR values than those with T1DM alone.

1. Introduction

Type 1 diabetes mellitus (T1DM) is associated with an increased risk of developing other autoimmune conditions due to a common genetic background [1]. Among these, celiac disease (CD) is one of the most frequently associated autoimmune disorder, with a prevalence ranging from 1.9 to 7.9% depending on the populations and differences in screening practices [2–7]. The question whether the coexistence of CD may worsen glycemic control and the course of chronic complications in patients with T1DM is still controversial. Two previous studies highlighted higher $HbA1_c$ levels and more frequent hypoglycemic episodes in T1DM patients at diagnosis of CD as compared with patients with T1DM alone [8,9]. Conversely, other studies failed to find a difference in the metabolic control in T1DM + CD patients compared with

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those without CD [10,11]. One study reported a better glycemic control in patients with T1DM + CD, which was likely due to a higher rate of patients using continuous subcutaneous insulin infusion system [12].

With regard to microvascular complications among patients with both T1DM and CD, the data available are also conflicting, with some studies reporting increased rate of complications [9,13,14] and others showing no difference or even a lower incidence of complications [10,12,15,16]. However, not all studies took into consideration the degree of glycemic control.

One additional factor possibly confounding the interpretation of the literature on the burden of coexisting T1DM and CD is the adherence to the gluten-free diet (GFD). It is widely recognized that poor or non-adherence to GFD can cause nutrient and carbohydrates malabsorption making glucose control quite unstable. Moreover, untreated CD is associated with a chronic, low-grade inflammation, which could itself exert unfavourable effects on microcirculation, increasing the complications risk [17,18]. In support of this hypothesis, Pham-Short et al. showed that T1DM + CD patients non-adherent to a GFD had a higher albumin excretion rate than those following a GFD, suggesting that the GFD may have a protective effect on diabetes-related complications [12]. To date, few studies have examined the risk of microvascular complications in patients with T1DM + CD following a GFD since the diagnosis and most of them have been performed in children or young adults [7,8,11,12]. Against this background, in the present case-control study we evaluated the metabolic control and the status of microvascular complications in patients with T1DM and long-lasting, GFD-treated CD compared with patients with T1DM alone.

2. Subjects, materials and methods

2.1. Study groups

Thirty-four patients with T1DM + CD and sixty-six patients with T1DM alone matched for age, sex and diabetes duration were studied. All participants attended the Outpatient Diabetes Unit of Federico II University of Naples. Patients' clinical and biochemical variables, smoking status, insulin dose, scores of diabetic complications tests, presence of comorbidities and medication use were evaluated at their most recent visit during the yearly complication assessment protocol in the period 2011–2016.

T1DM was diagnosed by clinical criteria and the presence of islet antibodies (glutamic acid decarboxylase (GAD) and islet antigen 2 (IA-2). CD was diagnosed by positive serology, i.e. anti-tissue transglutaminase (anti-tTG) IgA or anti-endomysial (EMA) IgA antibodies, and confirmed by typical histological changes in biopsy duodenal specimens according to the European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) criteria [19]. Adherence to GFD diet was defined as anti-tTG IgA antibodies within the normal range.

All procedures were performed in accordance with the Helsinki Declaration. All patients gave their informed consent to the use of their clinical and laboratory data and for being included in the study. The study was approved by the Ethics Committee of Federico II University.

2.2. Complications assessment

All participants underwent a complete screening of chronic complications according to our standardized protocol including clinical examination and dilated eye exam for diabetic retinopathy screening. Nephropathy was evaluated by the assessment of urinary albumin excretion rate (UAE), serum creatinine and estimated glomerular filtration rate (eGFR). Autonomic nerve function was examined by standardized cardiovascular reflex tests: parasympathetic function was evaluated by the heart rate variability through a deep breathing test (beat-to-beat variation test) and sympathetic function was assessed by the blood pressure response to standing. Peripheral neuropathy was evaluated with bilateral vibration perception examination, tactile perception test with the Semmes-Weinstein monofilament and ankle reflex assessments.

2.3. Measurements

Plasma concentrations of glucose, creatinine, and lipids were determined by standard procedures. Glycated hemoglobin ($HbA1_c$) was evaluated with HPLC method. Anti-tTG were measured by enzyme-linked immunosorbent assay (ELISA) tests and anti-EMA IgA were measured by immunofluorescence assay. Albumin concentration in spot urine was measured by immunonephelometry. Plasma and urine creatinine were determined by the modified Jaffé reaction using an autoanalyzer (Pentra 400, Horiba ABX Diagnostics). All biochemical analyses were performed in a central laboratory.

