

Celiakija kot izziv za razvoj brezglutenskih živil

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Pregled

- Celiakija kot bolezen in izziv
- Ajda kot hrana za bolnike
- Dobre izkušnje z ajdo
- Slabe izkušnje z ajdinimi proizvodi
- Nove perspektive
- Zaključek



CD – diagnostic criteria ESPGHAN

CLINICAL GUIDELINE

European Society for Pediatric Gastroenterology, Hepatology, and Nutrition Guidelines for the Diagnosis of Coeliac Disease

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ABSTRACT

Objective: Diagnostic criteria for coeliac disease (CD) from the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) were published in 1990. Since then, the autoantigen in CD, tissue transglutaminase, has been identified; the perception of CD has changed from that of a rather uncommon enteropathy to a common multiorgan disease strongly dependent on the haplotypes human leukocyte antigen (HLA)-DQ2 and HLA-DQ8; and CD-specific antibody tests have improved. **Methods:** A panel of 17 experts defined CD and developed new diagnostic

Results: In group 1, the diagnosis of CD is based on symptoms, positive serology, and histology that is consistent with CD. If immunoglobulin A anti-tissue transglutaminase type 2 antibody titers are high (>10 times the upper limit of normal), then the option is to diagnose CD without duodenal biopsies by applying a strict protocol with further laboratory tests. In group 2, the diagnosis of CD is based on positive serology and histology. HLA-DQ2 and HLA-DQ8 testing is valuable because CD is unlikely if both haplotypes are negative.

Conclusions: The aim of the new guidelines was to achieve a high

Celiakija - definicija

- Sistemska avtoimunska bolezen
- Gluten (pšenica, rž, ječmen, oves?)
- Genetska predispozicija (HLA DQ2/DQ8)
- Karakterizirana z:
 - prisotnostjo različnih kliničnih simptomov odvisnih od glutena
 - Prisotnostjo za celiakijo specifičnih protiteles (EMA, t-TG, d-AG)
 - HLA-DQ2 ali DQ8
 - enteropatijo (atrofija resic, hiperplazija kript, povečano št. IEL)

Epidemiologija celiakije danes

1 : 100

Epidemiologija celiakije danes

**Nediagnosticirani:
Diagnosticirani**

5:1 do 13:1

Diagnostične zamude

odrasli >10 let

otroci >2 leti

velike regionalne razlike

Bai J, et al. WGO - OMGE Practice guideline. Celiac disease. World Gastroenterol, 2005; 10: 1-8.

Klinična slika – sistemska bolezen

Splošni-	zaostanek v rasti in zakasnela puberteta maligne bolezni anemija
GIT -	driska, bruhanje, malabsorpcija malnutricija, izguba teže abdominalne bolečine hepatitis
Koža in sluznice-	dermatitis herpetiformis - Duhring aftozni stomatitis, izguba las
Kosti-	osteoporoza, zlomi, artritis okvare sklenine
CŽS -	ataksija, epilepsija, depresija
Srce-	karditis
Reprodukcija -	splavi, neplodnost



Klinična slika

- simptomatska celiakija
 - “tipična” celiakija
 - GIT simptomi in znaki
 - “atipična” celiakija
 - ne - GIT simptomi in znaki
- asimptomatska celiakija



