PREGLEDNI RAD

UDK BROJEVI:
616.34-008.1:663/664
DOI: https://www.doi.org/10.5937/zdravzast51-39445

INTOLERANCIJA NA HRANU

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SAŽETAK

Intolerancija na hranu je neimunološki odgovor indukovan hranom ili komponentom hrane u dozi koja se normalno toleriše. Obuhvata pseudoalergijske i farmakološke efekte uzrokovane: salicilatima, biogenim aminima, sulfitima, natrijum glutamatom, bojama i konzervansima, zaslađivačima, ili enzimopatijama. U okviru ovog preglednog rada prikazana je patofiziologija, kliničke manifestacije, dijagnostikovanje i lečenje najučestalijih intolerancija na hranu. Prietraživanje literature je sprovedeno korišćenjem sledećih ključnih reči: intolerancija, hrana, aditivi, ugljeni hidrati i gluten u okviru *PubMed*, *Emabase*, *Scopus*, *SCIndex* i Hrčak za period od 2001. do 2022. godine. Na osnovu pregleda literature može se konstatovati da nedostatak standardizovanih testova uslovljava nesklad između percipirane prevalencije štetnih efekata povezanih s hranom, koji su izuzetno česti, i stvarne prevalencije neimunoloških reakcija na hranu unutar ovih događaja. Intolerancija na hranu se manifestuju u prvom redu gastrointerstinalnim, a zatim i ekstrainterstinalnim (neurološkim, kardiovaskularnim, respiratornim i dermatološkim) znakovima i simptomima. Dijagnoza zahteva detaljnu anamnezu, fizikalni pregled, kao i vođenje dnevnika ishrane i pojave simptoma, sprovođenje eliminacijske dijete i dvostruko slepih placebom kontrolisanih oralnih ekspozicijskih testova na hranu. Lečenje podrazumeva modifikaciju ishrane, suplementaciju i lečenje osnovnog stanja kod osoba sa sekundarnom intolerancijom.

Ključne reči: intolerancija, hrana, aditivi, enzimopatije

Uvod

Neželjene reakcije na hranu podrazumevaju svaku abnormalnu reakciju nakon uzimanja hrane (1). Uključuju intoleranciju na hranu, alergiju na hranu i averziju na hranu (1). Intolerancija na hranu je neimunološki odgovor indukovan hranom ili komponentom hrane u dozi koja se normalno toleriše (1,2). Obuhvata pseudoalergijske i farmakološke efekte uzrokovane: salicilatima, biogenim aminima, sulfitima, natrijum glutamatom, bojama i konzervansima, zaslađivačima, ili enzimopatijama (3). Intolerancija nezavisna od domaćina podrazumeva odgovor na prirodne sastojke hrane (vazoaktivni amini i salicilati) ili aditive u hrani (glutamat, sulfiti i benzoati) (4). Neimunološka preosetljivost na laktozu, fruktozu, fermentabilne oligosaharide, poliole i gluten predstavlja intoleranciju zavisnu od domaćina (4).

Nedostatak standardizovanih testova uslovljava nesklad između percipirane prevalencije štetnih efekata povezanih s hranom, koji su izuzetno česti, i stvarne prevalencije neimunoloških reakcija na hranu unutar ovih događaja (5-7). Dvostruko slepa, placebom kontrolisana istraživanja utvrdila su prevalenciju intolerancije na hranu od svega 1,8% (6). S druge strane, prevalencija samoprijavljene „bolesti“ ili „nelagode“ uzrokovane unosom određene hrane u epidemiološkim istraživanjima iznosi do 31,1% (5,7).

Intolerancija na hranu se obično karakteriše odloženim početkom simptoma (nastaju nakon nekoliko sati ili dana od uzimanja hrane) i prolongiranom simptomatskom fazom (4,8). Česta je intolerancija na nekoliko namirnica, ili skupina namirnica istovremeno (4). Količina unesene

REVIEW ARTICLE

UDK NUMBERS:
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DOI: https://www.doi.org/10.5937/zdravzast51-39445

FOOD INTOLERANCE

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SUMMARY

Food intolerance is a non-immunological response induced by a food or food component in a dose that is normally tolerated. It includes pseudo allergic and pharmacological effects caused by: salicylates, biogenic amines, sulphites, sodium glutamate, colours and preservatives, sweeteners, or enzymopathies. The pathophysiology, clinical manifestations, diagnosis and treatment of the most common food intolerances have been presented in this review article. The literature search was done with the help of the following keywords: intolerance, food, additives, carbohydrates and gluten within PubMed, Embase, Scopus, SCIndeks and Hrčak databases. According to the literature, it may be argued that the lack of standardized tests accounts for the discrepancy between the perceived prevalence of food-related adverse effects, which are extremely common, and the actual prevalence of non-immunological reactions to food within these events. Food intolerance is manifested primarily by gastrointestinal and then extraintestinal (neurological, cardiovascular, respiratory and dermatological) signs and symptoms. Diagnosis requires a detailed medical history, physical examination, as well as keeping a diet and symptom diary, implementing an elimination diet and double-blind placebo-controlled oral food exposure tests. Treatment includes dietary modification, supplementation and treatment of the underlying condition in persons with secondary intolerance.

Key words: intolerance, food, additives, enzymopathy

Introduction

Adverse food reactions are defined as any abnormal reaction following the ingestion of food (1). They include food intolerance, food allergy and food aversion (1). Food intolerance is a non-immunological response induced by a food or food component in a dose that is normally tolerated (1,2). It includes pseudoallergic and pharmacological effects caused by: salicylates, biogenic amines, sulfites, sodium glutamate, colorants, preservatives, sweeteners, or enzymopathies (3). Host-independent intolerance involves the reaction to natural ingredients (vasoactive amines and salicylates) or additives in food (glutamate, sulfites and benzoates) (4). Non-immunologic hypersensitivity to lactose, fructose, fermentable oligosaccharides, polyols, and gluten is host-dependant intolerance (4).

The lack of standardized tests accounts for the discrepancy between the perceived prevalence of food-related adverse effects, which are extremely common, and the actual prevalence of non-immunological reactions to food within these events (5-7). Double-blind, placebo-controlled studies have found the prevalence of intolerance to food of 1.8% (6). On the other hand, the prevalence of self-reported “disease” or “discomfort” caused by the intake of certain foods in epidemiological studies amounts to 31.1% (5,7).

Food intolerance is usually characterized by a delay in symptom onset (they appear a few hours or days after the intake) and a prolonged symptomatic phase (4,8). Intolerance to several foods is common, as well as to food groups simultaneously. The amount of food is often

hrane neretko je direktno povezana sa ozbiljnošću simptoma (4,8).

Intolerancija na hranu se manifestuju u prvom redu gastrointerstinalnim (bol u trbuhu, nadimanje i dijareja), a zatim neurološkim (vrtoglavica i glavobolja) i kardiovaskularnim znakovima i simptomima (palpitacija, tahikardija, hipotenzija) (4). Respiratorne (hronična rinoreja, kijanje, dispneja) i dermatološke manifestacije (svrab, crvenilo lica i/ili tela, urtikarija) i angioedem su veoma retki (4).

