Cardiovascular risk factors in coeliac disease (ARCTIC): a protocol of multicentre series of studies

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ABSTRACT

Introduction There is only limited and controversial information available on the cardiovascular (CV) risk in coeliac disease (CD). In this study, we plan to investigate the body composition and CV risk-related metabolic parameters at the diagnosis of CD and on a gluten-free diet in a Hungarian cohort of patients with CD.

Methods and analysis This study consists of two case–control studies and a prospective cohort study, involving newly diagnosed and treated patients with CD with age and sex-matched non-CD control subjects with an allocation ratio of 1:1. CD-related symptoms, quality of life, quality of the diet and CV risk will be assessed with questionnaires. Our primary outcomes are body composition parameters, which will be estimated with InBody 770 device. Secondary outcomes are CV-risk related metabolic parameters (eg, serum lipids, haemoglobin A1c, homeostatic model assessment index, liver enzymes, homocysteine, interleukin 6, galectin-3) and enteral hormones (leptin, ghrelin, adiponectin) measured from venous blood samples for all participants. Fatty liver disease will be assessed by transabdominal ultrasonography. In statistical analysis, descriptive and comparative statistics will be performed. With this study, we aim to draw attention to the often neglected metabolic and CV aspect of the management of CD. Findings may help to identify parameters to be optimised and reassessed during follow-up in patients with CD.

Ethics and dissemination The study was approved by the Scientific and Research Ethics Committee of the Hungarian Medical Research Council (27521-5/2022/EÜIG). Findings will be disseminated at research conferences and in peer-reviewed journals.

Trial registration number NCT05530070.

INTRODUCTION

Coeliac disease (CD) is a chronic, autoimmune disease, which is triggered by gluten consumption in genetically predisposed people. The global prevalence of CD is currently approximately 1%. There is a trend for increasing prevalence, which contributes to the disease’s significant public healthcare burden. Although the typical clinical presentation of CD is malabsorption, the proportion of non-classical and silent forms has become more frequent in the recent decades.

Patients with non-classical CD are not necessarily lean; they usually have normal body weight but can also be overweight or obese. The latter groups tend to extend both among children and adults: patients with normal body weight may account for 80% of the total, whereas the prevalence of obesity can exceed 30% in some studies. Also, the nutritional status and metabolic parameters of patients with CD deviate from that of the normal population. Data on nutritional status and the effects of the gluten-free diet (GFD) derive from small, mainly retrospective studies. Indicators of nutritional status (eg, body mass index [BMI], body fat mass [FM], body fat-free mass [FFM], bone density, blood lipids) of patients with classical CD, not commencing a GFD, are usually worse than that of the average population, but as the global prevalence of obesity is increasing, this phenomenon is expected to change. The effects of the GFD on body composition and metabolic parameters are controversial. A common misbelief is that the GFD alone results in weight loss. However, data on more than 30,000 subjects without CD from the UK...
Biobank refuted this belief. The body weight tends to increase during a GFD in women and favourable changes in metabolic parameters fail to occur.\textsuperscript{12} In patients with CD, body weight also tends to elevate, whereas the body composition changes unfavourably (with a substantial gain in FM and a modest increase in FFM) during a GFD.\textsuperscript{11–17} Our study supported these observations: FM increased significantly, but FFM did not change during a GFD.\textsuperscript{18}