Mičetić-Turk D, et al. ICDS 2011



Dermatitis herpetiformis



Down syndrome

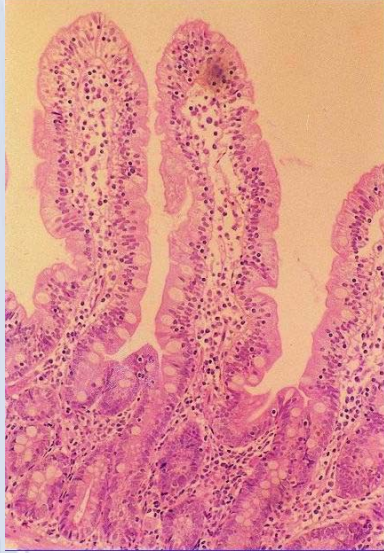


Dental enamel defects

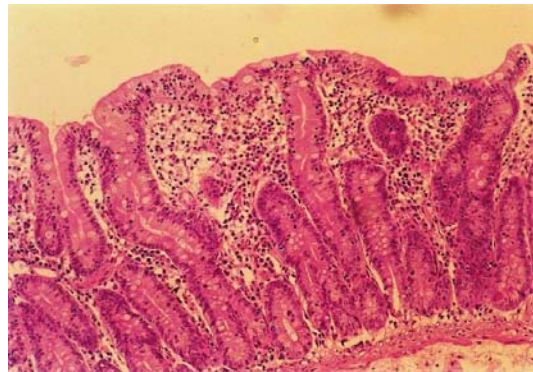
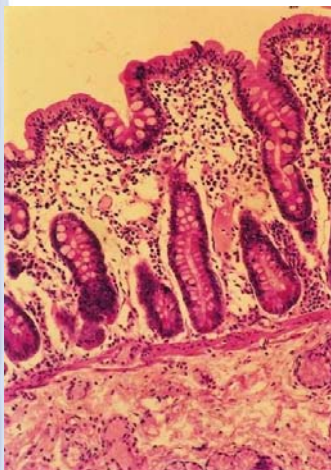


Turner syndrome

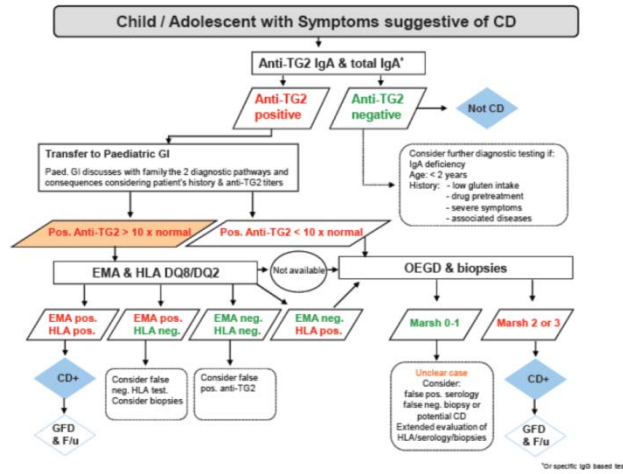
Celiakija – histologija



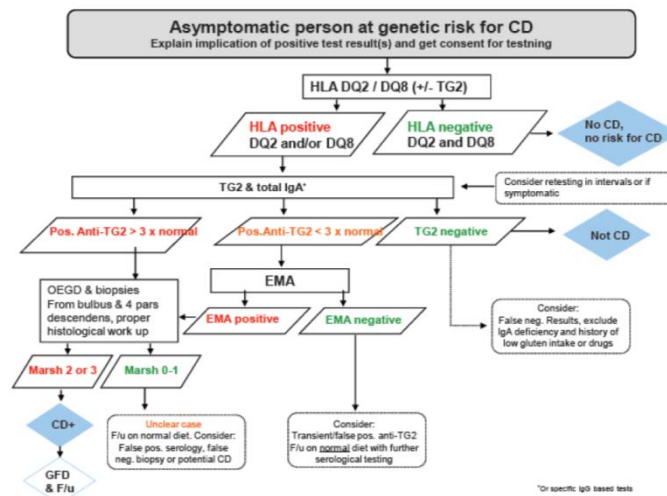
Celiakija – histologija



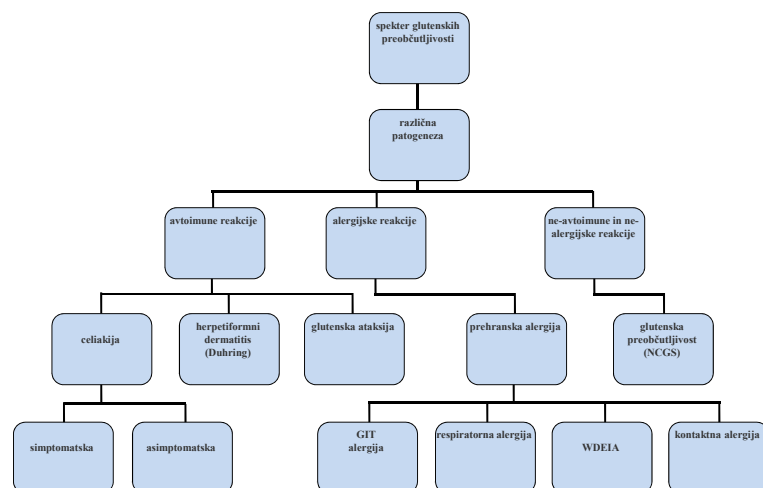
Nova ESPGHAN merila



Nova ESPGHAN merila



Spekter glutenskih preobčutljivosti



WDEIA – z naporom povzročena od pšenice odvisna anafilaksija (*angl.* wheat-dependent exercise induced anaphylaxis)

Zdravljenje

zgodnje odkrivanje

❖ **Doživljenska brezglutenska prehrana !!!**

Novi terapevtski pristopi:

Encimska terapija

Detoksifikacija glutena – genetična modulacija

Imunomodulatorne strategije

Obnova črevesne pregrade



Zdravljenje bolnikov s celiakijo

Potreba po doživljenski brezglutenski prehrani temelji na:

- 1. Poškodba mukozne plasti \rightleftharpoons gluten**
- 2. Histološki relaps brez kliničnega relapsa**
- 3. Zaščitni učinek pred razvojem malignosti**

Ajda kot hrana za bolnike s celiakijo

Uporaba žit brez vsebnosti glutena, kot je to npr. ajda, odpira nove možnosti za napredek na področju razvoja brezglutenske prehrane in izboljšanja kakovosti življenja bolnikov s celiakijo



Klasifikacija beljakovin žitaric

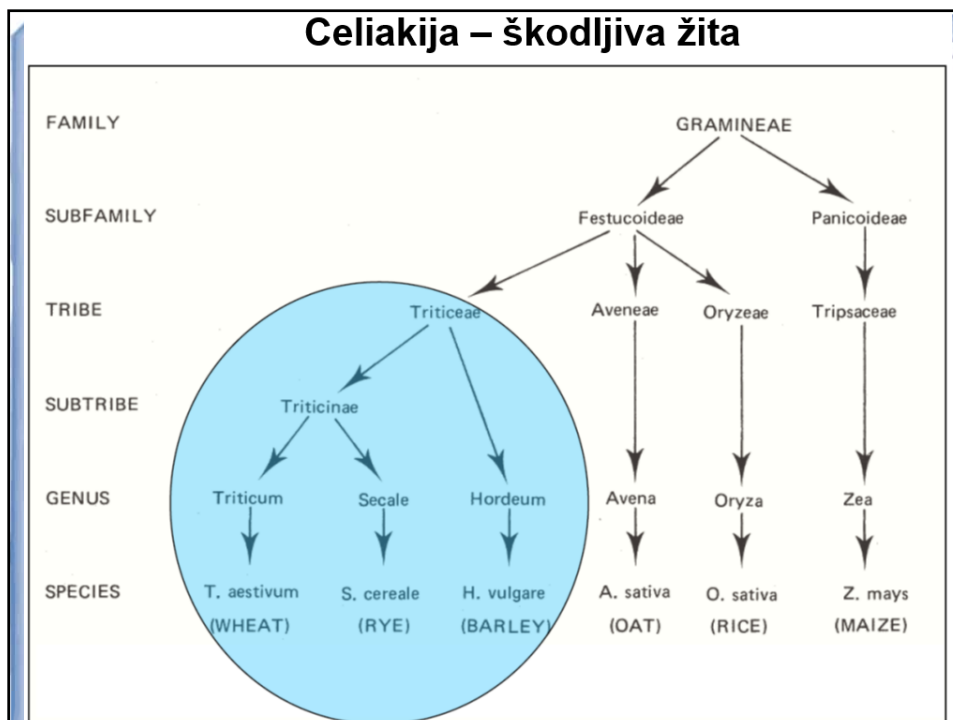


Prolamini
Gliadin (pšenica)
Sekalin (rž)
Hordein (ječmen)
Avenin (oves)



Prolamini pšenice, rža in ječmena so bogati na glutaminu (35-37 mol.-%) in prolinu (17-23 mol.-%). Te aminokisliline se zaporedno ponavljajo.

Celiakija – škodljiva žita



Vsebnost prolina (P) in glutamina (Q) v beljakovinah žitaric izražena v %

Vrsta beljakovine	% P	% Q	% P+Q
<u>α-gliadin</u>	17	38	55
<u>ω-gliadin</u>	30	50	80
<u>glutenin</u> z nizko mol. težo	15	38	53
<u>avenini</u> (oves)	8	33	41
<u>zeini</u> (koruza)	9	21	30

Procenti (mol/100 mol) se razlikujejo odvisno od tipa žitaric.

Dobre izkušnje z ajdo

Ajdo odlikuje zelo dobra hranilna vrednost.



