

BMJ Open Influence of a structured, 1-year-long dietary intervention regarding body composition and cardiovascular risk (ARCTIC) in coeliac disease: a protocol of a multicentre randomised controlled trial

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ABSTRACT

Introduction Coeliac disease (CD) affects 1% of the population worldwide. The only available evidence-based treatment is a strict gluten-free diet (GFD), which can readily lead to weight gain and unfavourable metabolic changes (eg, dyslipidaemia, fatty liver disease and insulin resistance) if followed without adequate dietary control. That can lead to increased cardiovascular risk (CV). We planned a randomised controlled trial to test the effect of a group-based, structured, 1-year, advanced dietary education, per the proposal of a Mediterranean diet vs standard of care, regarding the most relevant CV risk factors (eg, metabolic parameters and body composition) in CD patients.

Methods and analysis Randomisation will occur after the baseline dietary education and interview in a 1:1 allocation ratio. Outcomes include anthropometric parameters (body composition analysis including weight, Body Mass Index, fat mass, per cent body fat, skeletal muscle mass, visceral fat area and total body water) and CV risk-related metabolic parameters (eg, lipid profile, homocysteine, fasting glucose, haemoglobin A1c, Homeostatic Model Assessment Index, metabolic hormones, waist circumference, blood pressure, liver function tests, liver steatosis rate and diet composition). In this study, we aim to draw attention to a new aspect regarding managing CD: dietary education can lead to a better quality of the GFD, thereby reducing the risk of potential metabolic and CV complications.

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 disorder affecting approximately 1%

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ The main strength of our study is the first-time provision of high-quality evidence regarding the effectiveness of a 1-year extended, group-based, structured dietary education vs standard of care on body composition and cardiovascular risk-related parameters among adult coeliac disease patients.
- ⇒ We investigate specific body composition-related metabolic markers (interleukin-6, leptin, ghrelin and adiponectin).
- ⇒ This study's challenge is sustaining the patients' motivation to minimise drop-outs during the long study period.

of the population, for which the only available treatment is a lifelong strict gluten-free diet (GFD). Once adjusted to a well-managed diet, symptoms often disappear, the intestinal mucosa regenerates, CD-specific antibodies normalise and deficiency states resolve. Furthermore, the patients' body weight and Body Mass Index (BMI) increase with GFD.^{1 2} There is a complex reason for this: as absorption improves, the nutrients are better utilised, but the hyperphagia, which is often characteristic, does not always disappear.³ Unfortunately, the quality of the GFD is unbalanced and generally does not meet the requirements of a healthy diet: the GFD is high in simple carbohydrates, fat, saturated fatty acids, meat and processed meat products and low in complex carbohydrates and fibres.⁴⁻⁷ According to a meta-analysis, GFD appears to increase body weight and per cent body fat (FM%) only in patients with CD,

while this effect was not observed in individuals without CD following a GFD.⁸

Weight gain is desirable among the underweight; however, there is an increasing number of CD patients with normal or high body weight on diagnosis. Another problem is that weight gain is mainly due to an increase in body fat mass (FM) rather than fat-free mass (FFM), leading to an unfavourable change in body composition.⁹ The trend seen in the increasing proportion of obese individuals worldwide is also appearing among CD patients.² The burden of metabolic and cardiovascular (CV) complications of obesity is expected to increase in the long term. Recent investigations suggest that individuals with CD, compared with the general population, may be at a higher risk of CV diseases. Moreover, CV risk has been reported to be higher in CD, although generally, these patients expressed fewer classical CV risk factors (eg, smoking, obesity and hypercholesterinaemia).^{10 11} In 2015, two systematic reviews and meta-analyses examined the association between CD and CV disease. Both studies suggested that CD was associated with a slightly increased risk of CV disease; however, data were heterogeneous, and the evidence strength had limitations.^{12 13}

Potter *et al* studied the impact of the GFD on CV risk factors, reporting a significant increase in total cholesterol, high-density lipoprotein (HDL) cholesterol, fasting glucose level and BMI; whereas, low-density lipoprotein (LDL) cholesterol, triglycerides and blood pressure were not significantly changed.¹⁴ A meta-analysis examined changes in BMI and lipid parameters during GFD in CD patients. The results showed a statistically significant increase in BMI and HDL cholesterol during GFD; however total cholesterol and triglyceride were not changed significantly.¹⁵

