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PREGLEDNI RAD
REVIEW

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Impaired Gustation in Liver Diseases: A Comprehensive Narrative Literature Review

Poremećaj okusa kod bolesti jetre – sveobuhvatan narativni pregled literature

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Abstract
Objective: Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) is one of the fastest-growing liver disorders worldwide. It is driven by obesity and type 2 diabetes. Taste perception plays a key role in appetite regulation and nutrition, also influencing other liver diseases progression. This review summarizes past and current evidence on taste disorders in liver diseases and their clinical implications. **Materials and Methods:** A narrative review of PubMed, Web of Science, Google Scholar, and ResearchGate databases was conducted using selected MeSH terms. **Results:** Taste disturbances have been reported in viral hepatitis, cirrhosis, Wilson's disease, amebic liver abscesses, and NAFLD/MASLD, as well as in nutritional deficiencies (zinc, magnesium, vitamin A, branched-chain amino acids). Dysgeusia was linked to reduced appetite, sarcopenia, malnutrition, altered food preferences, and obesity risk in MASLD. Taste impairments worsen with liver dysfunction progression. Several drugs (e.g., interferon, metronidazole) contribute to dysgeusia. Zinc deficiency was the most consistent factor. Glucagon-like peptide-1 (GLP-1) receptor modulators, affecting appetite and sweet/umami perception, appear promising in MASLD therapy. **Conclusions:** Taste disorders are prevalent and still under-recognized in populations with liver diseases. The cause of these disorders remains unclear. Most of available studies affecting nutrients deficiencies are outdated. More research targeting molecular pathways of taste modulation (e.g., GLP-1 receptors), as well as determining the prevalence and clinical consequences of dysgeusia in specific liver disease stages is needed to better understand how micronutrient deficiencies and medications affect taste disorders.

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Introduction

Proper gustation is an important element of the eating meals process which conditions food intake habits and physiological digestion. In fact it also affects mental health (1). There are five basic types of taste including: sour, sweet, salty, bitter and umami (2). Taste disorders can manifest in various forms including dysgeusia, defined as a distortion or abnormal perception of taste (such as metallic, bitter, or otherwise altered sensations), and hypogeusia, understood as a partial reduction in taste sensitivity (3).

Dietary and oral hygiene patterns can influence oral health, induce structural changes in the oral mucosa, tongue, or brain, and consequently affect taste perception in different populations. Studies conducted at the University of Zagreb

Uvod

Pravilan osjet okusa važan je element u procesu jedenja koji uvjetuje navike unosa hrane i fiziološku probavu. Zapravo, utječe i na mentalno zdravlje (1). Pet je osnovnih vrsta okusa: kiseli, slatki, slani, gorki i umami (2). Poremećaji okusa mogu se manifestirati u različitim oblicima, primjerice, kao disgeuzija koja je definirana kao iskrivljenje ili abnormalna percepcija okusa (poput metalnoga, gorkoga osjeta, ili na drugi način promijenjenog osjeta) i hipogeuzija, što se shvaća kao djelomično smanjenje osjeta okusa (3).

Prehrambeni i oralno-higijenski uzorci mogu utjecati na oralno zdravlje, izazvati strukturne promjene u usnoj sluznici, jeziku ili mozgu i posljedično utjecati na percepciju okusa u različitim populacijama. Studija provedena na Sveučilištu demonstrated that attitudes toward oral hygiene are an important factor shaping oral health, which may directly affect taste perception and potentially modulate the risk of taste disorders in various population groups (4–8).

Taste disturbances may impact health outcomes and lead to a deterioration in quality of life, changes in eating habits, which may result in malnutrition or even obesity, potentially leading to MASLD (9,10). By 2050, it is estimated that in the majority of U.S. states, one-third of adolescents (aged 15–24) and approximately two-thirds of adults (aged 25 and older) will be suffering from obesity (11). Additionally, 19% of Americans over the age of 40 reported taste impairments, and 5% of them had dysgeusia. Prevalence increases with age up to 27% for people ≥ 80 (12). Many causes of taste disorders have been identified so far. Liver diseases are considered to be one of them (13). Currently, most publications focus on the nutritional status of patients and the nutrient deficiencies. Disturbed taste sensation has been demonstrated in both acute and chronic liver disease, including alcoholic/viral hepatitis, cirrhosis or metabolic associated steatotic liver disease (MASLD) (14,15). Changes in taste perception in this group may result from nutritional deficiencies, disturbances in signal transmission through neuronal pathways, coexisting diseases or medication intake (13). Taste disorders may contribute to reduced appetite in patients with liver cirrhosis, which, in turn, is significantly associated with the occurrence of sarcopenia and weight loss in this population (13,16). Moreover, taste disturbances in this group of patients may also result from coexisting oral diseases. It has been confirmed that oral lichen planus (OLP) occurs more frequently in individuals with viral hepatitis and may contribute to the presence of dysgeusia (17,18). Furthermore, vitamin D deficiency, which commonly coexists in patients with liver disease, is known to exacerbate the course of the OLP (19,20).