Body mass index (BMI) was calculated as weight in kg/height in m^2. LDL-cholesterol was calculated by Friedewald's formula. eGFR was calculated with CKD-EPI formula. Estimated Insulin sensitivity (eIS) was calculated according to SEARCH IS score [20].

2.4. Definitions

Smoking status was defined as smoking one or more cigarettes per day. Hypertension was diagnosed as systolic blood pressure (SBP) $\geq$ 140 mmHg or diastolic blood pressure (DBP) $\geq$ 90 mmHg in accordance with the European Society of Hypertension [21]. Dyslipidemia was defined as the presence of at least one of the followings: LDL cholesterol >3.4 mmol/L, triglycerides >1.7 mmol/L, HDL cholesterol >1.03 mmol/L in men and >1.29 mmol/L in women.

Diabetic nephropathy was defined as two or more positive microalbuminuria tests (albumin to creatinine ratio of 3–30 mg/mmol on spot urine), obtained within 6 months. Peripheral neuropathy was diagnosed if two out of the three tests (bilateral vibration perception, tactile perception and ankle reflexes) were abnormal.

Autonomic neuropathy was diagnosed if at least beat-to-beat variation test was abnormal. Non proliferative and retinopathy and advanced retinopathy were defined in accordance with international guidelines by an expert operator [22].

2.5. Statistical analysis

Continuous data were expressed as means ± standard deviation (SD) or proportions (%). To compare continuous variables, an independent Student's *t test* was performed. Given the skewed distribution of triglycerides, creatinine, UAC, the statistical analysis of these variables was applied after log-transformation with back transformation to natural units for presentation in the text and. Pearson's test was used to assess correlations among continuous variables. The X^2 test was used to analyze categorical data. General linear model univariate analysis was performed adjusting for BMI, diastolic blood pressure, insulin dosage and number of associated autoimmune disorders. The statistical analysis was performed with IBM SPSS Statistics, version 24.0.

3. Results

As shown in Table 1, the two groups were comparable for the main anthropometric and clinical characteristics except for DBP that was significantly lower in T1DM + CD than in T1DM subjects. In the majority of T1DM + CD patients (88%), T1DM preceded the diagnosis of CD.

The two groups had similar glucose control evaluated both as mean $HbA1_c$ ($P = 0.57$) and as percentage of patients within different categories of $HbA1_c$, i.e. <7% (53 mmol/mol), 7–8% (53–64 mmol/mol), >8% (>64 mmol/mol). No differences in lipid profile was observed between the two groups.

With respect to other associated autoimmune conditions, 44% in the T1DM + CD group showed at least one autoimmune disease compared with 35% in the T1DM group ($P = 0.39$). Thyroiditis was the most frequent associated autoimmune condition with a frequency of 41% in the T1DM + CD and 27% in the CD groups ($P = 0.18$).

The percentage of patients using continuous subcutaneous insulin infusion system was 26% in T1DM + CD and 42% in T1DM (p = 0.15). Insulin requirement per day was significantly greater in T1DM + CD than in the CD group (0.69 ± 0.17 UI/Kg/day vs 0.62 ± 0.17 IU/Kg/day, respectively, $P = 0.04$) due to a higher pre-prandial insulin dose (0.40 ± 0.14 vs 0.31 ± 0.14 IU/Kg/day, $P = 0.004$), while no difference was found in basal insulin requirements. Insulin sensitivity, expressed by eIS score, was similar in the two groups. As shown in Table 2, the rate of microvascular complications was similar between the two groups. However, estimated glomerular filtration rate (eGFR) was significantly lower in T1DM + CD compared with T1DM patients (100 ± 20 vs 110 ± 16 ml/min/1.73 m^2, $P = 0.007$) (Fig. 1). This difference persisted even after the exclusion of treated hypertensive subjects (102 ± 17 vs 112 ± 13 ml/min/1.73 m^2, $P = 0.004$) and after adjustment for diastolic blood pressure, insulin dosage, number of associated autoimmune disorders ($P = 0.003$). The percentage of patients with

Table 1 – Clinical and metabolic characteristics of patients with T1DM+CD compared with T1DM alone.