Ciccione *et al* evaluated the metabolic changes that occur along a GFD in CD patients. The prevalence of metabolic syndrome and steatosis hepatitis had significantly increased in patients with CD keeping a GFD.¹⁶ A similar conclusion was drawn by Tortora *et al* where newly diagnosed CD patients were studied at the diagnosis and 1 year after starting GFD: the prevalence of metabolic syndrome increased from an initial 2% to 29.5% after 12 months of GFD.¹⁷ A recent meta-analysis of 11 studies found a high prevalence of fatty liver disease and metabolic syndrome in patients with CD (18.2% and 4.3%), which was further worsened by GFD (to 28.2% and 21.3%).¹⁸

There is epidemiologic evidence that the Mediterranean diet is most suitable for reducing the risk of CV disease, both in primary and secondary prevention.^{19 20} A questionnaire survey showed that adherence to the Mediterranean diet among individuals with a longstanding GFD is far worse than that of the general population, as they consume more processed meat products, potatoes and less fruit.¹⁹ Insufficient dietary care leads to poor compliance and long-term adverse effects of an unbalanced diet. Most dietary counselling focuses only on strict adherence to the GFD while hardly emphasising the importance of a healthy, balanced diet and the

disadvantages of gluten-free products. The ideal GFD is based on the pyramid of the GFD-Mediterranean diet: plenty of vegetables, fruits and pseudograin products. Additionally, consuming processed meat, gluten-free products and desserts should be reduced.^{20 21} The Mediterranean diet generally seems suitable for preventing obesity during a GFD.

A study in 2020 confirmed that dietary adherence and the quality of the GFD could significantly be enhanced through dietary counselling. Following a dietary intervention, adherence to the Mediterranean diet considerably increased, while the prevalence of obesity and the FM reduced and the FFM increased.²²

The forms of education go together with different levels of effectiveness. Online dietary intervention has also been proven to be effective: it has led to a significant improvement in dietary adherence and diet-related knowledge.²³ Online programmes have many advantages in our digital world—especially in the shadow of the COVID-19 pandemic. They are convenient for users, offer flexibility and reduce costs.²⁴ In addition to providing detailed information, the advantages of a group-based dietary and lifestyle education include the ability for group members to exchange information, ask questions and generally demonstrate an increase in self-motivation.^{25 26} Group education focusing on healthy eating improves the quality of patients' diet and nutritional status.²² Dietary education can even be integrated using digital platforms.²⁷ No randomised controlled trials (RCT) are available to compare a repeated dietary intervention with basic dietary counselling and comprehensively investigate CV risk factors among CD patients.

Study objectives

1. Primary objective

- To investigate the effect of a structured, 1-year, repeated, group-based dietary intervention regarding body composition, compared to standard of care (primary dietary education), among Hungarian CD patients.

2. Secondary objective

- To examine the association between dietary intervention and CV risk-related metabolic parameters (lipid profile, homocysteine, fasting glucose, haemoglobin (Hb) A1c, Homeostatic Model Assessment Index, metabolic hormones, waist circumference, blood pressure, sarcopenia, liver function tests, liver steatosis rate, diet composition), disease activity, CD-related symptoms, diet composition, dietary adherence (dietary interview, Coeliac Disease Adherence Test (CDAT)) and CD-specific quality of life.

METHODS AND ANALYSIS

Study design and setting

The study will be a multicentre RCT, including study sites at Pécs, Budapest and Szeged (involving three Hungarian university clinics). Sites will be provided with clinical trial infrastructure and skilled staff. All

participants will be recruited consecutively in the outpatient clinics of the participating centres. The locations of recruitment will be the Division of Gastroenterology, First Department of Medicine, Medical School, University of Pécs (Pécs, Hungary); the Department of Surgery, Transplantation and Gastroenterology, Faculty of Medicine, Semmelweis University (Budapest, Hungary); and the First Department of Internal Medicine, Albert Szent-Györgyi Medical School, University of Szeged (Szeged, Hungary). The expected recruitment period is from September 2022 to December 2026.