A reason for gaining weight is the improvement of malabsorption, but an important contributor is the nutrient composition of the GFD, which generally has a high carbohydrate density with high carbohydrate and fat content while being low in fibre.\textsuperscript{19,20} While terminating or mitigating the inflammatory process—if done without adequate dietary control—a GFD can readily lead to weight gain and unfavourable metabolic changes. The result can be an increase in cardiovascular (CV) risk in patients with CD with a normal or high body weight at diagnosis. The elevated CV risk in CD was confirmed by population-based studies.\textsuperscript{31–33} The CV risk proved to be higher in CD than in the average population, despite having fewer classic CV risk factors (eg, smoking, obesity, hypercholesterolemia) among patients with CD. The origin of the increased CV risk is only partly explained by the increased inflammatory cytokines, deficiency in folic acid with consequent hyperhomocysteinaemia and apoAI deficiency with a consequently low level of high-density lipoprotein (HDL). Endothelial dysfunction is assumed to be an important contributor.\textsuperscript{25} Studies observed early atherosclerosis, increased arterial stiffness and carotid intima-media thickness,\textsuperscript{16,25} insulin resistance, and an increased homeostatic model assessment (HOMA) index in CD,\textsuperscript{14} compared with the average population. During a GFD, ideally, intestinal absorption and nutrient deficiencies tend to improve (with a favourable increase of the level of HDL), and the inflammation settles so that many metabolic parameters can normalise (the levels of total cholesterol and triglyceride usually rise).\textsuperscript{16,24}

Fatty liver disease, the hepatic manifestation of metabolic syndrome, occurs more frequently in CD.\textsuperscript{23,24} One-third of patients with CD on a GFD can have fatty liver disease, the prevalence is three times higher than that observed in the average population. The difference was more prominent among lean subjects.\textsuperscript{27} The association between CD and fatty liver disease might root in the increased permeability of the intestinal mucosa (‘leaky gut’), causing the malfunction of the gut–liver axis, which is further aggravated by the elevation of FM, that is, the development of obesity. In a study, the prevalence of metabolic syndrome increased from 2% to 30% during a 1-year GFD,\textsuperscript{28} which further enhances the CV risk of patients with CD.

**Study objectives**

Currently, no prospective studies investigating CV risk factors comprehensively among patients with CD are available. Moreover, there is no evidence on how a GFD influences body composition and metabolic parameters relevant to CV risk in CD. Thus, we planned a series of studies to get a comprehensive view of the most important CV risk factors (eg, metabolic parameters, body composition) and their changes during a GFD in Hungarian patients with CD.

1. **Primary objective**
   - To investigate the difference in body composition and CV risk-related metabolic parameters between patients with CD and the average population, and between patients with CD before and after the GFD.

2. **Secondary objective**
   - To find an association between a strict GFD and metabolic parameters and CV risk factor.

**METHODS AND ANALYSIS**

**Design**

This investigation is a series of three multicentre studies, as follows:

1. A case–control study, which compares patients with newly diagnosed CD (group A) with a non-CD control group (group C) regarding body composition and CV risk-related metabolic parameters.

2. A case–control study, which compares patients with CD on a GFD at least 1 year (group B) with a non-CD control group (group C) regarding body composition and CV risk-related metabolic parameters.

3. A prospective cohort study, which investigates how body composition and CV risk-related metabolic parameters change during a 1-year GFD started after diagnosis of CD (group A).

This study does not change the routine management of the subjects included (by the WHO checklist, see table 1). The study protocol was planned in conformity with the Standard Protocol Items: Recommendations for Interventional Trials 2013 Statement.\textsuperscript{29}

**Population and eligibility**

We will include patients with newly diagnosed CD, treated patients with CD and non-CD control subjects. Eligibility criteria will be as follows:

1. **Inclusion criteria (apply to all subjects):**
   - Age should be over 18 years.
   - Blood collection must be indicated with medical conditions.
   - Signed informed consent.

2. **Inclusion criteria (apply to specific cohorts of patients):**
   - Patients with CD: the diagnosis should be set up according to the current guidelines (based on serology and histology in adults or as per the European Society for Paediatric Gastroenterology Hepatology and Nutrition guideline in children)\textsuperscript{30–34}; should be on a gluten-containing diet (group A) or a GFD for at least 1 year with good dietary adherence (group B).
**Table 1** WHO checklist