Impaired zinc metabolism is another possible mechanism. Zinc deficiency in patients with chronic liver disease seems to result from multiple factors such as impaired intake, absorption, transport, storage, and excretion of zinc (21). Recent studies emphasize malnutrition as one of the main causes of taste disorders related to micronutrients deficiency (15,22).

Considering a wide range of factors contributing to taste disturbances, liver diseases represent a significant area of interest due to their demonstrated impact on gustatory function. Evidence shows altered taste perception across various liver conditions - from hepatitis to cirrhosis which is often co-existing with nutritional deficiencies. However, the prevalence of dysgeusia and its connection to nutritional status in a group of liver diseases patients has not been thoroughly investigated. Existing studies on taste disturbances in cirrhosis are outdated, primarily centered on viral causes, and newer evidence shows that they do not evaluate the possible nutritional consequences (23–28). Understanding the relationship between liver dysfunction, micronutrient imbalances, and taste impairment can provide valuable insights into improving patient care and quality of life.

We aimed to compare older studies with the current knowledge to obtain a more comprehensive and up-to-date

u Zagrebu pokazala je da su stajališta prema oralnoj higijeni važan čimbenik koji oblikuje oralno zdravlje, što može izravno utjecati na percepciju okusa i potencijalno modulirati rizik od poremećaja okusa u različitim populacijskim skupinama (4 – 8).

Poremećaji okusa mogu utjecati na zdravstvene ishode i rezultirati pogoršanjem kvalitete života i promjenama u prehrambenim navikama, što može završiti pothranjenošću ili čak pretilošću, a to može potaknuti pojavu MASLD-a (9, 10). Procjenjuje se da će do 2050. godine u većini američkih saveznih država od pretilosti patiti jedna trećina adolescenata (u dobi od 15 do 24 godine) i otprilike dvije trećine odraslih u dobi od 25 i više godina (11). Osim toga, 19 % Amerikanaca starijih od 40 godina prijavilo je poremećaje okusa, od kojih je 5 % imalo disgeuziju. Prevalencija raste s dobi do 27 % za osobe ≥ 80 godina (12). Do sada je identificirano mnogo uzroka poremećaja okusa. Bolesti jetre smatraju se jednim od njih (13). Trenutačno se većina publikacija usredotočuje na nutritivni status pacijenata i nedostatke hranjivih tvari. Poremećaj osjeta okusa dokazan je i u slučaju akutnih i kroničnih bolesti jetre, uključujući alkoholni/virusni hepatitis, cirozu ili metabolički povezanu steatotičku bolest (MASLD) (14, 15). Promjene u percepciji okusa u toj skupini mogu biti posljedica nutritivnih nedostataka, poremećaja u prijenosu signala neuronskim putovima, istodobnih bolesti ili uzimanja lijekova (13). Poremećaji okusa mogu pridonijeti smanjenom teku pacijenata s cirozom jetre, što je pak značajno povezano s pojavom sarkopenije i gubitkom težine u toj populaciji (13, 16). Štoviše, poremećaji okusa u toj skupini pacijenata mogu biti i posljedica istodobnih oralnih bolesti. Potvrđeno je da se oralni lihen planus (OLP) češće pojavljuje kod osoba s virusnim hepatitisom i može pridonijeti nastanku disgeuzije (17, 18). Nadalje, poznato je da nedostatak vitamina D, koji često nastaje istodobno kod pacijenata s bolestima jetre, pogoršava tijek OLP-a (19, 20).

Drugi mogući mehanizam jest poremećeni metabolizam cinka. Čini se da je nedostatak toga kemijskog elementa kod oboljelih od kroničnih bolesti jetre posljedica više čimbenika poput poremećenog unosa, apsorpcije, transporta, skladištenja i izlučivanja cinka (21). Autori nedavnih studija ističu pothranjenost kao jedan od glavnih uzroka za poremećaj okusa povezanih s nedostatkom mikronutrijenata (15, 22).

information on taste disorders, thus highlighting potential causes, clinical implications and avenues for future research.