Participants will be randomly assigned in a 1:1 ratio to one of the two study arms ('standard of care' and 'dietary intervention'). This RCT recruits patients from other substudies of the ARCTIC study. The protocol of the observational studies has already been published.²⁸ The newly diagnosed CD patients in the case-control study (Group A) following 1 year of strict GFD and CD patients who have been on a GFD for at least 1 year from the other case-control study (Group B) can be recruited to this RCT. Screening can be repeated if the patient can potentially become eligible for the study in both cases.

The study protocol was planned in conformity with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 Statement.²⁹ For the WHO checklist, see [table 1](#).

Eligibility criteria

CD patients on GFD will be recruited with the following eligibility criteria:

A. Inclusion criteria:

- ▶ Age 18 years or older.
- ▶ Blood collection must be indicated with medical conditions.
- ▶ Signed informed consent.
- ▶ The diagnosis must be set up according to the current guidelines (based on serology and histology among adults or as per the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) guideline in children).^{30 31}
- ▶ Patients will be on a strict GFD for at least 1 year. Dietary adherence will be confirmed with CD-specific serology (normal level of serum antibodies), with urine gluten immunogenic peptides (GIP) (negative urine test), and with a dietary interview (convincing knowledge regarding the GFD and positive attitude towards strict adherence).
- ▶ Suboptimal adherence to the Mediterranean diet (patients with ≤ 8 Mediterranean Diet Score (MDS)).
- ▶ Patients must have internet access and be capable of attending the online sessions for 1 year.

C. Exclusion criteria:

- ▶ Chronic conditions:
- ▶ The estimated glomerular filtration rate was calculated using the Chronic Kidney Disease Epidemiology

Table 1 WHO checklist

Data category	Information
Primary registry and trial identifying number	NCT05530070
Date of registration in primary registry	03/08/2022
Secondary identifying numbers	None
Source(s) of monetary or material support	National Research, Development, and Innovation Office (grant FK 142942 to JB) National Research, Development, and Innovation Fund (grant ÚNKP-23-3-II-PTE-1855 to ZV) University of Pécs Medical School
Primary sponsor	None
Secondary sponsor(s)	None
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Public title	Influence of a structured, 1-year-long dietary intervention on body composition and cardiovascular risk (ARCTIC) in coeliac disease: a protocol of a multicentre randomised controlled trial
Scientific title	Influence of a structured, 1-year-long dietary intervention on body composition and cardiovascular risk (ARCTIC) in coeliac disease: a protocol of a multicentre randomised controlled trial
Countries of recruitment	Hungary
Health condition(s) or problem(s) studied	Coeliac disease
Intervention(s)	Dietary intervention (structured, group-based dietary counselling) vs standard of care (baseline dietary education)
Key inclusion and exclusion criteria	Inclusion criteria: adult patients (≥ 18 years of age) with treated coeliac disease (based on serology, histology, ESPGHAN guideline) following a strict gluten-free diet for at least 1 year 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 or refractory coeliac disease. Poor dietary compliance
Study type	Randomised controlled trial
Date of first enrolment	28/09/2022

Continued

Table 1 Continued

Data category	Information
Target sample size	Dietary intervention vs standard of care: 95 coeliac patients/group
Recruitment status	Recruiting
Primary outcome(s)	Per cent body fat
Key secondary outcomes	Anthropometric parameters, cardiovascular risk-related metabolic parameters, Mediterranean diet adherence
ESPGHAN, European Society for Paediatric Gastroenterology Hepatology and Nutrition.	

Collaboration (CKD-EPI) formula is $<60 \text{ mL/min/1.73 m}^2$ (CKD3 or more severe kidney failure).

- ▶ Liver cirrhosis in Child-Pugh B–C category.
- ▶ Heart failure (New York Heart Association (NYHA) III–IV).
- ▶ Active malignant diseases.
- ▶ Any acute disease or acute deterioration of underlying chronic conditions.
- ▶ Diseases that may be associated with clinically relevant malabsorption.
- ▶ Refractory CD.
- ▶ Pregnancy, lactation.
- ▶ Patients are unable to understand the essentials of the informed consent.
- ▶ Lack of consent or withdrawal of consent.