U nedostatku standardizovanih testova dijagnoza intolerancije na hranu zahteva detaljnu anamnezu, fizikalni pregled, kao i vođenje dnevnika ishrane i pojave simptoma, sprovođenje eliminacione dijete i dvostruko slepih placebom kontrolisanih oralnih ekspozicijskih testova na hranu (8,9).

Cilj rada je da se kroz pregled literature analizira patofiziologija, klinička manifestacija, postavljanje dijagnoze i lečenje najučestalijih intolerancija na hranu.

Metode

Literatura je pretražena korišćenjem ključnih reči: intolerancija, hrana, aditivi, ugljeni hidrati i gluten. Pretraživanje je sprovedeno za period od 2001. godine do 2022. godine u okviru sledećih baza podataka: *PubMed*, *Emabase*, *Scopus*, *SCIndex* i Hrčak. Zbog ograničenog broja dostupnih studija u pretraživanju baza nisu korišteni dostupni filteri. Nakon pročitanih sažetaka, radovi su detaljnije proučeni te su isključeni oni koji ne odgovaraju postavljenom cilju istraživanja.

Intolerancije na hranu nezavisne od domaćina

Hiljade različitih jedinjenja s potencijalnom farmakološkom aktivnošću prisutno je u hrani (4). To mogu biti prirodni sastojci hrane, kao što su vazoaktivni amini (npr. histamin) i salicilati, ili aditivi u hrani, kao što su glutamati (npr. mononatrijum glutamat), sulfiti i benzoati (4).

Histamin (2-[4-imidazolil]etilamin) je bioaktivni heterociklični diamin sa imidazolnim prstenom i etilaminom (10). Glavni put stvaranja histamina u hrani je dekarboksilacija histidina delovanjem enzima bakterijskog porekla, L-histidin dekarboksilaze (10). Samim tim, visoke koncentracije histamina se nalaze uglavnom u proizvodima mikrobne fermentacije, kao što su stari sir, kiseli kupus, vino i prerađeno meso ili u mikrobiološki pokvarenoj hrani (11).

Intolerancija na histamin (enteralna histaminoza ili osetljivost na histamin iz hrane) opterećuje 1-3% populacije (11). Nastaje usled poremećene degradacije ili povećane dostupnosti histamina (Tabela 1) (11).

Smanjen kapacitet degradacije histamina u crevima uzrokovan genetski uslovljenim ili stečenim poremećajem aktivnosti diamin oksidaze (engl. *diamine oxidase* - DAO) predstavlja vodeći uzrok intolerancije na histamin (10). Genetski uslovljena intolerancija podrazumeva jednonukleotidne polimorfizme u genu (promotorskoj regiji gena) koji kodira DAO (10). Stečenu intoleranciju mogu indukovati gastrointestinalne bolesti, hronična bubrežna insuficijencija, virusni hepatitis, uznapredovala ciroza jetre, hronična urtikarija, kao i kompetitivna inhibicija DAO (drugi amini, alkohol ili lekovi), kao i nedostatak kofaktora DAO (vitamin B6, vitamin C, bakar i cink) (10-12).

Povećanu dostupnost histamina uzrokuju endogena hiperprodukcija (alergijska reakcija, mastocitoza, inefekcija bakterijama, gastrointestinalno krvarenje, drugi biogeni amini, 1-karnozin) ili povećan egzogeni unos histidina ili histamina (hrana ili alkohol) (Tabela 1) (9-12).

Intolerancija na histamin se manifestuje širokim spektrom nespecifičnih gastrointestinalnih i ekstraintestinalnih simptoma i znakova (10-12). Tipični simptomi uključuju gastrointerstinalne manifestacije (postprandijalnu punoću, bol u trbuhu, konstipaciju, dijareju), kijanje, rinoreju, začepljenost nosa, glavobolju, dismenoreju, hipotoniju, aritmiju, urtikariju, pruritus, crvenilo i astmu (10-11).

Dijagnoza zahteva isključivanje prisustva alergije na hranu i lekove, mastocitoze, psihosomatske bolesti, kao i prisustvo dva ili više tipičnih simptoma intolerancije na histamin, kao i njihovo poboljšanje ili remisiju nakon dijete s niskim sadržajem histamina ili upotrebe antihistaminika (10-12). Terapija podrazumeva dijetu sa niskim sadržajem histamina uz eventualnu upotrebu antihistaminika, cinka, vitamina B6, vitamina C i stabilizatora mastocita (10-12).

Intolerancija na salicilate predstavlja neimunološki odgovor indukovan salicilnom kiselinom i njenim derivatima (13,14). U različitim koncentracijama derivati salicilne kiseline su prisutni u nesteroidnim antiinflamatornim lekovima (acetilsalicilna kiselina, diflunisal, natrijum salicilat, salsalat, sulfasalazin), hrani (pasulj, karfiol, kiselo

directly linked to the severity of symptoms (4,8).

Food intolerance is primarily manifested as gastrointestinal symptoms (abdominal pain, bloating, diarrhea), neurological (dizziness, headache), and cardiovascular signs and symptoms (palpitations, tachycardia, hypotension) (4). Respiratory (chronic rhinorrhea, sneezing, dyspnea) and dermatological manifestations (itching, flushing of the face and/or body, urticaria) and angioedema are very rare (4).

Due to the lack of standardized tests, diagnosis requires a detailed anamnesis, physical examination, as well as keeping a diet and symptom diary, implementing an elimination diet and double-blind placebo-controlled oral food exposure tests (8,9).

The aim of this paper is to analyze the pathophysiology, clinical manifestations, diagnosis and treatment of the most common food intolerances through the review of literature.

Methods

The literature was searched with the help of the following key words: intolerance, food, additives, carbohydrates and gluten. The search was conducted for the period 2001 to 2022 within the following databases: PubMed, Emabase, Scopus, SCIndex and Hrcak. Due to the limited number of available studies, available filters were not used during the search. Abstracts were read first, and then studies were analyzed in more detail and those that did not correlate with the aim of the research were excluded.

Host-independent food intolerance

Thousands of different chemicals with potential pharmacological activity are present in food (4). They can be natural food chemicals, such as vasoactive amines (e.g. histamine) and salicylates, or food additives, such as glutamates (e.g. monosodium glutamate), sulfites and benzoates (4).

Histamine (2-[4-imidazolyl]ethylamine) is a bioactive heterocyclic diamine with an imidazole ring and ethylamine (10). The main route for histamine formation in food is the decarboxylation of histidine through the action of L-histidine decarboxylase, an enzyme of bacterial origin (10). Therefore, high concentrations of histamine are present mainly in products of microbial fermentation, such as aged cheese, sauerkraut, wine and processed meat, or in microbially spoiled food (11).

Histamine intolerance (enteral histaminosis or sensitivity to histamine in food) affects 1-3% of the population (11). It appears due to an impaired histamine degradation and increased availability of histamine (Table 1) (11).