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<td>03 Aug 2022</td>
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<td>Source(s) of monetary or material support</td>
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<td>Contact for public queries</td>
<td>Zsófia Vereczkei, dietitian, <a href="mailto:vereczkei47@gmail.com">vereczkei47@gmail.com</a></td>
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<tr>
<td>Contact for scientific queries</td>
<td>Judit Bajor, <a href="mailto:bajor.judit@pte.hu">bajor.judit@pte.hu</a></td>
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<td>Health condition(s) or problem(s) studied</td>
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<td>Intervention(s)</td>
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<td>Key inclusion and exclusion criteria</td>
<td>Inclusion criteria: adult patients (≥18 years of age) suffering from newly diagnosed or treated coeliac disease (based on serology, histology, ESPGHAN guideline) and subjects without coeliac disease. Exclusion criteria: any acute disease or acute deterioration of underlying chronic conditions, advanced chronic diseases (including heart, kidney and liver failure), malignant tumours, pregnancy, lactation, refractory coeliac disease</td>
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<td>Date of first enrolment</td>
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<td>Target sample size</td>
<td>1. Case–control study, patients with newly diagnosed coeliac disease vs control subjects: at least 37 subjects/group 2. Case–control study, patients with coeliac disease on gluten-free diet vs control subjects: at least 99 subjects/group 3. Prospective cohort study, patients with coeliac disease at diagnosis vs same patients on a gluten-free diet for at least 1 year: at least 236 patients with coeliac disease</td>
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<td>Primary outcome(s)</td>
<td>Anthropometric parameters</td>
</tr>
<tr>
<td>Key secondary outcomes</td>
<td>Cardiovascular risk-related metabolic parameters</td>
</tr>
</tbody>
</table>

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- Non-CD control subjects (group C): does not match the criteria for CD30–34; should be on a gluten-containing diet.

3. Exclusion criteria (apply to all subjects):
   - Chronic conditions:
     - Estimated glomerular filtration rate calculated with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula is <60 mL/min/1.73 m² (CKD3 or more severe kidney failure).
     - Liver cirrhosis in Child-Pugh class B–C.
     - Heart failure (New York Heart Association III–IV).
     - Active malignant diseases.

- Any acute diseases or acute deterioration of underlying chronic conditions.
- Diseases that may be associated with clinically relevant malabsorption.
- Refractory CD.
- Pregnancy, lactation.
- Patients unable to understand the essentials of the informed consent.
- Lack of consent or withdrawal of consent.

**Flow and timing**

The studies will be multicentre including centres at Pécs, Budapest and Szeged. All participants will be recruited in the outpatient clinics of the participating centres.
consecutively. The places of recruitment will be the Division of Gastroenterology, First Department of Medicine, University of Pécs Medical School; the Department of Surgery, Transplantation and Gastroenterology, Semmelweis University; and the First Department of Internal Medicine, Albert Szent-Györgyi Medical School, University of Szeged. The expected recruiting period is between September 2022 and December 2026.

A multidisciplinary team will be involved to complete the project in the First Department of Medicine and Institute for Translational Medicine, University of Pécs, as well as in the collaborating centres. Parameters of interest will be assessed only once in the case-control study and twice in the cohort study. Table 2 shows the schedule for the study.

Body composition will be analysed with the InBody 770 device at the Institute for Translational Medicine, University of Pécs Medical School and with the same device at different Hungarian university centres. Laboratory measurements will be managed by the personnel of the Department of Laboratory Medicine, University of Pécs and the corresponding departments of the other sites. Special measurements (ghrelin, adiponectin, leptin, galectin-3, homocysteine) will be performed exclusively in the Department of Laboratory Medicine and in the Institute for Translational Medicine, University of Pécs. Coeliac-specific autoantibodies (tissue transglutaminase (tTG) IgG/A and endomysium IgA autoantibody levels (EMA)) will be detected at the Department of Immunology and Biotechnology, University of Pécs and the corresponding departments of the other sites. Frozen samples will be transferred from remote sites and stored in the Biobank of the Institute for Translational Medicine until processing.