Flow and timing

Parameters of interest will be assessed twice: the first, following inclusion, and the second, 1 year following the beginning of the dietary intervention. Table 2 shows the study schedule.

Baseline medical data referring to medical history, comorbidities and current medication will be collected before randomisation. The examinations will be performed as outlined in our previous publication.²⁸

Body composition will be analysed using the InBody 770 device in a standardised manner at all study sites. Laboratory measurements will be managed by the personnel of the Department of Laboratory Medicine, Medical School, University of Pécs; the radiology departments of the sites will carry out transabdominal ultrasonography. Special laboratory measurements (regarding ghrelin, adiponectin, leptin, galectin-3 and homocysteine levels) will be performed exclusively in the Department of Laboratory Medicine and the Institute for Translational Medicine, Medical School, University of Pécs. CD-specific antibodies (tissue transglutaminase (tTG) IgG/A and endomysium IgA autoantibody levels (EMA)) will be measured at the Department of Immunology and Biotechnology, Medical School, 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 further processing.

Participants will be furnished with information and assured of the opportunity to discuss any concerns. They

Table 2 Schedule for the study

Timepoint	Screening	Allocation	Counsels 1–6	Close-out
	Enrolment period	Day 0	Months 1–5, 9	After 12 months
Group	A, B	A, B	B	A, B
Enrolment				
Eligibility screening	x			
Informed consent	x			
Allocation		x		
Intervention				
Dietary consultation			x	
Assessments				
Disease activity	x			x
Interview and questionnaires	x			x
Dietary adherence	x			x
Anthropometric measurements		x		x
Cardiovascular risk estimation		x		x
Transabdominal ultrasonography		x		x
Handgrip strength assessment		x		x
Blood analysis	x			x
Urine analysis	x			x
Group A, 'standard of care' arm; Group B, 'dietary intervention' arm.				

must provide written consent prior to the enrolment in the study (online supplemental material). A medical doctor will collect informed consent. Participants are free to exit the study at any time. Information sheets and consent forms will be accessible at <https://tm-centre.org>. Patients can contact the research coordinator for any further questions. Participation in the study is entirely voluntary.

All patients will receive the printed results of laboratory tests and dietary evaluation. In the case of alarming findings, the treating physician will be contacted.

Intervention

Participants will be randomly assigned in a 1:1 ratio to dietary interventions, as follows:

1. A 'standard of care' arm in which patients will receive only baseline individual dietary education as a part of the standard of care.
2. A 'dietary intervention' arm in which groups containing 6–10 CD patients will be formed, and group-based consultations will be delivered. 1-hour/occasion consultations will occur using an online platform (via the Zoom application). The intervention will include 6 sessions in the 1-year study period (once a month in the first 5 months and one more time in the 9th month following randomisation). Expert study dietitians will conduct these consultations and will ensure interactive learning with group discussion. These meetings allow the group members to ask questions and share experiences. The dietitians prepared educational modules optimised for panel discussions consisting of clinicians. The content is based on evidence-based guidelines and dietary recommendations.³² Table 3 provides a summary of the content of each module.

Both groups will be advised to stay active with regular physical activity and to avoid a sedentary lifestyle. No study-related counselling will be given regarding physical activity.

Strategies have been developed to improve adherence to the interventions. Participation is supported through an optimal programme schedule and the possibility of

interacting with experts and other participants. The use of online mediums offers convenience to participants. We provide participants with the flexibility to personalise the sequence of the modules. Productivity is addressed through realistic goal setting and precise action planning. Motivation is supported by sparking interest in the pursuit of a healthy lifestyle.

Participants will be encouraged to engage in all modules actively; however, we consider the programme completed if the participant has taken part in 5 out of 6 modules (the content of the missing module will be sent by e-mail to the patient). During the study, participants will receive regular e-mail reminders and phone calls regarding the programme's schedule.

Participants are asked not to change their medication regimen during the study period unless it is indispensable.