The reduced capacity of histamine degradation in the intestines caused by genetically conditioned or acquired disorder of DAO activity (diamine oxidase-DAO) is the leading cause of histamine intolerance (10). Intolerance, which has a genetic origin, includes single-nucleotide polymorphisms in the DAO encoding gene (in the promoter region of the gene) (10). The acquired intolerance may be induced by gastrointestinal diseases, chronic kidney disease, hepatitis, advanced liver cirrhosis, chronic urticaria, as well as competitive DAO inhibition (other amines, alcohol, and medications) and the lack of DAO co-factors (vitamin B6, vitamin C, copper and zinc) (10-12).

The increased availability of histamine is caused by endogenous hyperproduction (allergic reaction, mastocytosis, bacterial infection, gastrointestinal bleeding, other biogenic amines, l-karnosine), or the increased intake of histidine or histamine (food or alcohol) (Table 1) (9-12).

Histamine intolerance is manifested by a wide range of non-specific gastrointestinal and extraintestinal signs and symptoms (10-12). Typical symptoms include gastrointestinal manifestations (postprandial fullness, abdominal pain, constipation, diarrhea), sneezing, rhinorrhea, nasal congestion, headache, dysmenorrheal, hypotonia, arrhythmia, urticaria, pruritus, flushing and asthma (10-11).

Diagnosis requires the exclusion of allergy to food and medications, mastocytosis, psychosomatic disease, as well as the presence of two or more typical symptoms of histamine intolerance, and their improvement or remission after diet with the low contents of histamine or the use of antihistamines (10-12). The treatment involves the diet with the low contents of histamine and the possible use of antihistamines, zinc, vitamin B6, vitamin C and mast cell stabilizers (10-12).

Salicylate intolerance is a non-immunological reaction induced by the salicylic acid and its derivatives (13,14). Derivatives of salicylic acid are present in different concentrations in non-steroidal anti-inflammatory drugs (acetylsalicylic acid, diflunisal, sodium salicylate, salsalate, sulfasalazin),

Tabela 1. Izvori histamina i mogući uzroci povećanja koncentracije u organizmu (12)

Prirodno proizveden histamin, uglavnom u mastocitima	
Namirnice sa visokim koncentracijama histamina	Paradajz, patlidžan, spanać, riba, piletina, uskladišteno meso, fermentisana hrana (sirevi, kobasice, kiseli kupus, vino, pivo, šampanjac...)
Namirnice koje oslobađaju histamin	Ananas, banane, agrumi, jagode, orasi, papaja, paradajz, sladić, začini, mahunarke, kakao, alkohol, riba, plodovi mora, svinjetina, belance
Aditivi koji oslobađaju histamina	Boje, konzervansi, stabilizatori, pojačivači ukusa, arome
Proizvodnja histamina indukovana kvascem i bakterijama	Namirnice sa održivim kvascem – kiselo testo, svež hleb
Supstance koje smanjuju aktivnost DAO u hrani	Alkohol
Lekovi koji smanjuju aktivnost DAO	Verapamil, propafenon, cefuroksim, cefotiam, klavulanska kiselina, doksiciklin, izoniazid, framicetin, metamizol, amitriptilin, diazepam, haloloperidol, prometazin, cimetidin, dihidralazin, hlorokin, aminofilin, teofilin, furosemide, N-acetilcistein, ambroksol, alkuronijum, pancuronijum, d –tubokurarin, akriflavinijum hlorid, hinidin
Lekovi koji oslobađaju histamin	Morfijum, petidin, kodein, metamizol, acetilsalicilna kiselina, d-cikloserin, hlorokin, pentamidin, dobutamin, verapamil, alprenolol, kodein, amilorid, kontrasna sredstva koje sadrže jod, mezokain, prokain, markain, prilokain d–tubokurarin, barbiturati, tiopental
Lekovi koji inaktiviraju piridoksin	Hidralazin, d-ciklosporin, izoniazid, hormonska kontracepcija
Alergijska reakcija	Oslobađanje histamina iz mastocita posredovano IgE
Lekovi koje potenciraju oslobađanje histamina posredovano IgE	Acetilsalicilna kiselina, diklofenak, flurbiprofen, indometacin, ketoprofen, mefenamin, naproksen…
Infekcija, trauma, šok	

DAO - diamin oksidaza

povrće, jagode, šljive, lubenice, maline, ananas, kikiriki, badem, grožđe, heljda, zob, kukuruz, kobasice, umaci i gotova jela, voćni sokovi, čaj, pivo, liker, rum, vino, začinsko bilje i začini), konzervansima i bojama (13-16).

Intolerancija na salicilate nastaje usled snažne inhibicije ciklooksigenaze tipa 1 (engl. *cyclooxygenase type 1* - COX-1) i posledičnog smanjenja proizvodnje prostaglandina, prostaciklina i tromboksana, kao i povećane dostupnosti leukotriena A4 (13,16). Manifestuje se, u prvom redu, rinosinuzitisom, polipozom nosa i sinusa, ili bronhijalnom astmom (17). Istovremeno postojanje intolerancije na nesteroidne antiinfllamatorne lekove, polipoze i astme označava se kao „trijada“ (17). Osim toga, mogu biti prisutni utrikarija, kolitis, ili dijareja (17). Anafilaktični šok je veoma redak (17).

Dijagnostička obrada započinje anamnezom koja ima za cilj da utvrdi moguću povezanost upotrebe derivata salicilne kiseline i simptoma intolerancije (17). Test izloženosti ili provokacije predstavlja zlatni standard u dijagnozi intolerancije (17). U slučaju kada je provokacija neprihvatljiva (ozbiljnost očekivane reakcije) ili kontraindikovana (infekcija ili bronhijalna astma) koriste se funkcionalni testovi (merenje količine leukotriena oslobođenih iz bazofilnih leukocita, merenje membranskog proteina CD63 povezanog s lizozimoma, prošireni funkcionalni eikozanoidni test) (17). Najpouzdaniji oblik profilakse i terapije je prekid upotrebe preparata salicilne kiseline (17).

Prehrambeni aditiv je supstanca poznatog hemijskog sastava koja se uobičajeno ne upotrebljava kao hrana sama za sebe, niti je tipičan sastojak hrane, a dodaje se namenski radi promene tehnoloških i organoleptičkih svojstava hrane, što dovodi ili se može očekivati da dovede do toga da on sam ili njegov sekundarni proizvod direktno ili indirektno postaje sastojak te hrane (18,19). Sulfiti, benzoati i glutamati se mogu naći u gotovo svim vrstama hrane, pića i nekim lekovima (Tabela 2) (18,19).

Prevalencija samoprijavljenih intolearancija na navedene prehrambene aditive u odraslih iznosi 0,01-0,23% (21).