	T1DM + CD (n 34)	T1DM (n 66)	P value
Female – n (%)	24 (71)	46 (70)	0.92
Age – years	28 ± 10	28 ± 8	0.93
T1DM duration – years	18 ± 7	17 ± 7	0.44
CD duration – years	15 ± 7	–	–
BMI – kg/m^2	23 ± 3	24 ± 3	0.14
WC – cm	80 ± 8	83 ± 10	0.10
$HbA1_c$ – %	7.8 ± 1	7.7 ± 1.1	0.57
$HbA1_c$ – mmol/mol	62 ± 11	61 ± 12	
• $HbA1_c$ < 7% (<53 mmol/mol) – n (%)	7 (21)	20 (30)	0.29
• $HbA1_c$ 7–8% (53–64 mmol/mol) – n (%)	18 (53)	25 (38)	0.16
• $HbA1_c$ > 8% (>64 mmol/mol) – n (%)	9 (26)	21 (32)	0.63
Total Cholesterol – mmol/l	4.5 ± 0.9	4.2 ± 0.8	0.12
HDL Cholesterol – mmol/l	1.7 ± 0.5	1.6 ± 0.4	0.51
LDL Cholesterol – mmol/l	2.4 ± 0.7	2.3 ± 0.7	0.36
Triglyceride – mmol/l	1.7 ± 0.7	1.5 ± 0.5	0.15
Creatinine – μmol/l	80 ± 18	71 ± 9	0.003
Systolic blood pressure – mmHg	112 ± 13	116 ± 16	0.17
Diastolic blood pressure – mmHg	69 ± 9	75 ± 9	0.003
Smoking status – n (%)	7 (21)	19 (29)	0.38
Total Insulin dose – IU/Kg/day	0.69 ± 0.17	0.62 ± 0.17	0.04
Prandial Insulin dose – IU/Kg/day	0.40 ± 0.14	0.31 ± 0.14	0.004
Basal Insulin dose – IU/Kg/day	0.30 ± 0.12	0.31 ± 0.10	0.60
eInsulin Sensivity – mg/Kg/min	4.76 ± 1.23	4.85 ± 1.21	0.74
Autoimmune disorders – n (%)	15 (44)	23 (35)	0.39
• Thyroiditis – n (%)	14 (41)	18 (27)	0.18
Dyslipidemia – n (%)	5 (15)	10 (15)	0.95
Hypertension – n (%)	2 (6)	8 (12)	0.32

T1DM, type 1 diabetes mellitus; CD, celiac disease; WC, waist circumference.

Table 2 – Parameters of renal function and proportions of microvascular complications in patients with T1DM+CD and T1DM alone.

	T1DM + CD (n 34)	T1DM (n 66)	*P* value
eGFR – ml/min/1.73 m^2	100 ± 20	110 ± 16	0.007
eGFR < 90 ml/min/1.73 m^2 – n (%)	13 (38.2)	7 (10.6)	0.001
ACR – mg/mmol	1.8 ± 1.4	2.0 ± 3.0	0.66
Nephropathy – n (%)	3 (10)	4 (6)	0.60
Retinopathy – n (%)	10 (29)	14 (21)	0.38
Peripheral Neuropathy – n (%)	1 (3)	2 (3)	0.98
Autonomic Neuropathy – n (%)	0 (0)	1 (1)	0.47

T1DM, type 1 diabetes mellitus; CD, celiac disease; eGFR, estimated glomerular filtration rate; ACR, albumin creatinine ratio.

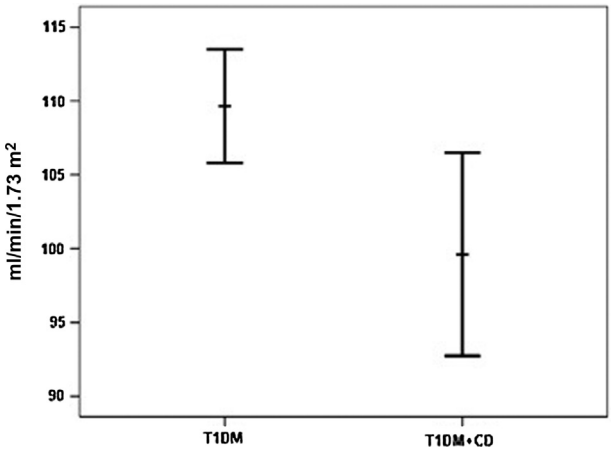

Fig. 1 – eGFR (95%CI) in patients with T1DM alone compared with T1DM+CD.

eGFR < 90 ml/min1.73 m^2 was significantly higher in the T1DM + CD than in the T1DM group (*P* = 0.001).