Participants will be supplied with an information sheet and must provide written consent before sampling. Informed consent will be collected by a medical doctor. Withdrawal from the study will be allowed for any reason at any time. Information sheets and consent forms will be accessible at https://tm-centre.org. Patients can contact the research coordinator at any time and ask further questions. Participation in the study is completely voluntary.

All patients will receive the results of their laboratory tests and dietary evaluation in written form. In case of

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### Table 2 Schedule for the study

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<thead>
<tr>
<th>Time point</th>
<th>Screening</th>
<th>Allocation</th>
<th>Interventions</th>
<th>Close-out</th>
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<td>Enrolment period</td>
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<td>Within 1 month</td>
<td>After 12 months</td>
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<tr>
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<tr>
<td>Allocation</td>
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<tr>
<td>Interventions</td>
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<tr>
<td>Anthropometric measurements</td>
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<tr>
<td>Interview and questionnaires</td>
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<td>Transabdominal ultrasonography</td>
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<td>Handgrip strength assessment</td>
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<td>Blood collection</td>
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<td>Urine collection (group B)</td>
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<td>Body composition analysis</td>
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<td>Disease activity (groups A and B)</td>
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<td>Medical history and medication</td>
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<td>Quality of life and symptom scores</td>
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<td>Dietary adherence (group B)</td>
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<tr>
<td>Blood analysis</td>
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<tr>
<td>Urine analysis (group B)</td>
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Group A: patients with newly diagnosed CD; group B: patients with CD on GFD at least 1 year; group C: non-CD control group. CD, coeliac disease; GFD, gluten-free diet; NAFLD-LFS, non-alcoholic fatty liver disease-liver fat score.
 alarming findings, patients will be referred to their general practitioners or a specialist for further management.

**Measurements**

Structured questionnaire will be used by the patient’s physician to record medical data (medical history including comorbidities, physical status and medication). Regular medications will be recorded at study entry and at study closure (administered by a person with a medical degree).

CD-related symptoms will be assessed by the Coeliac Symptom Index and a CD-specific quality of life questionnaire will be also used (Coeliac Disease Quality of Life) to get a comprehensive picture about the health condition of patients with CD (administered by a person with a medical degree).35 36

Disease activity will be estimated by tTG levels (determined by the gastroenterologist enrolling the patient). tTG IgA and IgG levels will be measured with high-quality commercial test (Orgentec Diagnostika, Mainz, Germany). IgA and IgG antibodies as well as total IgA are determined simultaneously.

CV risk assessment will be performed by the European Society of Cardiology Systematic Coronary Risk Evaluation 2 chart (administered by a person with a medical degree) and by measuring blood pressure, waist circumference (administered by a health worker) and laboratory parameters (details in diagnostic and research laboratory tests).37 38

From anthropometric parameters, body height will be measured with a stadiometer. Body weight and body composition will be estimated with bioelectrical impedance analysis using the InBody 770 device (administered by a health worker). Sarcopenia will be assessed based on body composition and handgrip strength via handgrip dynamometer (administered by a health worker).

Transabdominal ultrasonography will be used to assess the extent of fatty liver disease (based on non-alcoholic fatty liver disease-liver fat score, with a score range of 0–3; scores will be determined by a radiologist).

Dietary adherence of patients with CD will be determined by (1) dietary interview provided by an expert dietician, (2) the Coeliac Disease Adherence Test (CDAT), (3) coeliac-specific antibodies (tTG and EMA) and (4) urine gluten immunogenic peptides (GIP) measurement.39

The composition of a GFD will be evaluated with the indicator of adherence to the Mediterranean diet, the Mediterranean Diet Score (administered by a dietician).40

Routine laboratory measurements will be managed by laboratories of the three centres from venous blood. Blood samples for research will be collected in plastic tube for a total of 10 mL blood from each individual and centrifuged at 1500 g for 10 min after clotting. Midstream urine (at least 100 mL) will be collected in sterile urine sample containers. Serum and urine samples will be deep frozen at −80°C immediately after sampling and stored at this temperature until transfer. These samples will be transferred on dry ice to the Biobank at the Institute for Translational Medicine, University of Pécs Medical School, where samples will be stored at −80°C until utilisation. After preparation, urine GIP detection will be performed with Biomedical (Spain) products.