Table 1. Sources of histamine and possible causes of increase of concentration in organism (12)

Naturally produced histamine, mostly in mast cells	
Histamine naturally occurring	Tomatoes, eggplant, spinach, fish, chicken and stored meat, fermented food (cheeses, sausages, sauerkraut, wine, beer, champagne...)
Histamine liberators	Pineapple, bananas, citrus fruits, strawberries, nuts, papaya, tomatoes, liquorice, spices, legumes, cocoa, alcohol, fish, seafood, pork, egg white
Histamine liberators of additives	Colourants, preservatives, stabilisers, taste enhancers, flavourings
Histamine production induced by yeast and bacteria	Foods with viable yeast – sourdough, fresh bread
Substances decreasing DAO activity in food	Alcohol
Medication decreasing DAO activity in food	Verapamil, propafenone, cefuroxime, cefotiame, acidum clavulanicum, doxycyclinum, isoniazid, framycetin, metamizole, amitriptiline, diazepam, haloperidol, promethazine, cimetidine, dihydralazine, chloroquin, aminophylline, theophylline, furosemide, N-acetylcysteine, alcuronium, pancuronium, d-tubocurarin, acriflavinium chloride
Histamine liberators in medication	Morfijum, petidin, kodein, metamizol, acetilsalicilna kiselina, d -cikloserin, hlorokin, pentamidin, dobutamin, verapamil, alprenolol, kodein, amilorid, kontrasna sredstva koje sadrže jod , mezokain, prokain, markain, prilokain d –tubokurarin, barbiturati, tiopental
Pyridoxine inactivating drugs	Hydralazine d-cyklosporine, isoniazid, hormonal contraception
Allergic reaction	IgE-mediated histamine release from mast cells
Medication potentiating allergic IgE-mediated histamine release	Acetylsalicylic acid, diclofenac, flurbiprofen, indomethacin, ketoprofen, mefenamin, naproxen
Infection, trauma, shock	

DAO - diaminooxidase

in food (beans, cauliflower, sour vegetables, strawberries, plums, watermelons, raspberries, pineapple, peanuts, almond, grapes, buckwheat, oat, corn, sausages, sauces, ready-made meals, fruit juices, tea, beer, liqueur, rum, wine, herbs, spices), preservatives and colorants (13-16).

Salicylate intolerance is induced by a marked inhibition of cyclooxygenase type 1 (COX-1) and the resulting diminished production of prostaglandin, prostacyclin and thromboxan, as well as the increased availability of leukotriene A4 (13,16). It is manifested, first of all, by rhinosinusitis, nasal and sinus polyps, or bronchial asthma (17). The simultaneous existence of intolerance to non-steroidal anti-inflammatory drugs, polyposis and asthma is marked as a "triad" (17). In addition, urticaria, colitis or diarrhea may appear (17). Anaphylactic shock is very rare (17).

Diagnostic analysis starts with anamnesis aimed at establishing the possible connection between the derivatives of salicylic acid and symptoms of intolerance (17). Exposure testing or provocation testing is a gold standard in the diagnostics of intolerance (17). When provocation is not acceptable (the severity of expected reaction) or if it is contraindicated (infection or bronchial asthma), functional tests are used (measurement of the quantity of leukotriene liberated from the basophilic leukocytes, measurement of membrane protein CD63 associated with lysosomes, extended functional eicosanoid test) (17).

The most reliable form of prophylaxis and treatment is the elimination of salicylic acid products (17). Food additive is a substance that has known chemical composition, which is not used as food alone, and it is not a typical food ingredient, but it is added to food in order to change its technological and organoleptic properties. Therefore, it may be expected that the food additive alone or its secondary product directly or indirectly becomes the food ingredient (18,19).

Sulfites, benzoates and glutamates may be found in almost all kinds of food, drinks, and some medications (Table 2) (18,19).

Tabela 2. Namirnice i lekovi sa visokim sadržajem sulfita, mononatrijum glutamata i benzoata (18,20)

Namirnice	Sulfiti	Benzoati	Mononatrijum glutamat
Meso, živina i plodovi mora	Kozice, jastog, sušeni bakalar, rakovi štapići, lignje, pljeskavica od mesa, kobasice	Jela sa ljutim sosom, gotova jela koja sadrže benzoate	Riblji sos
Mleko i jaja		Jogurt, sir	Parmezan
Voće	Sušene kajsije, smokve, suhe šljive, datulje, suhe banana, kandirano voće sušeni kokos, ribizla	Brusnice, borovnice, suve šljive, papaja, sušeno voće, avokado	
Povrće, orašasti plodovi, semenke i slane grickalice	Sušene pečurke i druge gljive, smrznuti, konzervisani ili vakuumirani krompir, pomfrit, instant kaše, njoke, kroketi od krompira, vegetarijanski hamburgeri i kobasice, šparoge u konzervi, mahune, pasulj, kesteni,	Bundeva, mahunarke, soja pasulj, sojino brašno, brokoli, spanać, pečeni pasulj i paradajzu u ljutom sosu, pečeni orasi, čips (osim gotovih usoljenih), grickalice od krompira ili kukuruza,	Pečurke, spanać, slane grickalice, čips
Začini i ostalo	Umak od hrena, karamel boja	Kari u prahu, aleva paprika, mješavina začina, muškatni oraščić, karanfilić, cimet, čokolada, kakao, kečap, soja sos, preliv za salatu, krema za salatu, majonez, džem, kiseli krastavci	Supe, temeljac, umaci, premazi, gotova jela, soja sos, sos od crnog pasulja, sos od ostriga, paradajz sos, instant pirinač i jela sa rezancima
Piće	Jabukovača, vino, pivo, kašasti i gazirani sokovi, sok od grožđa, sok od narandže, kola	Čaj, kašasti i gazirani sokovi, pivo, žestoka pića, žestoka pića sa dodatkom začina	
Lekovi	Isopterenalin, isoproksiharimetrin, dopamin, lokalni anestetici, propofol, aminoglikozidni antibiotici, metoklopramid, doksiciklin, vitamini B kompleks, topikalne antifugalne i kortikosteroidne kreme		Natrijumfenilacetat/ natrijum benzoat

S obzirom na značajne varijacije u simptomima i ozbiljnosti reakcije postoji nekoliko patogenetskih mehanizama intolerancije na sulfite (20,22).

Udisanje sumpor dioksida, nastalog iz unesenih sulfita u toploj kiseloj sredini usta i želuca, može uzrokovati respiratorne simptome (20,22). Nedostatak sulfit oksidaze i posledična prekomerna akumulacija sulfita uzrokuje holinergički posredovanu bronhokonstrikciju (20,22). Sulfiti uzrokuju degranulaciju mastocita (u odsustvu IgE) te oslobađanje histamina i drugih medijatora intolerancije (20,22). Osim toga, smanjuju dostupnost prostaglandina i povećavaju koncentraciju leukotriena (21,22).

Hipersulfatinemija može uzrokovati inhibiciju enzima uključenih u sintezu/aktivaciju neurotransmitera nukleus akumbensa (23). Sulfiti narušavaju integritet mitohondrijalne membrane neurona (smanjuju proizvodnju adenozin tri fosfata i povećavaju koncentraciju reaktivnih vrsta kiseonika) (24,25).