4. Discussion

This study demonstrates that in patients with concomitant T1DM and GFD-treated CD, both glycemic control and the rate of microvascular complications were similar to those of patients with T1DM alone. However, compared to T1DM, patients with T1DM + CD showed a lower GFR that appeared to be independent of metabolic and blood pressure control.

The extent to which the co-occurrence of CD negatively influences glycemic control in patients with T1DM is still debated. In a longitudinal retrospective case-control study, no difference was found in $HbA1_c$ levels between patients with T1DM and duodenal-biopsy-confirmed CD and T1DM patients matched for gender, age and duration of diabetes [23]. In contrast, Leeds et al. found a worse glucose control in T1DM patients with overt CD than the T1DM control group [9]. These heterogeneous results may depend on the time elapsed since CD diagnosis (at onset or during the follow-up) and, above all, the adherence to a GFD. In fact, Pham-Short et al. showed a worse glycemic control in T1DM patients with untreated CD compared to patients following a GFD [12].

Our patients with T1DM + CD were adherent to a GFD, as evidenced by the absence of anti-tTG, and had a glycemic control similar to that of T1DM patients, supporting the view that CD does not worsen glycemic control provided that an adequate clinical management for both T1DM and CD is pursued. On the other hand, a strict adherence to a GFD is known not only to relieve gastro-intestinal symptoms but also to revert intestinal mucosal inflammation and damage thus restoring a normal nutrient absorption [24].

A number of studies exploring the impact of CD on microvascular complications has provided conflicting results. In a large population study, Rohrer et al. demonstrated that in T1DM patients, CD is an independent risk factor for both retinopathy and nephropathy when adjusted for age, sex, duration of diabetes, $HbA1_c$, hypertension and dyslipidemia [14]. Moreover, microalbuminuria occurred 10 years earlier in patients with concomitant T1DM and CD [14]. It should be noted, however, that most of the patients involved in the study were untreated for CD [14]; therefore the true burden of CD in patients with T1DM remains undefined since in real life CD is generally treated with a GFD. In a cohort study based on the Swedish National Patient Register, the authors observed that the coexistence of T1DM + CD was protective for the risk of retinopathy development for the first 5 years after the CD diagnosis, had a neutral effect between 5 and 10 years of CD duration, and finally became a risk factor for retinopathy in patients with over 10 years of CD duration [13]. In the same population, the authors found an increased risk of chronic renal diseases in individuals with T1DM + CD and CD duration >10 years compared to T1DM alone [16]. However, glycemic control, blood pressure and lipid status were not considered in the analysis. Finally, in a cross-sectional study, Leeds and coll. reported a higher rate of nephropathy and retinopathy in T1DM patients at the time of diagnosis of CD compared to T1DM alone, and an improvement of nephropathy after 1 year of a GFD [9]. However, in this study the two groups were not matched for $HbA1_c$ levels.

The present study is the first one examining patients with long-lasting T1DM and GFD-treated CD. We found no difference in the rate of microvascular complications between patients with T1DM + CD and T1DM patients matched for sex, age, diabetes duration, and $HbA1_c$, indicating that the co-occurrence of GFD-treated CD does not negatively impact the clinical course of T1DM. This finding highlights a possible

protective role of a GFD in the development of diabetes-related complications in line with previous small clinical studies [9,10,15]. Interestingly, GFD has been reported to reduce weight gain, inflammation and insulin resistance though up-regulation of PPARs expression in an experimental model of obesity [25]. However, a conclusive evidence on the clinical efficacy of GFD treatment in patients with T1DM + CD will only come from randomized controlled trials currently ongoing [26].