We will perform:

- Diagnostic laboratory tests: triglyceride, cholesterol (total, HDL and low-density lipoproteins), fasting glucose, fasting insulin, haemoglobin Alc, HOMA index, bilirubin, uric acid, urea, creatinine, sodium, potassium, calcium, vitamin D, vitamin B12, folic acid, iron, ferritin, transferrin, transferrin saturation, international normalised ratio, aspartate aminotransferase, alanine aminotransferase, fibrosis-4 index, total protein, albumin, immunoglobulins, high-sensitivity C reactive protein, fibrinogen, blood counts, coeliac-specific antibodies (tTG IgA/IgG, EMA IgA).

- Research laboratory parameters: homocysteine, interleukin 6, leptin, ghrelin, adiponectin, galectin-3, GIP.

**Outcomes**

1. Primary outcomes

- Anthropometric parameters (body height, results of body composition analysis: body weight, BMI, FM, per cent body fat (FM%), skeletal muscle mass, visceral fat area, total body water).

2. Secondary outcomes

- CV risk-related metabolic parameters (diagnostic and research laboratory tests (see the Measurements section), waist circumference, blood pressure, fatty liver disease (liver function tests, liver steatosis rate), disease activity, CV risk assessment, CD-related symptoms, sarcopenia, diet composition, dietary adherence (dietary interview, CDAT) and CD-specific quality of life).

**Target number of patients**

The chosen endpoint for sample size calculation was FM%. The estimated sample size was calculated for α=0.05, β=0.90, assuming normal distribution of data:

1. Case–control study, patients with newly diagnosed CD versus non-CD control subjects (no dropouts, 1:1 case–control ratio, independent sample t-test): at least 37 subjects/group (based on the paper of Capristo et al47).

2. Case–control study, patients with CD on GFD versus non-CD control subjects (no dropouts, 1:1 case–control ratio, independent sample t-test): at least 99 subjects/group (based on the paper of Nunes-Silva et al48).

3. Prospective cohort study, patients with CD at diagnosis versus the same patients on a GFD for at least 1 year (10% dropout rate, no interim analysis, paired t-test): at least 236 patients with CD (based on the paper of Newnham et al49).

**Patient and public involvement**

Before starting recruitment, randomly selected patients with CD reviewed the questionnaires and the information sheet to facilitate participants’ better understanding.
Blinding

Blinding in the study is presented in table 3.

Data management

A subject identification (ID) number will be provided consecutively to every patient after inclusion. ID numbers with sensitive data on patients (including the name, insurance number and date of enrolment) will be stored in a locked file separately from other data. De-identified data will be added to the source documentation stored in locked cabinets. Source documentation will be entered in an electronic case report file (e-CRF). The principal investigators will ensure that the collected data in an e-CRF are precise, complete and reliable (range checks for data values). The e-CRFs will be stored on a secure server at the Institute for Translational Medicine, University of Pécs Medical School. Access to data will be restricted through a password system to personnel involved in data management. A three-level data check will be continuously performed, and final data will be finally approved by the principal investigators to ensure data quality. To provide precise data collection, administrative and medical staff members will be invited to participate in training sessions to familiarise them with the study requirements, standardised data recording and biological specimen collection.

The de-identified dataset will be delivered for the purpose of sharing on request.

Statistical analysis

Data will be curated and analysed with IBM-SPSS Statistics 28 and R statistical language. We will perform descriptive analysis. For continuous variables, mean and SD or median and IQR will be computed, depending on the distribution of the data. For categorical variables, we will calculate proportions. In analysis, we will use one-sample and two-sample t-tests or Wilcoxon and Mann-Whitney tests, depending on the distribution of the data. Besides, univariable and multivariable regression models, \( X^2 \) and Fisher’s tests will be used. In the longitudinal study, we will use the general linear mixed model, in which the random effect will be defined by the subject IDs. In the assessment of the questionnaires, rank correlation will be used. Threshold for statistical significance will be defined as \( p<0.05 \). If the amount of data will allow us to do so, we will set up subgroups by CV risk in the substudies to assess within-group associations across anthropometric parameters.