Bogat je vir :

- **Škroba** (vsebnost škroba v ajdovih semenih je 65-75%, spreminja se glede na proizvodno območje in vrsto)
- **Beljakovin** (vsebnost beljakovin v ajdovi moki je 8,5-18,8% odvisno od sorte. Bogata je z albumini in globulini, ki vsebujejo zelo malo prolamina in glutelina. Beljakovine ajde so zelo bogate s Liz in Arg, vsebujejo manj Thr in Met)
- **Nenasičenih maščobnih kislin** (vsebnost maščob v ajdovih semenih je 1.99-3.25%, od tega je največ polinenasičenih MK (oleinska (C18:1), linolna (C18: 2) in linolenska kislina (C18: 3)).
- **Mineralov** (Ajda ima višjo vrednost K, Mg, Cu, Zn, Ca, Fe, Mn, in Cr kot druga žita).
- **Vitaminov** (Vitaminski kompleks B, lutelin in zeaksantin, holin, vit.E)
- **Vlaknin** (Ajdova semena vsebujejo 3,4-5,2% prehranskih vlaknin, od tega 20-30% topnih vlaknin)
- **Antioksidanti** (flavoni, 6 flavonoidov-rutin, orientin, vitexin, quercetin, isovitexin, isoorientin, fitosteroli, fagopirini, tiamin –vezujoče beljakovine)

Buckwheat Enhanced Gluten-free Bread a Healthier Gluten-free Alternative.

International Journal of Food Science and Technology, October 2010; 45(10):1993-2000

Buckwheat starch is a good energy source.

China's Research of Agricultural Modernization Journal, April 2009.

Buckwheat protein shows promise for lowering blood glucose.

Journal of Jilin Agricultural University, 2009; 31(1):102-4.

Germinated Buckwheat extract decreases blood pressure.

Phytotherapy Research, July 2009; 23(7):993-998.

Buckwheat provides prebiotic-like benefits and can be considered a healthy food.

Nutrition Research, June 2003; 23(6):803-14.

Eating buckwheat products lower GI response.

Journal of Agricultural and Food Chemistry, January 2001; 49(1): 490-96.



Pozitivni učinki ajde na zdravje ljudi

Celiakija - ajda ne vsebuje gluten

Deficit lizina - ajda je bogata z lizinom in argininom

Anti hiperholesterolemično delovanje - Rastlinske beljakovine imajo učinek na zniževanje holesterola

Antihipertenzivni učinek - Enzimski hidrolizat ajde ima močan ACE inhibitorji učinek

Kardiovaskularne bolezni, ateroskleroza - flavonoidi so učinkoviti v zniževanju krvnega pritiska in holesterola.



Slabe izkušnje z ajdo

Alergijske reakcije na ajdo:

- Astma
- Alergijski rinitis
- Urtikarija
- Angioedem



Izzivi za prihodnost



Ajda je živilo prihodnosti, ne le zaradi vrste pozitivnih učinkov, ki jih ima na zdravje ljudi, temveč tudi glede na ohranjanje zdravih tal, vode in zraka, saj je danes ena redkih rastlin, ki jih še lahko pridelujemo brez kemičnih pripravkov za varstvo rastlin ter mineralnih gnojil.

Področja raziskav ajde:

- preiskovanje mehanizmov delovanja funkcionalnih sestavin in njihove interakcije,
- optimalni prehranski in referenčni vnos zdravilnih sestavin ajde ni znan,
- razumevanje porazdelitve bioaktivnih komponent v ajdi,
- ohranjanje sestavin z ugodnim vplivom na zdravje in določanje pogojev pod katerimi bodo sestavine maksimalno ohranjene med predelavo.

Encimska terapija

- Prolil endopeptidaza
- Terapija s kombinacijo dveh encimov
 - glutamin-specifična endoproteaza in prolil endopeptidaza
- Probiotiki (laktobacili zmanjšajo toksičnost glutena *in vivo*)
 - VSL#3 probiotična mešanica – sposobna hidrolizirati gliadin

„Celiac pill“

Shan L, Molberg O, Parrot I, et al. Structural basis for gluten intolerance in celiac sprue. *Science* 2002; 297:2218-20.

De Angelis M, Rizzelli CG, Fasano A, et al. VSL#3 probiotic preparation has the capacity to hydrolyze gliadin polypeptides responsible for Celiac Sprue. *Biochim Biophys Acta* 2006; 1762:80-93.

AN-PEP, glutenaza *Aspergillus niger* DSM, The Netherlands

bacterial prolyl oligopeptidase as it degrades both whole gluten and gluten peptides into non-immunogenic residues within minutes^[11,12]. Moreover, the enzyme is active

11 Stepniak D, Spaenij-Dekking L, Mitea C, Moester M, de Ru A, Baak-Pablo R, van Veelen P, Edens L, Koning F. Highly efficient gluten degradation with a newly identified prolyl endoprotease: implications for celiac disease. *Am J Physiol Gastrointest Liver Physiol* 2006; 291: G621-G629 [PMID: 16690904 DOI: 10.1152/ajpgi.00034.2006]