A novel finding of our study is the occurrence of a significantly lower eGFR in T1DM + CD patients compared to T1DM alone. The reduction in eGFR does not appear to be related to metabolic and/or hemodynamic factors since $HbA1_c$ blood pressure and lipid levels were similar in the two groups; rather, it is likely linked to CD *per se*, as confirmed by the analysis adjusted for confounders. An increased prevalence of chronic kidney disease among non-diabetic patients with CD was reported in previous clinical studies [27–29], and a recent meta-analysis showed a two-fold higher risk to develop chronic kidney disease in CD patients than in healthy subjects [30]. One hypothesis to explain the increased risk of kidney disease in CD patients is an accumulation of IgA complexes in the mesangial cells, whose production is exacerbated by the intestinal exposure to gluten [31,32]. Moreover, mechanisms related to low grade inflammation due to a discontinuous adherence to a GFD could also contribute to renal damage [33,34].

An interesting observation of our study is the higher prandial insulin requirement in T1DM + CD patients compared to T1DM, despite the two groups had a similar insulin sensitivity, estimated by the SEARCH score. This finding may be due to the higher glycemic index and lower fiber content of gluten-free food as reported in the International Tables of the American Society for Clinical Nutrition [35]. Consistent with this interpretation, Pam-short et al. demonstrated greater post-prandial glucose excursions and higher glucose peak in young T1DM + CD patients adhering to GFD compared to T1DM alone despite correction doses of insulin administered pre-meal [36].

We acknowledge that our study has some limitations. First, the design is observational and cross-sectional, which precludes evaluation of the changes of renal function over time and the elucidation of the mechanisms underlying the reduction in eGFR found in TIDM + CD patients. Second, since the diagnosis all patients were followed up in our outpatient tertiary care center with periodic clinical assessment of both T1DM and CD. Therefore, our results may not be applicable to the whole population of patients with coexisting T1DM and CD who may not undergo a strict monitoring. Furthermore, our patients showed a good adherence to a GFD at the time of the study; however, given the long duration of CD, we cannot assume that dietary compliance has been optimal for the whole disease duration, which may have played a role in reducing eGFR.

In conclusion, in patients with T1DM, the co-occurrence of long-term, GFD-treated CD does not negatively impact glycemic control and microvascular complications, supporting the beneficial effects of GFD on glucose homeostasis and vascular function. However, compared to patients with T1DM alone, patients with T1DM + CD have a lower eGFR value and its clinical significance will be clarified by *ad hoc* prospective studies. This study highlights the need for carefully monitoring renal function in patients with T1DM and CD.

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AC conceived and designed the study, performed statistical analysis, interpreted results and drafted the manuscript; EL, GL, GDP and NT collected clinical data; BC, RL, PDB, GR performed statistical analysis, interpreted results and performed critical revision of the manuscript. All authors read and approved the final manuscript. BC is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of data analysis. No potential conflicts of interest were reported. The authors thank the patients and their families.

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REFERENCES

[1] Barker JM. Type 1 diabetes-associated autoimmunity: natural history, genetic associations, and screening. J Clin Endocrinol Metab 2006;91:1210–7. https://doi.org/10.1210/jc.2005-1679.

[2] Gujral N, Freeman HJ, Thomson ABR. Celiac disease: prevalence, diagnosis, pathogenesis and treatment. World J Gastroenterol 2012;18:6036–59. https://doi.org/10.3748/wjg.v18.i42.6036.

[3] Rubio-Tapia A, Ludvigsson JF, Brantner TL, Murray JA, Everhart JE. The prevalence of celiac disease in the United States. Am J Gastroenterol 2012;107:1538–44. https://doi.org/10.1038/ajg.2012.219.

[4] Logan RFA, Rifkind EA, Turner ID, Ferguson A. Mortality in celiac disease. Gastroenterology 1989;97:265–71. https://doi.org/10.1016/0016-5085(89)90060-7.

[5] Elfström P, Sundström J, Ludvigsson JF. Systematic review with meta-analysis: associations between coeliac disease and type 1 diabetes. Aliment Pharmacol Ther 2014;40:1123–32. https://doi.org/10.1111/apt.12973.

[6] Craig ME, Prinz N, Boyle CT, Campbell FM, Jones TW, Hofer SE, et al. Prevalence of celiac disease in 52,721 youth with type 1 diabetes: international comparison across three continents. Diabetes Care 2017;40:1034–40. https://doi.org/10.2337/dc16-2508.