Intolerancija na sulfite se predominantno manifestuju respiratornim simptomima (20,22). Mogu se javiti i dermatološki i gastrointestinalni znaci i simptomi (20,22). Izbegavanje sulfita u intolerantnih osoba može ublažiti tinitus, hiperakuziju, kao i manifestacije bolesti povezanih sa smanjenom dopaminergičkom ili serotonergičkom aktivnošću (23).

Konzumiranje visoke doze mononatrijum glutamata na prazan želudac u malog broja ljudi uzrokuje pojavu „sindroma kineskog restorana“ koji se karakteriše glavoboljom, crvenilom lica, utrnulošću gorneg dela tela, glave i vrata, opštom slabošću, palpitacijom, urtikarijom, bolom u sto-

Table 2. Foods and medications with high levels of sulfites, monosodium glutamate and benzoate (18,20)

Foods	Sulphites	Benzoates	Monosodium glutamate
Meat, poultry and seafood	Prawns, lobster, dried salt cod, crab sticks, squid, meat burger, sausages	Dishes with a spicy sauce, ready to eat meals containing benzoates	Fish sauce
Milk and eggs		Yoghurt, cheese	Parmesan cheese
Fruits	Dried apricots, sultanas, figs, prunes, dates, dried banana, candied, glace fruit desiccated coconut, currants	Cranberries, bilberries, prunes, papaya, dried fruit, avocado	
Vegetables, nuts, seeds and savoury snacks	Dried mushrooms and other fungi, frozen, tinned or vacuum packed potatoes, french fries, instant mash, gnocchi, potato cakes, potato croquettes, vegetarian burgers and sausages, tinned asparagus, broad beans, french beans, chestnuts	Pumpkin, kidney beans, soy beans, soy flour, broccoli, spinach, baked beans, tomato in spicy sauce, dry roasted and spicy nuts, crisps (except ready salted), potato or corn snacks	Mushrooms, spinach, savoury snacks, crisps
Condiments and miscellaneous	Horseradish sauce, caramel colouring	Curry powder, allspice, mixed spice, nutmeg, clove, cinnamon, chocolate, cocoa, ketchup, soy sauce, Worcestershire sauce, salad dressing, salad cream, mayonnaise, jam, pickles	Soups, stock, gravy, coatings, ready-meals, soy sauce, black bean sauce, oyster sauce, tomato sauce, miso, marmite, instant rice and noodle dishes
Drinks	Cider, wine, beer, fruit squash and cordials, soft drinks, grape juice, fruit juice drinks, cola drinks	Tea, squash, cordial, carbonated drinks, milkshake syrup, beer, ready-to-drink alcohol and mixers, spirits with added spices	
Medication	Isoprenaline, isoproterenol, isoetharine, phenylephrine, dexamethasone and injectable corticosteroids, dopamine, local anaesthetics, propofol, aminoglycoside antibiotics, metoclopramide, doxycycline and vitamin B complex, Topical anti-fungal and corticosteroid creams		Sodium phenylacetate/ sodium benzoate

The prevalence of self-reported intolerance to the above mentioned food additives in adults is 0.01-0.23% (21).

Considering significant variations in the symptoms and severity of reactions, there are several pathogenetic mechanisms of intolerance to sulfites (20,22).

The inhalation of sulphur dioxide from the ingested sulfites in the warm acidic environments of the mouth and stomach may cause respiratory symptoms (20,22). The lack of sulfite oxidase and the resulting excess accumulation of sulfites cause the cholinergic-mediated bronchoconstriction (20,22). Sulfites cause degranulation of mast cells (in the absence of IgE), and the liberation of histamines and other mediators of intolerance (20,22). In addition, they reduce the availability of prostaglandin and increase the concentration of leukotriene (21,22).

Hypersulfitemia may cause the inhibition of enzymes involved in the synthesis/activation of neurotransmitters nucleus accumbens (23). Sulfites disturb the integrity of mitochondrial membrane of neurons (reduce the production of adenosine 3 phosphate and increase the concentration of reactive forms of oxygen) (24,25).

Intolerance to sulfites is predominantly manifested by respiratory symptoms (20,22).

maku i odgođenim angioedemom (26-28). Predloženo je nekoliko etioloških mehanizama uključujući nedostatak vitamina B6, hipernatrijemiju, intoksikaciju histaminom, vazokonstrikciju, gastroezofagealni refluks, povećanu produkciju intermedijera Krepsovog ciklusa (28). U nedostatku dokaza koji potvrđuju bilo koji od navedenih, tačan uzrok i dalje nije poznat (28).

Kratkotrajno izlaganje benzoatima može izazvati iritaciju očiju, kože i respiratornog trakta, (29). Produžen kontakt rezultuje ekcemom, urtikarijom i perzistentnim rinitisom (29,30). Upotreba visokih doza benzoata može uzrokovati promenu sekrecije želudačne sluzi i razvoj ulkusa, te disfunkciju jetre i bubrega i hiperaktivnost (29). Zbog dokazane interkalacije u DNK natrijum benzoat se smatra genotoksičnim (31).

Dijagnoza intolerancija zahteva vođenje dnevnika ishrane i pojave simptoma, sprovođenje eliminacijske dijete te ponovno postepeno uvođenje u ishranu uz praćenje simptoma (17). Najpouzdaniji oblik profilakse i terapije je prekid upotrebe aditiva (17).

Intolerancije na hranu zavisne od domaćina

Laktoza je disaharid izgrađen od D-galaktoze i D-glukoze (32-35). Prisutan je u mlečnim proizvodima (32-35).

Intoleranciju na laktozu predstavlja nemogućnost apsorpcije laktoze u crevima uzrokovana smanjenjem ili gubitkom aktivnosti enzima laktaze (32,33). Intolerancija na laktozu ima visoku prevalenciju koja se kreće između 57% i 65% (34). Najčešće je prisutna kod adolescenata i mladih odraslih osoba (33).

Intolerancija laktoze može biti primarna (postepeni pad aktivnosti laktaze sa starenjem), stečena (u prisustvu gastroenteritisa, celijakije, Kronove bolesti, ulceroznog kolitisa, upotrebe antibiotika, hemoterapije, ozlede sluznice crieva), kongenitalna (odsustvo ili pad aktivnosti enzima laktaze u novorođenčeta koji se nasleđuje autozomno recesivno) i razvojna (nedonoščad sa nerazvijenim crevima) (33). Neapsorbovana laktoza u crevima povećava sadržaj vode u lumenu creva što uzrokuje osmotsku dijareju (33,35). Dodatni priliv tečnosti uzrokuju bakterije debelog creva koje fermentišu laktozu u kratkolančane masne kiseline i gasove (vodonik, ugljen dioksid i metan) (33,35).