Assessments

The patient's physician will use a structured questionnaire to record medical data (medical history including comorbidities, physical status and current medication). The assessment and the outcomes are similar to our observational studies.²⁸

CD-related symptoms will be assessed by the Coeliac Symptom Index (CSI) and a CD-specific. A quality of life questionnaire will also be used (Coeliac Disease Quality of Life (CD-QoL)) (by a team member with a medical degree).³³ TTG IgA and IgG levels will be measured using a commercial test (Orgentec Diagnostika GmbH, Mainz, Germany). IgA and IgG antibodies and total IgA will be evaluated simultaneously.

A CV risk assessment will be performed using the European Society of Cardiology Systematic Coronary Evaluation 2 (ESC SCORE2) chart (by a team member with a medical degree) and by measuring blood pressure and waist circumference (by a healthcare practitioner) and laboratory parameters.³⁴

Regarding anthropometric parameters, body height will be measured using a stadiometer. Body weight and body composition will be estimated with bioelectrical

Table 3 Modules of the dietary intervention

Module	Content
1. Basics of Mediterranean diet	Mediterranean GFD. Role of antioxidants and unsaturated fatty acids. Alcohol consumption.
2. Balanced GFD, role of fibres	Disadvantages of an unbalanced GFD. Naturally gluten-free products. Safe fibre consumption in GFD. Role of oats and pseudocereals.
3. Weight management	Weight management, optimal weight and body composition. Prevention of osteoporosis.
4. Special diets in CD	Fad diets in CD. Alternative diets (vegetarian, vegan) are available on CD.
5. Dietary supplements, microbiome	Dietary supplementation, vitamins and minerals. Restoration of the microbiome. Natural sources of prebiotics and probiotics.
6. Follow-up	Revision of the knowledge, problems and sharing the experiences.
CD, coeliac disease; GFD, gluten-free diet.	

impedance analysis using the InBody 770 device (by a healthcare practitioner).

Sarcopenia will be assessed using body composition parameters and handgrip strength via handgrip dynamometer (by a healthcare practitioner).

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) (a radiologist will determine scores).

Dietary adherence of CD patients will be determined by (1) a dietary interview provided by an expert dietitian with the CDAT, (2) coeliac-specific antibodies (tTG and EMA) and (3) urine GIP measurement.³⁵ The composition of a GFD will be evaluated using the MDS as an indicator of adherence to the Mediterranean diet (by a dietitian).³⁶

Routine laboratory measurements will be conducted by the laboratories of the study sites using venous blood. Blood samples for research will be collected in plastic tubes 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 undergo deep freezing at -80°C immediately following 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, Medical School, University of Pécs where samples will be stored at -80°C until processing. Following preparation, urine GIP detection will be performed with Biomedal (Spain) products.

The following tests will be performed:

- Diagnostic laboratory tests: triglyceride, cholesterol (total, HDL and LDL), fasting glucose, fasting insulin, HbA1c, Homeostatic Model Assessment Index, bilirubin, uric acid, urea, creatinine, sodium, potassium, total 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 (IgA, IgG, IgM and IgE), high-sensitivity C-reactive protein, fibrinogen, blood count and coeliac-specific antibodies (tTG IgA/IgG, EMA IgA).
- Research laboratory parameters: homocysteine, interleukin-6, leptin, ghrelin, adiponectin, galectin-3 and GIP.

Outcomes

1. Primary outcome (table 4).

- FM%.

2. Secondary outcomes (table 5).

- Anthropometric parameters (body height, results of body composition analysis: body weight, BMI, FM, skeletal muscle mass, visceral fat area and total body water); CV risk-related metabolic parameters (diagnostic and research laboratory tests (see section ‘Assessments’), waist circumference, blood pressure, fatty liver disease (liver function tests, liver steatosis rate), disease activity, CV risk assessment, CD-related symptoms, sarcopenia, diet composition (MDS), dietary adherence (dietary interview, CDAT) and CD-specific quality of life).

Sample size estimation

The planned sample size has been calculated to ensure adequate statistical power. The chosen endpoint for sample size calculation was FM%. The estimated sample size was calculated for $\alpha=0.05$, $\beta=0.90$, assuming normal distribution of data (10% drop-out rate, no interim analysis, assuming 5% point difference change between groups, calculated with the highest standard deviation (SD) identified from the papers listed above): at least 95 coeliac patients/group (based on papers of Capristo *et al*, Nunes-Silva *et al*, Newnham *et al*).^{37 37 38 38 39 39}

Randomization and allocation concealment

Central randomisation will be done following the enrolment in a 1:1 allocation ratio with a randomly permuted block size using a computer-generated random sequence. Inclusion and exclusion criteria will be rechecked before computer-aided randomisation to ensure that only eligible patients are included in the trial. A team member who did not screen and consent the study subject will perform the randomisation procedure.