12 Mitea C, Havenaar R, Drijfhout JW, Edens L, Dekking L, Koning F. Efficient degradation of gluten by a prolyl endoprotease in a gastrointestinal model: implications for coeliac disease. *Gut* 2008; 57: 25-32 [PMID: 17494108 DOI: 10.1136/gut.2006.111609]

WJG World Journal of Gastroenterology

Online Submission: <http://www.wjgpt.com/cgi/>
wjg@wjgpt.com
doi:10.3748/wjg.v17.i35.3837

World J Gastroenterol 2013; September 21; 19(35): 3837-3847
ISSN 1007-9327 (print) ISSN 2219-2840 (online)
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ORIGINAL ARTICLE

Consumption of gluten with gluten-degrading enzyme by celiac patients: A pilot-study

Greetje J Tack, Jolanda MW van de Water, Maaike J Bruins, Engeline MC Kooy-Winkelaar, Jeroen van Bergen, Petra Bonnet, Anita CE Vreugdenhil, Ilma Korponay-Szabo, Luppo Edens, B Mary E von Blomberg, Marco WJ Schreurs, Chris J Mulder, Frits Koning

antibodies and mucosal healing classified as Marsh 0 or I were included. In a randomised double-blind placebo-controlled pilot study, patients consumed toast (approximately 7 g/d gluten) with AN-PEP for 2 wk (safety phase). After a 2-wk washout period with adherence of the usual GFD, 14 patients were randomised to gluten intake with either AN-PEP or placebo for 2 wk (efficacy phase). Measurements at baseline included complaints,

efficacy phase. Duodenal biopsies were collected after the safety phase and after the efficacy phase. A change in histological evaluation according to the modified Marsh classification was the primary endpoint.

CONCLUSION: AN-PEP appears to be well tolerated. However, the primary endpoint was not met due to lack of clinical deterioration upon placebo, impeding an effect of AN-PEP.

Alba Therapeutics: Larazotide acetate, tight-junction regulator peptide (former name zonulin inhibitor)

Larazotide acetate in patients with coeliac disease undergoing a gluten challenge: a randomised placebo-controlled study

C. P. Kelly*, P. H. R. Green[†], J. A. Murray[‡], A. DiMarino[§], A. Colatrella[¶], D. A. Leffler*, T. Alexander***, R. Arsenescu^{††}, F. Leon^{††}, J. G. Jiang^{††}, L. A. Arterburn^{††}, B. M. Paterson^{††} & R. N. Fedorak^{§§} for the Larazotide Acetate Celiac Disease Study Group

Aliment Pharmacol Ther 2013; 37: 252-262

Conclusions

Larazotide acetate reduced gluten-induced immune reactivity and symptoms in patients with coeliac disease undergoing gluten challenge and was generally well tolerated; however, no significant difference in LAMA ratios between larazotide acetate and placebo was observed. Results and design of this exploratory study can inform the design of future studies of pharmacological interventions in patients with coeliac disease.

A Randomized, Double-Blind Study of Larazotide Acetate to Prevent the Activation of Celiac Disease During Gluten Challenge

Am J Gastroenterol 2012; 107:1554-1562

Daniel A. Leffler, MD, MS¹, C.P. Kelly, MD¹, H.Z. Abdallah, MD^{1,6}, A.M. Colatrella, MD¹, L.A. Harris, MD¹, F. Leon, MD, PhD^{2,7}, L.A. Arterburn, PhD^{8,9}, B.M. Paterson, MD¹⁰, Z.H. Lan, PhD^{11,12} and J.A. Murray, MD¹

WHAT IS NEW HERE

- ✓ Larazotide acetate is a tight-junction regulator that, *in vitro*, prevents the opening of intestinal epithelial tight junctions.
- ✓ The primary efficacy outcome of this study was not met. In one of the secondary endpoints, larazotide acetate appeared to limit gluten-induced worsening of gastrointestinal symptom severity as measured by the Gastrointestinal Symptom Rating Scale at some lower doses but not at the higher dose. Larazotide acetate was generally well tolerated by patients with coeliac disease who were given a gluten challenge.

Zaključek

Zgodba o celiakiji še ni zaključena

- pogosto nediagnosticirana bolezen
- prevalenca narašča
- prizadeti so otroci in odrasli
- veliki zapleti če se nediagnosticira/ne zdravi
- diagnostične metode dobro uveljavljene
- nova odkritja na področju terapije?
- uporaba žit brez vsebnosti glutena, kot je ajda, odpira nove možnosti za napredek na področju razvoja brezglutenske prehrane in izboljšanja kvalitete življenja bolnikov s celiakijo.