Simptomi i znakovi inetolerancije na laktozu manifestuje se u periodu od 30 minuta do 2 sata nakon uzimanja mlečnih proizvoda (33). Njihova ozbiljnost zavisi od količine unete laktoze, preostale funkcije laktaze, enteričkog mikrobiona i vremena prolaska hrane kroz tanko crevo (33,35). Uobičajeni znakovi i simptomi uključuju: bol u stomaku, nadutost, dijareju, zatvor, mučninu i povraćanje (33,35,36). Ekstrainterstinalni simptomi (otežana koncentracija, glavobolja, bol u kostima i mišićima, depresija, anksioznost, promene na sluznici usta i poremećaj srčanog ritam) su retko prisutni (35). Dijagnoza intolerancije na laktozu se postavlja na osnovu anamneze, fizikalnog pregleda, funkcionalnih testova (izdisajni test na vodonik, test tolerancije na mleko, test kiselosti stolice, test tolerancije na laktozu), sprovođenja eliminacijske dijete, biopsije creva i genotipizacije (33,35).

Lečenje podrazumeva modifikaciju ishrane, suplementaciju laktazom i lečenje osnovnog stanja kod osoba sa sekundarnim nedostatkom laktaze (33,37).

Fruktoza je prirodno prisutna u raznim namirnicama (36-39). Osim toga, fruktoza se proizvodi iz kukuruza (kukuruzni sirup s visokim sadržajem fruktoze je prisutan u bezalkoholna pićima i zaslađivačima hrane) (Tabela 3) (36-39).

Intolerancija na fruktozu se manifestuje u obliku nasledne ili stečene intolerancije na fruktozu (38,39).

Naslednu intoleranciju na fruktozu uzrokuje nedostatak enzima fruktoza-1-fosfat aldolaze, i posledična akumulacija fruktoza-1-fosfata u jetri (40). Fruktoza-1-fosfat inhibira fosforilazu, enzim glikogenolize, što dovodi do laktacidoze i hipoglikemije (40). Osim toga, konzumiranje fruktoze u intolerantnih osoba indukuje hipofasfatemiju, oštećenje proksimalnih tubula bubrega i jetre (40). Ozbiljnost simptoma je proporcionalna količini unete fruktoze (40). Manje količine uzrokuju povraćanje, bol u trbuhu, dijareju i hipoglikemiju (40). U ranom dojenačkom dobu velike količine unete fruktoze mogu rezultovati šokom, akutnim zatajenjem jetre i bubrega i smrću (40). Dijagnoza nasledne intolerancije na fruktozu se postavlja uz pomoć genetskog testa koji je komercijalno dostupan (40). Terapija podrazumeva izbegavanje fruktoze u ishrani (40). Stečena intolerancija na fruktozu nastaje kao posledica malapsorpcije uzrokovane promenama u proteinu za transport glukoze 5 i 2 (eng. *Glucose Transporter 5 and Glucose Transporter 2* - GLUT 5 i GLUT 2) (38-42).

Dermatological and gastrointestinal signs and symptoms may appear, as well (20,22). The avoidance of sulfites in persons who are intolerant may alleviate tinnitus, hyperacusis, and manifestations of disease connected with the reduced dopaminergic and serotonergic activity (23).

The consumption of higher doses of monosodium glutamate on an empty stomach may cause in the small number of people the "syndrome of Chinese restaurant", which is manifested by headache, flushing, numbness of upper part of the body, head and neck, weakness, palpitation, urticaria, abdominal pain and prolonged angioedema (26-28). A few etiological mechanisms were recommended including the lack of vitamin B6, hypernatremia, intoxication with histamine, vasoconstriction, gastroesophageal reflux, the increased production of Crebs cycle intermediate (28). Due to the lack of evidence, which would prove any of the above mentioned, the actual cause is still not known (28).

A short-term exposure to benzoates may cause the irritation of eyes, skin, respiratory tract (29). The prolonged contact results in eczema, urticaria and persistent rhinitis (29,30). The use of high doses of benzoates may cause the change of the secretion of stomach mucosa and the development of ulcus, and dysfunction of liver and kidneys and hyperactivity (29). Due to the proved intercalation in DNA, sodium benzoate is deemed to be genotoxic (31).

The diagnosis of intolerance requires keeping a diary of diet and symptoms, implementing the elimination diet, and gradual introduction of ingredients into the diet together with observing the symptoms (17). The most reliable form of prophylaxis and treatment is the elimination of additives (17).

Intolerance to host-dependent food

Lactose is a disaccharide that consists of D-galactose and D-glucose (32-35). It is present in dairy products (32-35).

Lactose intolerance is the inability of absorption of lactose in the intestines caused by the deficiency or loss of the enzyme lactase (32,33). Lactose intolerance has high prevalence which ranges between 57% and 65% (34). It is most common in adolescents and young adults (33).

Lactose intolerance can be primary (a gradual decline in lactase enzyme activity with increasing age), secondary (caused by gastroenteritis, celiac disease, Crohn disease, ulcerative colitis, antibiotics, chemotherapy, injury to intestinal mucosa), congenital (a decrease or absence of lactase enzyme activity since birth due to autosomal recessive inheritance) and developmental (newborns with immature intestines) (33). The unabsorbed lactose within the bowel results in an influx of fluid into the bowel lumen resulting in osmotic diarrhea (33,35). The additional influx of fluids is caused by colonic bacteria that ferment the lactose thus producing short-chain fatty acids and gas (hydrogen, carbon dioxide, and methane) (33,35).

Signs and symptoms of lactose intolerance manifest 30 minutes to 2 hours after ingesting dairy products (33). The severity of symptoms depends on the amount of consumed lactose, the residual lactase function, and the small bowel transit time (33,35). Common signs and symptoms include the following: abdominal pain, abdominal bloating, diarrhea, constipation, nausea and vomiting (33,35,36). Extraintestinal symptoms (loss of concentration, headache, muscle pain, joint pain, mouth ulcers and arrhythmia) are rarely present (35). The diagnosis of lactose intolerance is established based on anamnesis, physical examination and functional tests (hydrogen breath test, milk tolerance test, stool acidity test, lactose tolerance test, dietary elimination, small bowel biopsy, and genotyping) (33,35).

The treatment of lactose intolerance consists of dietary modification, lactase supplementation, and treating an underlying condition in people with secondary lactase deficiency (33,37).

Fructose is naturally present in various foods (36-39). Also, fructose is produced from corn (corn syrup with the high amount of fructose is present in many non-alcoholic drinks and sweeteners) (Table 3) (36-39).

Fructose intolerance is manifested as hereditary or acquired fructose intolerance (38,39).