Patient and public involvement

Prior to initiating recruitment, three randomly selected CD patients reviewed the questionnaires. The education topics were discussed with the local organisation among coeliac patients before the trial registration. The method and timing of the education were discussed with the national organisation following the protocol registration, accomplishing the required corrections.

Blinding

Blinding in the study is presented in table 6.

Accessory research

CD patients will be offered an opportunity to participate in the observational part of our study and 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

Table 4 Primary outcome measure

Outcome measure	Measure description	Time frame
Per cent body fat	Per cent body fat in percentage measured by an InBody 770 body composition analyser.	1 year

Table 5 Secondary outcome measures

Outcome measure	Measure description	Time frame
Body height	Height in centimetres measured by a stadiometer.	1 year
Body weight	Weight in kilogrammes measured by an InBody 770 body composition analyser.	
Body Mass Index	BMI in kg/m ² calculated by an InBody 770 body composition analyser.	
Body fat mass	Body fat mass in kilogrammes measured by an InBody 770 body composition analyser.	
Skeletal muscle mass	Skeletal muscle mass in kilogrammes measured by an InBody 770 body composition analyser.	
Visceral fat area	Visceral fat area in cm ² measured by an InBody 770 body composition analyser.	
Total body water	Total body water in litres measured by an InBody 770 body composition analyser.	
Waist circumference	Cardiovascular risk assessment will be performed by measuring waist circumference in centimetres.	
Blood pressure	Cardiovascular risk assessment will be performed by measuring blood pressure in mm Hg.	
Fatty liver disease	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).	
Cardiovascular risk assessment	Cardiovascular risk assessment will be performed by the Systematic Coronary Risk Evaluation chart.	
CD-related symptoms	CD-related symptoms will be assessed by the Coeliac Symptom Index.	
CD-specific quality of life	CD-specific quality of life questionnaire will be also used (Coeliac Disease Quality of Life).	
Disease activity	Disease activity will be estimated by tissue transglutaminase levels.	
Sarcopenia	Sarcopenia will be assessed based on body composition and handgrip strength via handgrip dynamometer.	
Dietary interview	Dietary adherence will be determined by dietary interview provided by an expert dietitian.	
Diet composition	The composition of a GFD will be evaluated with the indicator of adherence to the Mediterranean diet, the Mediterranean Diet Score.	
Coeliac Disease Adherence Test	Dietary adherence will be determined by the Coeliac Disease Adherence Test.	
Urine gluten immunogenic peptide	Dietary adherence will be determined by urine gluten immunogenic peptide measurement.	
Coeliac-specific antibodies	Dietary adherence will be determined by coeliac-specific antibodies (tissue transglutaminase IgA/IgG and endomysium antibody level IgA) in U/mL.	
Triglyceride level	Triglyceride level in mmol/L.	
Cholesterol level	Cholesterol (total, HDL and LDL lipoproteins) level in mmol/L.	
Fasting glucose level	Fasting glucose level in mmol/L.	
Fasting insulin level	Fasting insulin level in mmol/L.	
Haemoglobin A1c level	Haemoglobin A1c level in percentage.	
Homeostasis Model Assessment (HOMA) Index	HOMA Index.	
Bilirubin level	Bilirubin level in µmol/L.	
Uric acid level	Uric acid µmol/L.	
Urea level	Urea level in mmol/L.	
Creatinine level	Creatinine level in µmol/L.	
Sodium level	Sodium level in mmol/L.	
Potassium level	Potassium level in mmol/L.	
Calcium level	Calcium level in mmol/L.	
Vitamin D	Vitamin D level in ng/mL.	
Vitamin B12	Vitamin B12 level in pg/mL.	
Folic acid level	Folic acid level in µg/L.	
Iron level	Iron level in µmol/L.	
Ferritin level	Ferritin level in µg/L.	
Transferrin level	Transferrin level in g/L.	
Transferrin saturation	Transferrin saturation in percentage.	
International Normalised Ratio (INR)	INR.	
Aspartate aminotransferase level	Aspartate aminotransferase level in U/L.	
Alanine aminotransferase level	Alanine aminotransferase in U/L.	
Fibrosis-4 Index	Fibrosis-4 Index for liver fibrosis.	
Total protein level	Total protein level in g/L.	
Albumin level	Albumin level in g/L.	
Immunoglobulins	Immunoglobulins in U/mL.	