Material and Methods

This review study was conducted through an analysis of articles available in the PubMed, Web of Science, Google Scholar and ResearchGate databases. The MeSH terms used for search included: liver diseases, taste, taste perception, taste disorders, taste buds, taste receptors type 2, taste receptors type 1, liver cirrhosis, dysgeusia, MASLD.

Consistency and terminological accuracy were maintained in accordance with the principles of medical language and characteristic collocations (29).

1. Inclusion criteria for this review were as follows:
   · Human clinical studies: RCTs, cohort, observational, or cross-sectional studies on taste disorders in liver diseases.
   · Experimental animal studies addressing mechanisms of taste disturbances in liver disease.
   · Case reports and case series on taste disorders related to liver disease or pharmacological treatment.
   · Interventional studies evaluating drugs or supplements on taste perception.
   · Systematic reviews and meta-analyses providing synthesized evidence on prevalence, mechanisms, and interventions.
   · Publications in English or Polish.
2. Exclusion criteria:
   · Studies which are not related to liver disease or taste disorders,
   · Papers which are not available in full text or of insufficient methodological quality (e.g., no description of study population, no clear assessment of taste evaluation methods),
   · Studies involving drugs no longer used in current clinical practice for the treatment of liver disease,
   · Publications in foreign languages other than those mentioned in inclusion criteria.

A total of 65 articles were included in the review: 3 case reports (including case series), 28 review articles (including 3 meta-analyses), 32 original studies, and 2 studies conducted on animal models.

The selected articles explain the connection between taste disorders and various liver diseases both on humans and animal models. These study review papers describe the effects of drugs administration or potential impact of nutrients including zinc, vitamin A, magnesium or branched-chain amino acids (BCAA) on taste disorders. Despite many variables that qualify articles for review, searched databases contain a small number of up-to-date studies of up to date studies directly involving this issue.

Results

Alterations in Taste Perception in Liver Disease

Associations between oral health and liver diseases suggest that periodontitis may lead to progression of liver disease (30,31). It is also known that taste impairments may

Materijali i metode

Ovaj pregledni rad temelji se na analizi članaka dostupnih u bazama podataka PubMed, Web of Science, Google Scholar i ResearchGate. Termini MeSH-a korišteni za pretraživanje uključivali su bolesti jetre, okus, percepciju okusa, poremećaje okusa, okusne pupoljke, okusne receptore tip 2, okusne receptore tip 1, cirozu jetre, disgeuziju i MASLD.

Dosljednost i terminološka točnost održavane su u skladu s načelima medicinskog jezika i karakterističnim kolokacijama (29).

1. Kriteriji za uključivanja u ovaj pregled bili su sljedeći:
   • kliničke studije na ljudima: RCT-ovi, kohortne, opservacijske ili presječne studije o poremećajima okusa kod oboljelih od bolesti jetre
   • eksperimentalne studije na životinjama koje se bave mehanizmima poremećaja okusa kod bolesti jetre
   • izvješća o slučajevima i serije slučajeva o poremećajima okusa, a povezani su s bolešću jetre ili farmakološkim liječenjem
   • intervencijske studije u kojima se procjenjuje utjecaj lijekova ili dodataka prehrani na percepciju okusa
   • sustavni pregledi i metaanalize koje pružaju sintetizirane dokaze o prevalenciji, mehanizmima i intervencijama
   • časopisi na engleskome ili poljskom jeziku
2. Kriteriji za isključivanje:
   • studije koje nisu povezane s bolestima jetre ili poremećajima okusa
   • radovi koji nisu dostupni cjeloviti ili nisu dovoljno metodološki kvalitetni (npr., nema opisa ispitivane populacije, nema jasne procjene metoda procjene okusa)
   • studije koje uključuju lijekove koji se više ne koriste u kliničkoj praksi za liječenje bolesti jetre
   • časopisi na stranim jezicima, osim onih navedenih u kriterijima za uključivanje.

U pregled je obuhvaćeno ukupno 65 članaka: 3 prikaza slučaja (uključujući serije slučajeva), 28 preglednih članaka (uključujući 3 metaanalize), 32 izvorne studije i 2 studije provedene na životinjskim modelima.