Biobank storage and accessory research

After laboratory analysis, urine and blood (serum and plasma, at least 1 mL each) residues will be stored in the Institute for Translational Medicine Biobank at −80°C and labelled with the subject ID number, thus samples will be absolutely de-identified.

The check-up results (after 1-year GFD) of patients included in group A will be used in group B (if the diet was properly followed), since they will already suit to its inclusion criteria. Patients with CD will be offered an opportunity to participate in the ‘Monitoring the prevalence, symptoms, complications and family history of CD and the effect of a GFD—Coeliac registry’ research project (approved by the Scientific and Research Ethics Committee of the Medical Research Council, ref. no. 45098-2/2016/EKU). We are also planning a randomised controlled trial to investigate how a structured, 1-year-long, Mediterranean diet-based, repeated dietetic intervention influences body composition and CV risk-related metabolic parameters in patients with CD. Participation in this project will be offered to patients in group B.

Protocol amendments and disseminating policy

This protocol is the first version completed on 27 September 2022. The trial has been registered at ClinicalTrials.gov (NCT05530070). Amendments will be published under this registration number. If required, the online version at ClinicalTrials.gov will be updated. The study will be performed in accordance with the Declaration of Helsinki, the principles of local legal and regulatory requirements. The trial status is recruiting; recruitment began on 1 September 2022. The expected date of completion is 31 December 2026.
DISCUSSION

Current coeliac guidelines do not give recommendations on CV risk assessment and prevention of metabolic diseases.30–34 Our investigation examines the most important CV risk factors (eg, metabolic parameters, body composition) and their changes in CD. This series of studies allows us to assess body composition and CV risk-related metabolic parameters of newly diagnosed CD in their complexity and to test if they change during therapy. Findings will help to identify which parameters are beneficial to optimise and reasses during follow-up in CD as well as will provide new data on the pathomechanism of elevated CV risk in CD (eg, on the role of enteral media tors). Furthermore, with this study, we aim to draw attention to the new challenge in the management of patients with CD who are obese and have metabolic syndrome and are at high CV risk, therefore requiring special care. Detailed risk assessment, monitoring body composition and metabolic parameters, and elimination of modifiable risk factors are expected to improve the quality of life, morbidity and mortality of patients with CD.

A limitation of our study is that we will not investigate hard CV outcomes (such as overall or CV-specific mortality). Such investigations would require longer follow-up and much greater study population or patients with higher CV risk, compared with our general population of patients with CD.

ETHICS AND DISSEMINATION

Findings are planned to be published in English-language journals with Q1/D1 prestige factor and high impact factor. Also, they will be presented at Hungarian and international congresses and be incorporated into Hungarian guidelines on CD. We will adhere to authorship criteria for manuscripts submitted for publication set by the International Committee of Medical Journal Editors.

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Contributors All authors were involved in the study design and edited the manuscript. JB is the principal investigator; ZV, MI, ZS, BK, BS and JB conceptualised the study, and drafted and revised this manuscript. NF and ZS performed the sample size calculation and planned the statistical analyses. JB, VP and ZL provided us with special expertise in the management of coeliac disease.

BS is performing the laboratory measurements and biochemical analyses, and interpreting the results. TB provided us with special expertise in immunological measurements. ZV and MB planned the anthropometric and body composition measurements. MB also provided us with special expertise in metabolic measurements. ZV also planned and is carrying out the dietary assessment of the patients with coeliac disease. TH provided us with special expertise in cardiology. BK is responsible for data management and administrative coordination. PH, TH and JB have given significant intellectual input and supervised the work. All the authors have read and approved the final manuscript.

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