Continued

Table 5 Continued

Outcome measure	Measure description	Time frame
High-sensitivity C reactive protein level	High-sensitivity C reactive protein level in mg/L.	
Fibrinogen level	Fibrinogen level in g/L.	
Blood counts	Blood counts in Giga/L.	
Homocysteine level	Homocysteine level in μ mol/L.	
Interleukin-6 level	Interleukin-6 level in ng/L.	
Leptin level	Leptin level in ng/mL.	
Ghrelin level	Ghrelin level in pg/mL.	
Adiponectin level	Adiponectin level in μ g/mL.	
Galectin-3 level	Galectin-3 level in ng/mL.	

Change from baseline will be calculated if possible.
 BMI, Body Mass Index; CD, coeliac disease; GFD, gluten-free diet; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

and Research Ethics Committee of the Medical Research Council, Ref. No. 45098-2/2016/EKU).

Data management

A subject identification (ID) number will be provided consecutively to every patient following inclusion. ID numbers with sensitive data of the 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 and stored in locked cabinets. Source documentation will be entered in an electronic case report file (e-CRF). In the case of withdrawal, personal data will be deleted. The principal investigators will ensure that all collected data in an e-CRF are precise, complete and reliable (range checks for data values). E-CRFs will be stored on a secured research centre computer server. Access to data will be restricted through a password system to personnel involved in data management. The principal investigator will approve the final data to ensure data quality. To provide precise data collection, administrative and medical staff members will be invited to participate in

training sessions to familiarise themselves with the study requirements, standardised data recording and biological specimen collection. The de-identified dataset will be delivered and shared on request.

Statistical analysis

An expert biostatistician will analyse all data, which will be curated and analysed using R statistical language. A descriptive analysis will be performed. In consideration of continuous variables, mean and SD or median and interquartile range (IQR) will be computed, dependent on the distribution of the data. Concerning categorical variables, proportions will be calculated. Through the analysis, the difference in the values from the baseline will be used, and t-tests or corresponding non-parametric tests will be applied. χ^2 or Fisher's tests, Spearman's rank correlation and random effects regression models will be used to analyse connection. The threshold for statistical significance will be defined as $p < 0.05$ and corrected for false discovery rate (FDR method). This study will not include an interim analysis. Subgroup analysis will be performed among diabetic patients. Intention-to-treat

Table 6 Blinding in the study

	Physician enrolling patients	Physician administering questionnaires	Physician performing US	Healthcare practitioner	Dietitian	Laboratory assistant
Group allocation	Blinded	Blinded	Blinded	Blinded	Blinded	Blinded
Disease questionnaires	Blinded	N/A	Blinded	Blinded	Blinded	Blinded
US measurements	Blinded	Blinded	N/A	Blinded	Blinded	Blinded
Anthropometric measurements	Blinded	Blinded	Blinded	N/A	Blinded	Blinded
Dietary interview/questionnaires	Blinded	Blinded	Blinded	Blinded	N/A	Blinded
Dietary intervention	Blinded	Blinded	Blinded	Blinded	N/A	Blinded
Laboratory tests	Blinded	Blinded	Blinded	Blinded	Blinded	N/A

N/A, not applicable; US, ultrasonography.

(all patients randomised) and per-protocol analyses (all patients completing at least 5 modules) are planned to handle protocol non-adherence. Statistical methods to handle missing data are not planned.

Protocol amendments and dissemination policy

This protocol is the first version completed on 10 March 2023. The trial has been registered at clinicaltrials.gov (NCT05530070). Amendments will be published under this registration number. The online version at clinicaltrials.gov was updated on 11 December 2023 following consultation with a Hungarian Coeliac Society representative regarding the timing of the education. The study will be performed in full 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. Patients will be informed of their results via letter.