U odabranim člancima objašnjena je veza između poremećaja okusa i različitih bolesti jetre i kod ljudi i kod životinjskih modela. U ovoj studiji pregledani su radovi u kojima se opisuju učinci primjene lijekova ili potencijalni utjecaj hranjivih tvari, uključujući cink, vitamin A, magnezij ili aminokiseline razgranatog lanca (BCAA) na poremećaje okusa. Unatoč mnogim varijablama koje kvalificiraju članke za pregled, pretražene baze podataka sadržavaju malo ažuriranih studija koje se izravno bave ovim problemom.

Rezultati

Promjene percepcije okusa kod bolesti jetara

Povezanost između oralnoga zdravlja i bolesti jetre sugerira da parodontitis može potaknuti progresiju bolesti jetre (30, 31). Također je poznato da parodontitis može prouzrobe induced by periodontitis through mediation by halitosis (32). The available literature contains the results of the occurrence of taste disorders in both acute and chronic liver diseases. The analyzed studies often included groups with different stages of liver injury. Symptoms may be less severe in mild stages. However, in advanced stages including liver cirrhosis, severe taste impairments and oral pain are observed, co-existing with poorer oral hygiene (31,33). Disturbances in feeling of salty and umami flavors are mostly observed in this group (34).

Evidence for the occurrence of taste impairments in the viral liver infection is the case of a patient with acute hepatitis- E virus (HEV)-associated Guillain-Barre syndrome (GBS). Despite the illness related symptoms, the patient also referred dysgeusia of sweet, salty, sour, and bitter and umami tastes. Intravenous immunoglobulin (IVIg) was administered to the patient at a dose of 400 mg/kg per day for five days with effect of full gustatory function recovery. The authors revealed its two potential mechanisms including: acute hepatitis and GBS (35). During the acute phase of hepatitis, urinary zinc excretion may increase, leading to a decrease in serum zinc concentration (36). The underlying mechanism likely involved damage to gustatory neural pathways-from taste buds and peripheral nerves to central structures such as the brainstem, thalamus, and cortex (37).

Smith et al. (38) investigated taste disturbances in a cohort of 22 patients with acute viral hepatitis and 16 patients with chronic liver disease, including 14 patients with cirrhosis. Compared with a healthy control population, the patients demonstrated both subjective complaints and objective impairments in gustatory function. Specifically, the mean detection thresholds for bitter, salty, sweet, and sour tastes, as well as the mean recognition thresholds for bitter, salty, and sour tastes, were significantly elevated in both the acute and chronic hepatitis groups. The alterations were reversible with hepatic function recovery. Although the exact mechanism of hypogeusia remained unclear, the current evidence suggests that nutritional disturbances associated with cirrhosis are the most likely contributing factor.

Probably, the first published study examining the relationship between the perception of all five tastes and patients with liver disease was the research conducted by Musialik et al. Forty patients with chronic viral C hepatitis (CHC) were examined (39). Patients were stratified according to the degree of liver fibrosis, with one subgroup representing an early-stage fibrosis and the other representing advanced fibrosis. The results showed that recognition of sour, bitter, and sweet tastes was similar between CHC patients and the healthy controls. However, the recognition threshold for umami taste was significantly increased ($P < 0.01$) in CHC patients compared with controls, indicating reduced ability to identify umami. In addition, the perception of sweet taste was significantly heightened ($P < 0.05$). These alterations were more pronounced in patients with advanced fibrosis. A similar trend was noted for salty taste recognition ($P = 0.075$), while the intensity of sour taste perception was lower. In summary, the authors reported alterations across all taste modalities except bitter (39).

čiti poremećaje okusa posredovanjem halitoze (32). Dostupna literatura sadržava rezultate o pojavi poremećaja okusa i u slučaju akutnih i kroničnih bolesti jetre. U analiziranim studijama autori su često uključivali skupine s različitim stadijima oštećenja jetre. Simptomi mogu biti manje teški u blagim stadijima. No u napredovalim stadijima, uključujući cirozu jetre, uočavaju se teški poremećaji okusa i bol u ustima koji koegzistiraju s lošijom oralnom higijenom (31, 33). Poremećaji osjeta slanog okusa uglavnom se uočavaju u toj skupini (34).