[7] Camarca ME, Mozzillo E, Nugnes R, Zito E, Falco M, Fattorusso V, et al. Celiac disease in type 1 diabetes mellitus. Ital J Pediatr 2012;38:10. https://doi.org/10.1186/1824-7288-38-10.

[8] Narula P, Porter L, Langton J, Rao V, Davies P, Cummins C, et al. Gastrointestinal symptoms in children with type 1 diabetes screened for celiac disease. Pediatrics 2009;124:e489–95. https://doi.org/10.1542/peds.2008-2434.

[9] Leeds JS, Hopper AD, Hadjivassiliou M, Tesfaye S, Sanders DS. High prevalence of microvascular complications in adults with type 1 diabetes and newly diagnosed celiac disease. Diabetes Care 2011;34:2158–63. https://doi.org/10.2337/dc11-0149.

[10] Bakker SF, Tushuizen ME, Von Blomberg ME, Mulder CJ, Simsek S. Type 1 diabetes and celiac disease in adults: glycemic control and diabetic complications. Acta Diabetol 2013;50:319–24. https://doi.org/10.1007/s00592-012-0395-0.

[11] Jessup AB, Law JR, Spagnoli A. Are HDL levels lower in children with type 1 diabetes and concurrent celiac disease compared with children with type 1 diabetes only? J Pediatr Endocrinol Metab 2014;27:1213–6. https://doi.org/10.1515/jpem-2013-0464.
[12] Pham-Short A, Donaghue KC, Ambler G, Chan AK, Hing S, Cusumano J, Craig ME, et al. Early elevation of albumin excretion rate is associated with poor gluten-free diet adherence in young people with coeliac disease and diabetes. Diabet Med 2014;31:208–12. https://doi.org/10.1111/dme.12329.
[13] Mollazadegan K, Kugelberg M, Montgomery SM, Sanders DS, Ludvigsson J, Ludvigsson JF. A population-based study of the risk of diabetic retinopathy in patients with type 1 diabetes and celiac disease. Diabetes Care 2013;36:316–21. https://doi.org/10.2337/dc12-0766.
[14] Rohrer TR, Wolf J, Liptay S, Zimmer KP, Fröhlich-Reiterer E, Scheuing N, et al. Microvascular complications in childhood-onset type 1 diabetes and celiac disease: a multicenter longitudinal analysis of 56,514 patients from the German-Austrian DPV database. Diabetes Care 2015;38:801–7. https://doi.org/10.2337/dc14-0683.
[15] Malalasekera V, Cameron F, Grixti E, Thomas MC. Potential reno-protective effects of a gluten-free diet in type 1 diabetes. Diabetologia 2009;52:798–800. https://doi.org/10.1007/s00125-009-1277-z.
[16] Mollazadegan K, Fored M, Lundberg S, Ludvigsson J, Ekbom A, Montgomery SM, et al. Risk of renal disease in patients with both type 1 diabetes and coeliac disease. Diabetologia 2014;57:1339–45. https://doi.org/10.1007/s00125-014-3223-y.
[17] Rybak A, Cukrowska B, Socha J, Socha P. Long term follow up of celiac disease-Is atherosclerosis a problem? Nutrients 2014;6:2718–29. https://doi.org/10.3390/nu6072718.
[18] Pitocco D, Giubilato S, Martini F, Zaccardi F, Pazzano V, Manto A, et al. Combined atherogenic effects of celiac disease and type 1 diabetes mellitus. Atherosclerosis 2011;217:531–5. https://doi.org/10.1016/j.atherosclerosis.2011.04.042.
[19] Husby S, Koletzko S, Korponay-Szabó IR, Mearin ML, Phillips A, Shamir R, et al. European Society for Pediatric Gastroenterology, Hepatology, and Nutrition Guidelines for the diagnosis of coeliac disease. J Pediatr Gastroenterol Nutr 2012;54:136–60. https://doi.org/10.1097/MPG.0b013e31821a23d0.
[20] Dabelea D, D'Agostino RB, Mason CC, West N, Hamman RF, Mayer-Davis EJ, et al. Development, validation and use of an insulin sensitivity score in youths with diabetes: the SEARCH for diabetes in youth study. Diabetologia 2011;54:78–86. https://doi.org/10.1007/s00125-010-1911-9.
[21] Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Bohm M, et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension. Blood Press 2013;22:193–278. https://doi.org/10.3109/08037051.2013.812549.