Hereditary fructose intolerance is caused by the lack of the enzyme fructose-1-phosphate aldolase, and the resulting accumulation fructose-1-phosphate in the liver (40). Fructose-l-phosphate inhibits phosphorylase, the enzyme of glycogenolysis, which causes lactacidosis and hypoglycemia (40). Also, the consumption of fructose in intolerant people induces

Tabela 3. Namirnice sa visokim sadržajem fruktoze (41)

Kategorija	Namirnice
Voće	Svo voće (osim avokada, brusnice, limete, dinje, limuna, ananasa, jagoda, mandarina, banane), voćni sokovi, sušeno voće i voće konzervirano u soku ili sirupu.
Povrće	Artičoka, šparoge, brokoli, praziluk, šampinjoni, bamija, luk, grašak, crvena paprika, proizvodi od paradajza (pasta, kečap, konzervirani paradajz).
Žitarice	Namirnice sa pšenicom kao glavnim sastojkom (pšenični hleb, testenina, kus-kus), žitarice sa dodatkom suvog voća, žitarice sa dodatkom kukuruznog sirupa s visokim sadržajem fruktoze.
Meso	Marinirano ili prerađeno meso
Mlečni proizvodi	Mlečni proizvodi sa dodatkom kukuruznog sirupa s visokim sadržajem fruktoze (jogurt, aromatizovano mleko...)

GLUT 5 je jedini specifični transporter fruktoze koji pasivno prenosi fruktozu sa apikalne membrane enterocita (predominantno u duodenumu i proksimalnom jejunumu) (42). GLUT 2 predstavlja pomoćni transporter koji ima nizak afinitet za fruktozu (u stanju je transportovati i druge monosaharide kao što su glukoza i galaktoza) (40). Apsorpcija fruktoze u tankom crevu je ograničena, značajan broj odraslih osoba ne može apsorbovati više od 25 g/dan (42).

Smanjena aktivnost transportera frukoze uzrokuje povećano osmotsko opterećenje lumena, povećanu fermentaciju bakterija debelog creva, narušava gastrointestinalni motilitet i vodi promeni u crevnoj flori (42).

Stečena intolerancija na fruktozu se manifestuje nadutošću, bolom u stomaku, mučninom i dijarejom (41). Dijagnoza se postavlja izdisajnim testom na vodonik i/ili metan (od 1,5 do 3 sata nakon konzumiranja fruktoze) (40). Najpouzdaniji oblik profilakse i terapije je prekid upotrebe fruktoze (38-41).

Polioli predstavljaju posebnu grupu alkohola koji nastaju katalitičkom hidrogenacijom ugljenih hidrata (42,43). Polioli se nalaze u određenom voću (jabuka, kajsija, avokado, kupina, trešnja, nektarina, kruška, suve šljive, grožđice), povrću (karfiol) i gljivama (42,43). Osim toga oni se koriste kao veštački zaslađivači (u zamenu za saharozu jer daju manje kalorija po gramu) u mnogim industrijskim proizvodima (bombone, žvakaće gume, sladoledi, peciva, pekarski proizvodi i čokolade) (42,43). Polioli se mogu naći u pasti za zube i vodicama za ispiranje usta (41). Agencija za hranu i lekove (engl. *Food and Drug Administration* - FDA) Sjedinjenih Američkih Država je odobrila upotrebu osam različitih poliola, koji uključuju eritritol, hidrogenizovane hidrolizate skroba, izomalt, laktitol, maltitol, manitol, sorbitol i ksilitol (43).

Intolerancija na poliole nastaje kao rezultat promena u crevnom mikrobiomu (43). Manifestuje se nadimanjem, bolovima u stomaku i dijarejom (42,43). Simptomi se povećavaju sa količinom unetih poliola i konzumiranjem drugih ugljenih hidrata (43). Dijagnoza intolerancije na poliole se postavlja izdisajnim testom (polioli koji se dobro apsorbuju poput sorbitola) ili sprovođenjem eliminacione dijete (polioli koji se slabo apsorbuju poput manitola) (44).

Galaktani predstavljaju polimere galaktoze (42). Prisutni su u mahunarkama poput pasulja, leblebija i proizvodima od soje, prokelju, orašastim plodovima i kupusu (42). Ove namirnice su neretko deo vegetarijanske ishrane, indijske i meksičke kuhinje (42).

Intolerancija na galaktane nastaje kao posledica povećane fermentacije bakterija debelog creva (45). Simptomi uključuju nadimanje i grčeve u stomaku (45). Dijagnoza i terapija su slične ostalim fermentabilnim ugljenim hidratima (42).

Gluten predstavlja protein za skladištenje semena visoke molekularne težine koji se obično nalazi u žitaricama kao što su pšenica, ječam i raž (1,46). On hrani seme tokom cvetanja i klijanja, čime doprinose uspešnoj reprodukciji vrste (46). Gluten je kompozitni protein, sastavljen od glutenina i prolamina (46). Doprinosi kvalitetu testa i predstavlja sastavnu komponentu velikog broja namirnica koje sadrže pšenicu, uključujući hleb, žitarice i testeninu (1,46).

Intolerancija na gluten (necelijakijska osetljivost na gluten) podrazumeva sindrom kojeg karakterišu interstinalni i ekstraintestinalni simptomi povezani s konzumiranjem hrane koja sadrži

Table 3. Foods to contain high levels of fructose

Category	Food
Fruits	All fruits not on the allowed list, especially juices, dried fruits (such as prunes, raisins or dates) and fruits canned in juice or syrup)
Vegetables	Artichoke, asparagus, broccoli, chutney, leeks, mushrooms, okra, onions, peas, red pepper, shallots, tomato paste, tomato products (canned tomatoes, ketchup)
Cereals	Foods with wheat as a major ingredient (wheat bread, pasta, couscous), grains with added dried fruit, grains with added fructose
Meats	Marinated or processed meats
Dairy Products	Dairy product with fructose (yogurts, and flavored milks...)

hypophosphatemia, damage of proximal tubules of kidneys and liver (40). The severity of symptoms is proportional to the amount of ingested fructose (40). Smaller quantities cause vomiting, abdominal pain, diarrhea and hypoglycemia (40). In breastfed infants, great amounts of fructose may result in shock, acute kidney and liver failure and death (40).

Diagnosis of hereditary fructose intolerance is established with the help of genetic test which is commercially available (40). The treatment includes avoidance of fructose in the diet (40).

Acquired fructose intolerance appears as a consequence of malabsorption caused by the changes in the proteins glucose transporter 5 and glucose transporter 2 (GLUT 5 and GLUT 2) (38-42).

GLUT 5 is the only specific transporter of fructose that transports fructose passively from the apical membrane of enterocytes (predominantly in the duodenum and proximal jejunum) (42). GLUT 2 is an assistant transporter which has a low affinity with fructose (it may transport other monosaccharides such as glucose and galactose) (40). The absorption of fructose in the small intestines is limited, and a significant number of people cannot absorb more than 25 g/day (42).

The reduced activity of fructose transporters causes an increased osmotic load of the lumen, increased fermentation of bacteria in the colon, it harms the gastrointestinal motility and leads to the change in the intestinal flora (42).

Acquired intolerance to fructose is manifested as abdominal bloating, abdominal pain, nausea and diarrhea (41). Diagnosis is established with the help of hydrogen and/or methane breath test (1.5 to 3 hours after fructose consumption) (40). The most reliable form of prophylaxis and treatment is the elimination of fructose from the diet (38-41).