Jedan od dokaza za pojavu poremećaja okusa kod virusne infekcije jetre jest slučaj pacijenta s akutnim Guillain-Barréovim sindromom (GBS) povezanim s virusom hepatitisa E (HEV). Unatoč simptomima povezanima s bolešću, pacijent je također spomenuo disgeuziju slatkoga, slanoga, kiseloga i gorkog okusa. Zato mu je intravenski apliciran imunoglobulin (IVIg) u dozi od 400 mg/kg na dan tijekom pet dana s učinkom potpunog oporavka gustatorne funkcije. Autori su otkrili dva potencijalna mehanizma, uključujući akutni hepatitis i GBS (35). Tijekom akutne faze hepatitisa izlučivanje cinka urinom može se povećati, što smanjuje koncentraciju toga kemijskoga elementa u serumu (36). Temeljni mehanizam vjerojatno uključuje oštećenje gustatornih živčanih putova – od okusnih pupoljaka i perifernih živaca do središnjih struktura poput moždanoga debla, talamusa i korteksa (37).

Smith i suradnici (38) istraživali su poremećaje okusa u kohorti od 22 pacijenta s akutnim virusnim hepatitisom i 16 pacijenata s kroničnom bolešću jetara, uključujući 14 s cirozom. U usporedbi sa zdravom kontrolnom populacijom, pacijenti su pokazali i subjektivne tegobe i objektivna oštećenja gustatorne funkcije. Točnije, prosječni pragovi detekcije gorkoga, slanoga, slatkoga i kiselog okusa, te prosječni pragovi prepoznavanja gorkoga, slanoga i kiseloga, bili su značajno povišeni i u skupini s akutnim hepatitisom i u onoj s kroničnim oblikom te bolesti. Promjene su bile reverzibilne s oporavkom jetrene funkcije. Iako točan mehanizam hipogeuzije ostaje nejasan, trenutačni dokazi upućuju na to da su prehrambeni poremećaji povezani s cirozom najvjerojatniji čimbenik koji joj pridonosi.

Pretpostavlja se da je prva objavljena studija u kojoj je ispitivan odnos između percepcije svih pet okusa i pacijenata s bolešću jetre bilo istraživanje Musialika i suradnika. Pregledali su 40 pacijenata s kroničnim virusnim hepatitisom C (CHC) (39). Svi su stratificirani prema stupnju fibroze jetre, pri čemu jedna podskupina predstavlja fibrozu u ranom stadiju, a druga napredovalu fibrozu. Rezultati su pokazali da je prepoznavanje kiseloga, gorkoga i slatkoga okusa bilo slično kod pacijenata s CHC-om i zdravih kontrolnih skupina. No prag prepoznavanja okusa umami bio je značajno povećan ($P < 0,01$) kod pacijenata s CHC-om u usporedbi s kontrolnom skupinom, što upućuje na smanjenu sposobnost prepoznavanja slanoga. Uz to, percepcija slatkoga okusa bila je značajno pojačana ($P < 0,05$). Te promjene bile su izraženije kod pacijenata s napredovalom fibrozom. Sličan trend uočen je pri prepoznavanju slanog okusa ($P = 0,075$), a intenzitet percepcije kiseloga bio je niži. Ukratko, autori su izvijestili o promjenama u svim modalitetima okusa, osim gorkoga (39).

There is a connection between liver cirrhosis and taste disorders which often include sweet taste aversion and salty taste intolerance. Sturniolo et al. (40) presented, in spite of impaired perception of sweet and salty taste, some abnormalities in sour taste perception among a liver cirrhosis group.

An animal model study, conducted by Fernandes et al. (41), on fourteen male Wistar rats with liver cirrhosis showed some morphological changes in the structure of the tongue. There have been some differences related to a significant reduction in the foliate papillae (not responsible for the sense of taste), papillae narrowing particularly in the base diameter and the apical region. It has been found that some rats in the cirrhosis group had only one taste bud per field, whereas others contained no taste buds. The presence of taste buds per field ranged from two to six in the control group. There was also positive immunoreactivity for the T1R3 receptor (belonging to the T1R family, responsible for the proper perception of sweet taste) in controls, not observed in the study group.