[22] American Diabetes Association. Standards of medical care in diabetes–2014. Diabetes Care 2014;37:S14–80. https://doi.org/10.2337/dc14-S014.
[23] Taler I, Phillip M, Lebenthal Y, De Vries L, Shamir R, Shalitin S. Growth and metabolic control in patients with type 1 diabetes and celiac disease: a longitudinal observational case-control study. Pediatr Diabetes 2012. https://doi.org/10.1111/j.1399-5448.2012.00878.x.
[24] Ciacci C, Cirillo M, Cavallaro R, Mazzacca G. Long-term follow-up of celiac adults on gluten-free diet: prevalence and correlates of intestinal damage. Digestion 2002;66:178–85. https://doi.org/10.1159/000066757.
[25] Soares FLP, de Oliveira Matoso R, Teixeira LG, Menezes Z, Pereira SS, Alves AC, et al. Gluten-free diet reduces adiposity, inflammation and insulin resistance associated with the induction of PPAR-alpha and PPAR-gamma expression. J Nutr Biochem 2013;24:1105–11. https://doi.org/10.1016/j.jnutbio.2012.08.009.
[26] Mahmud FH, De Melo EN, Noordin K, Assor E, Sahota K, Davies-Shaw J, et al. The Celiac Disease and Diabetes-Dietary Intervention and Evaluation Trial (CD-DIET) protocol: a randomised controlled study to evaluate treatment of asymptomatic coeliac disease in type 1 diabetes. BMJ Open 2015;5. https://doi.org/10.1136/bmjopen-2015-008097.
[27] Peters U, Askling J, Gridley G, Ekbom A, Linet M. Causes of death in patients with celiac disease in a population-based Swedish cohort. Arch Intern Med 2003;163:1566–72. https://doi.org/10.1001/archinte.163.13.1566.
[28] Ludvigsson JF, Montgomery SM, Olén O, Ekbom A, Ludvigsson J, Fored M. Coeliac disease and risk of renal disease – a general population cohort study. Nephrol Dial Transplant 2006;21. https://doi.org/10.1093/ndt/gfl117.
[29] Welander A, Prutz KG, Fored M, Ludvigsson JF. Increased risk of end-stage renal disease in individuals with coeliac disease. Gut 2012;61:64–8. https://doi.org/10.1136/gutjnl-2011-300134.
[30] Wijarnpreecha K, Thongprayoon C, Panjawatanan P, Thamcharoen N, Pachariyanon P, Nakkala K, et al. Celiac disease and the risk of kidney diseases: a systematic review and meta-analysis. Dig Liver Dis 2016;48:1418–24. https://doi.org/10.1016/j.dld.2016.08.115.
[31] Floege J, Feehally J. The mucosa–kidney axis in IgA nephropathy. Nat RevNephrol 2015;12:147–56. https://doi.org/10.1038/nrneph.2015.208.
[32] Matysiak-Budnik T, Moura IC, Arcos-Fajardo M, Lebreton C, Ménard S, Candalh C, et al. Secretory IgA mediates retrotranscytosis of intact gliadin peptides via the transferrin receptor in celiac disease. J Exp Med 2008;205:143–54. https://doi.org/10.1084/jem.20071204.
[33] Tuire I, Marja-Leena L, Teea S, Katri H, Jukka P, Päivi S, et al. Persistent duodenal intraepithelial lymphocytosis despite a long-term strict gluten-free diet in celiac disease. Am J Gastroenterol 2012;107:1563–9. https://doi.org/10.1038/ajg.2012.220.
[34] Saraheimo M, Teppo AM, Forsblom C, Fagerudd J, Groop PH. Diabetic nephropathy is associated with low-grade inflammation in Type 1 diabetic patients. Diabetologia 2003;46:1402–7. https://doi.org/10.1007/s00125-003-1194-5.
[35] Foster-Powell, Holt SH, Brand-Miller JC. International table of glycemic index and glycemic load values: 2002. Am J Clin Nutr 2002;76:5–56. https://doi.org/10.1093/ajcn/76.1.5.
[36] Pham-Short A, Donaghue KC, Ambler G, Garnett S, Craig ME. Greater postprandial glucose excursions and inadequate nutrient intake in youth with type 1 diabetes and celiac disease. Sci Rep 2017;7. https://doi.org/10.1038/srep45286.