DISCUSSION

The beneficial effect of improved adherence to the Mediterranean diet in CV prevention has already been demonstrated in patients without CD. The PREDIMED study provided strong evidence that adherence to Mediterranean dietary patterns could help to prevent CV disease.⁴⁰ An inverse association was found between adherence to a Mediterranean diet and obesity indexes in adult subjects at high CV risk.⁴¹ The interim analysis of the ongoing PREDIMED-Plus trial showed that an energy-reduced Mediterranean diet and physical activity significantly reduced total and visceral fat in older adults with overweight or obesity and metabolic syndrome.⁴² In the PREDIMED-Reus study, the Mediterranean diet was effective without calorie restriction in preventing diabetes in patients at high CV risk. The risk reduction occurred without significant changes in body weight or physical activity.⁴³ In the CORDIOPREV trial, the Mediterranean diet was superior to the low-fat diet in preventing major CV events in secondary prevention.⁴⁴

Dietary education is effective in different patient groups to improve Mediterranean diet adherence and promote healthy eating. Nutrition intervention was effective among firefighters in a US study: in the intervention group, the MDS significantly increased.⁴⁵ In the PREDIMED study, a 1-year-long dietary intervention conducted by dietitians successfully improved adherence to a Mediterranean diet in patients with high CV risk.⁴⁶ CD patients have lower adherence to a Mediterranean diet; they consume less vegetables and fish.⁴⁷ This eating habit is especially disadvantageous because of their proven increased CV risk.¹⁰ This highlights the importance of promoting the Mediterranean diet among these patients; furthermore, dietary education and counselling should not only focus on strict GFD.

Current coeliac guidelines do not give recommendations regarding CV risk assessment and prevention of

metabolic diseases. The 2019 European guideline poses a strong recommendation (with moderate evidence) regarding dietary education assessment of nutritional status on diagnosis and highlights the importance of fibre intake yet neglects to advise for follow-up patient care.

CD guidelines should cover nutritional counselling, healthy lifestyle and patient follow-up, encouraging patients and dietitians to participate actively in their development.^{48 49} Moreover, patients should also be informed about the adverse changes that may occur with GFD, the increased CV risk and its prevention, and the importance of an adequate lifestyle.^{2 3 16 50}

The effect of Mediterranean dietary education on body composition and CV risk-related metabolic parameters of CD were never studied. There is no ongoing or completed study on this topic. In this prospective RCT, we aim to test the effect of a group-based, structured, 1-year, advanced dietary education regarding the most crucial CV risk factors (eg, metabolic parameters, body composition) among CD patients. The dietary intervention aims to promote the Mediterranean diet and healthy menu choices to reduce the risk of unfavourable metabolic consequences associated with an unbalanced GFD. Early intervention is essential in cases where CV risk factors are observed among young individuals. The study will ensure contributions to the literature regarding the effectiveness of an online dietary intervention in CD.

We hypothesise that this dietary intervention favourably impacts CD patients' body composition and cardiometabolic parameters. We hope these results will also contribute towards guideline developments.

ETHICS AND DISSEMINATION

The study was approved by the Scientific and Research Ethics Committee of the Hungarian Medical Research Council (27521-5/2022/EÜIG).

The results will be presented at international and Hungarian congresses and published in English-language journals with a Q1/D1 prestige factor. They will also be disseminated on the Hungarian Coeliac Society's website (www.liszterzeken.hu) and periodicals.

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Contributors All authors were involved in the study design and edited the manuscript. JB is the principal investigator. ZV, MZSP, ZS and JB conceptualised the

study and drafted and revised this manuscript. NF and ZS performed the sample size calculation and planned the statistical analyses. ZV, KL, MZSP, ED, SD and SL perform anthropometric and body composition measurements. EM and GP also provided unique expertise in metabolic diseases. NF, KH, GS and GP are performing the ultrasound measurements. ZV, ED, SD and SL have planned and are carrying out the dietary assessment and the dietary intervention of the coeliac patients. JB is responsible for data management and administrative coordination. All the authors have read and approved the final manuscript. JB acted as guarantor.

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