MASLD is currently the most prevalent chronic liver disease worldwide, affecting over 30% of the global population and closely associated with obesity and type 2 diabetes mellitus (42,43). Appetite regulation and energy balance play central roles in MASLD pathogenesis. Glucagon-like peptide-1 (GLP-1) receptor agonists are the most promising therapeutic targets, which improves the metabolic dysfunction in MASLD (44). These agents reduce food intake, promote weight loss, and improve glucose tolerance through both central and peripheral mechanisms (45–47). Recent studies have also identified an additional, less recognized role of GLP-1 - signaling in modulating taste perception. The presence of GLP-1 receptors on gustatory nerve fibers suggests the involvement in sensory regulation (48). Supporting this notion, animal models lacking these receptors show significantly diminished responses to sweet stimuli, implicating GLP-1 pathways in the maintenance of sweet taste sensitivity and potentially influencing food preferences and intake behavior (49).

In an observational study conducted by Dallio et al. (15) the prevalence of dysgeusia in patients with advanced chronic liver disease (ACLD) related to MASLD was assessed, comparing its severity to stage of liver function. Dysgeusia increased with liver disease progression. Only 5% of patients without liver fibrosis were affected, comparing to 33% of patients with advanced stages of liver impairment. Taste disturbances increased from 7% in compensated (cACLD) to 59% in decompensated (dACLD). No significant difference was found between dACLD patients with active vs. past decompensation, suggesting dysgeusia is linked to liver injury stage rather than current symptoms. Dysgeusia was most commonly observed in both ascites and hepatic encephalopathy group. Importantly, 90.2% of dACLD patients with dysgeusia also had appetite loss, while none of them showed appetite loss without dysgeusia, thus indicating that dysgeusia may contribute to reduced appetite.

Emelyanov and Petrushanko (50) examined the oral and sensory alterations in a cohort of 258 patients with non-alcoholic fatty liver disease (NAFLD), a condition recognized

Veza između ciroze i poremećaja okusa često uključuje averziju prema slatkom okusu i intoleranciju na slani okus. Sturniolo i suradnici (40) istaknuli su, unatoč oštećenoj percepciji slatkoga i slanog okusa, i abnormalnosti u percepciji kiseloga u skupini s cirozom jetre. Studija na temelju životinjskog modela koju su proveli Fernandes i suradnici (41) na četrnaest mužjaka štakora Wistar s cirozom jetre pokazala je morfološke promjene u strukturi jezika. Razlike su se odnosile na veliko smanjenje lisnatih papila (koje nisu odgovorne za osjet okusa), sužavanje papila, posebno u promjeru baze i apikalnoj regiji. Utvrđeno je da su neki štakori u skupini s cirozom imali samo jedan okusni pupoljak po polju, a drugi ih nisu imali. Broj okusnih pupoljaka po polju kretala se od dva do šest u kontrolnoj skupini. Također je postojala pozitivna imunoreaktivnost za receptor T1R3 (pripada obitelji T1R, a odgovoran je za pravilnu percepciju slatkog okusa) u kontrolnoj skupini, što nije uočeno u ispitivanoj skupini.

MASLD je trenutačno najraširenija kronična bolest jetre na svijetu – pogađa više od 30 % svjetske populacije i usko je povezana s pretilošću i dijabetesom tip 2 (42, 43). Regulacija apetita i energijska ravnoteža najvažniji su u patogenezi te bokesti. Agonisti receptora sličnoga glukagonu peptida-1 (GLP-1), najperspektivniji su terapijski ciljevi koji poboljšavaju metaboličku disfunkciju u slučaju MASLD-a (44). Ti agensi smanjuju unos hrane, potiču gubitak težine i poboljšavaju toleranciju glukoze putem centralnih i perifernih mehanizama (45 – 47). U nedavnim studijama autori su također identificirali dodatnu, manje prepoznatu ulogu signalizacije GLP-1 u modulaciji percepcije okusa. Prisutnost receptora GLP-1 na vlaknima okusnih živaca sugerira uključenost u senzornu regulaciju (48). To potvrđuje i činjenica da životinjski modeli kojima nedostaju ti receptori pokazuju znatno smanjene odgovore na slatke podražaje, što implicira GLP-1 putove u održavanju osjetljivosti na slatki okus i potencijalno utječe na preferencije hrane i ponašanje pri unosu (49).