Polyols belong to the specific group of alcohols that are produced by hydrogenation of carbohydrates (42,43). Polyols are present in certain fruits (apple, apricot, avocado, blackberry, cherry, nectarine, pear, prunes, raisins), vegetables (cauliflower) and mushrooms (42,43). In addition, they are used as artificial sweeteners (instead of sacharose because they have fewer calories per gram) in many industrial products (candies, chewing gum, ice-cream, pastry, baked goods and chocolate) (42,43). Polyols may be found in toothpaste and mouthwash (41). The American Food and Drug Agency has approved the use of eight different polyols, including the following: erythritol, hydrogenated starch hydrolysates, isomalt, lactitol, maltitol, mannitol, sorbitol and xylitol (43).

Intolerance to polyols is the result o changes in the gut microbiota (43). It is manifested as abdominal bloating, pain and diarrhea (42,43). The symptoms increase with the amount of ingested polyols and consumption of other carbohydrates (43). Diagnosis of polyols intolerance is established with the help of breath test (polyols that are absorbed well such as sorbitol) or with the elimination diet (polyols that are not absorbed well such as manitol) (44).

Galactans are polymers of galactose (42). They are present in legumes such as beans, chick-pea, soy products, broccoli, nuts and cabbage (42). These foods are often part of vegetarian diet, of Indian and Mexican cuisine (42).

Intolerance to galactans is the result of increased fermentation of bacteria in the colon (45). The symptoms include abdominal bloating and cramps in the stomach (45). Diagnosis and treatment are similar to other fermentable carbohydrates (42).

gluten kod osoba kod kojih je isključena celijakija i alergija na gluten (1,47). Prevalencije samoprijavljene intolerancije na gluten iznosi 0,5-13,0% (45). Patofiziologija nije u potpunosti jasna (1,46,47). Predloženi mehanizmi uključuju crevnu disfunkciju te promenu crevnog mikrobioma (1,46,47).

Intolerancija na gluten može uzrokovati bol u trbuhu, dijareju, gubitak težine, glavobolju, umor, malaksalost, bol u mišićima, ponavljajuće oralne ulceracije i depresiju (47). U nedostatku seroloških i patohistoloških kriterija za postavljanje dijagnoze dvostruko slepo, placebom kontrolisano ispitivanje predstavlja zlatni standard u postavljanju dijagnoze (47). Terapija zahteva isključivanje glutena iz ishrane što neretko smanjuje nutritivnu adekvatnost i predstavlja socio-ekonomski teret (1,46-50). Obećavajuća većina terapija testiranih u kliničkim ispitivanjima (probiotici, modulatori crevne barijere, endopeptidaze, inhibitori transglutaminaze 2) pokazala je važna ograničenja (49).

Zaključak

Intolerancije na hranu predstavljaju zanimljivo i nedovoljno istraženo područje. Postoji značajna diskrepancija između prevalencije intolerancije na hranu utvrđene dvostruko slepim, placebom kontrolisanim istraživanjima i samoprijavljenih „bolesti“ ili „nelagode“' uzrokovanih unosom određene hrane.

Intolerancija na hranu se manifestuju širokim spektrom nespecifičnih gastrointestinalnih i ekstraintestinalnih simptoma i znakova. S druge strane, patogenetski mehanizmi određenih intolerancija na hranu, u prvom redu intolerancije na hranu nezavisni od domaćina nisu poznati.

Za mnoge intolerancije na hranu ne postoji pouzdan dijagnostički biomarker. Zbog toga se u postavljanju dijagnoze neretko koristi pristup pokušaja i greške koji podrazumeva uklanjanje jedinjenja s potencijalnom farmakološkom aktivnošću iz ishrane na kratak period, i njihovo postepeno ponovo uvođenje u ishranu. Odabir komponenti hrane za uklanjanje iz ishrane može se temeljiti na anamnestičkim podacima, kliničkim manifestacijama, i, gde je primenjivo, genetskim varijacijama.

Najpouzdaniji oblik profilakse i terapije intolerancija na hranu predstavlja isključivanje uzročnih komponenti iz ishrane. Međutim, promene u ishrani mogu uzrokovati smanjenje nutritivne adekvatnosti. Stoga je potrebna edukacija obolelih i, po mogućnosti, primena strategija za poboljšanje tolerancije na komponente hrane koja bi smanjila nivo neophodnih ograničenja u ishrani.

Konflikt interesa

Autori su izjavili da nema konflikta interesa.

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Gluten is a seed storage protein of high molecular weight usually found in grains such as wheat, barley and rye (1,46). It feeds the seed during flourishing and sprouting, thus contributing to the reproduction of species (46). Gluten is a composite protein, made of glutenin and prolamin. It contributes to the quality of dough and it is an ingredient of numerous foods that contain wheat, including bread, cereals, and pasta (1,46).

Gluten intolerance (non-celiac gluten sensitivity) is a disorder that is characterized by intestinal and extraintestinal symptoms associated with the consumption of food that contains gluten in persons, in whom celiac disease and allergy to wheat were excluded (1,47). The prevalence of self-reported intolerance to gluten amounts to 0.5-13.0% (45). The pathophysiology is not completely clear (1,46,47). The proposed mechanisms include intestinal dysfunction, and change in gut microbiome (1,46,47).

Intolerance to gluten may cause abdominal pain, diarrhea, weight loss, headache, fatigue, weakness, muscle pain, repeated oral ulcerations, and depression (47). Due to the lack of serological and pathohistological criteria necessary to make diagnosis, a double-blind, placebo-controlled examination is a gold standard of diagnostics (47). The treatment requires the elimination of gluten from the diet, which often reduces the nutritive adequacy and is a socio-economic burden (1,46-50). The majority of promising therapies tested in clinical trials (probiotics, modulation of gut barrier, endopeptidase, inhibitors of transglutaminase 2) have shown significant limitations (49).

Conclusion

Food intolerance is an interesting and insufficiently studied field of research. There is a significant discrepancy between the prevalence of food intolerance established by double-blind, placebo-controlled trials and self-reported “diseases” or “discomfort” caused by the ingestion of certain foods.

Food intolerance is manifested as a wide range of non-specific intestinal and extraintestinal signs and symptoms. On the other hand, pathogenetic mechanisms of certain food intolerances, first of all host-independent intolerance, are still not clear.There are no reliable diagnostic biomarkers for many food intolerances. Therefore, a trial-and-error approach is used, which means that food constituents with a potential pharmacological activity are reduced for a short period and then gradually reintroduced into the diet. The selection of components to be removed from the diet may be grounded on anamnestic data, clinical manifestations, and when it is applicable, by genetic variations.

The most reliable form of prophylaxis and treatment of food intolerances is the elimination of causative food components from the diet. However, changes in the diet may cause the reduction of nutritional adequacy. Therefore, the education of patients is necessary and possibly the implementation of strategies to improve tolerance to food components which would reduce the level of necessary limitations in the diet.

Competing interests

Authors declare no competing interests.

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Primljen: 09.08.2022. **Revizija:** 13.09.2022. **Prihvaćen:** 18.09.2022.

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Received: 08/09/2022. **Revised:** 09/13/.2022. **Accepted:** 09/18/.2022.