U opservacijskoj studiji koju su proveli Dallio i suradnici (15) procijenjena je prevalencija disgeuzije kod pacijenata s napredovalom kroničnom bolešću jetre (ACLD) povezanom s MASLD-om, uspoređujući njezinu težinu sa stadijem funkcije tog organa. Disgeuzija se povećavala s progresijom bolesti jetre. Samo 5 % pacijenata bez fibroze bilo je pogođeno, u usporedbi s 33 % s napredovalim stadijima oštećenja jetre. Poremećaji okusa povećali su se sa 7 % kod kompenziranih (cACLD) na 59 % kod dekompenziranih (dACLD). Nije pronađena značajna razlika između pacijenata s dACLD-om s aktivnom i prošlom dekompenzacijom, što sugerira da je disgeuzija povezana sa stadijem oštećenja jetre, a ne s trenutačnim simptomima. Disgeuzija je najčešće uočena i u skupini s ascitesom i u skupini s hepatičkom encefalopatijom. Važno je napomenuti da je 90,2 % pacijenata s dACLD-om s disgeuzijom također imalo gubitak apetita, a nitko nije pokazao gubitak teka bez disgeuzije, što upućuje na to da disgeuzija može pridonijeti smanjenom apetitu.

Emelyanov i Petrushanko (50) ispitali su oralne i senzorne promjene u kohorti od 258 pacijenata s nealkoholnom masnom bolešću jetre (NAFLD), stanjem koje je prepoznato kao dio šireg spektra MASLD-a. Autori su pokazali da je 82,6 % pacijenata iskusilo poremećaje okusa, uglavnom u as part of the broader MASLD spectrum. The study demonstrated that 82.6% of the patients experienced taste disturbances, primarily in the form of dysgeusia manifesting as a reduced or altered perception of taste. These alterations were frequently accompanied by signs of oral mucosal inflammation, dry mouth, and other dental pathologies, suggesting a multifactorial origin linked to both local (oral) and systemic metabolic dysfunction. The authors emphasized that such sensory impairments may negatively influence dietary patterns and food preferences, potentially contributing to further metabolic deterioration in patients with NAFLD/MASLD. Their findings underscore the importance of recognizing taste disorders as a relevant clinical feature in liver disease, particularly given their possible implications for nutritional status and disease progression.

In a Polish study (10) involving 84 individuals with NAFLD and 120 healthy controls, it was shown that most common taste alterations involve sweet and umami tastes. A significantly increased recognition threshold and decreased intensity of perception for these tastes were observed. Patients reported a reduced pleasure from consuming sweet products and increased enjoyment of foods rich in umami (e.g., fish, dairy). These changes were more pronounced in individuals with advanced liver fibrosis and steatosis. Additionally, the study found that taste disturbances may influence patients' food preferences and contribute to overweight and metabolic disorders.

In the searched databases there is only one research investigating taste dysfunction among patients with Wilson's disease (WD) (51). WD is a rare autosomal recessive, metabolic dysfunction contributing to abnormal copper accumulation in organs involving liver, brain and others. Pathomechanism involves impaired secretion of copper into bile which clinically presents as hepatic, psychiatric and neurological symptoms. A predominance of hepatic symptoms may lead to mild liver dysfunction, chronic hepatitis, cirrhosis or a rare acute liver failure. WD patients are treated with copper chelators trientine and penicillamine. The second group of medications is zinc which lowers intestinal copper absorption (52).

In the research Salmon et al. (51), the patients were stratified into two symptom subtypes: hepatic and neurologic predominant of WD. Regarding the obtained results, the patients with WD regardless of subtype had no decrease in taste function while a significant decrease in olfactory function was observed compared to healthy controls. Nonetheless, the factory and gustatory test scores were weakly correlated in both WD and control subjects. It is unclear whether WD, especially liver symptoms severity influences gustation. Also, the pathophysiologic mechanism responsible for test and smell disorders in this group remains unclear. Further research is required on larger cohorts.

Taste disorders during treatment of liver diseases

In the study conducted by Klimacka-Nawrot et al. (26) the correlation between pegylated interferon-alpha, ribavirin therapy and taste acuity in patients with chronic type C hepatitis was assessed. After 12 weeks of therapy, sensitivi-

obliku disgeuzije koja se manifestira kao smanjena ili promijenjena percepcija okusa. Te promjene često su bile praćene znakovima upale oralne sluznice, suhim ustima i drugim dentalnim patologijama, što sugerira multifaktorijalno podrijetlo povezano s lokalnom (oralnom) i sistemskom metaboličkom disfunkcijom. Autori su istaknuli da takva senzorna oštećenja mogu negativno utjecati na prehrambene modele i preferenciju hrane te potencijalno pridonositi daljnjem metaboličkom pogoršanju stanja pacijenata s NAFLD-om/MASLD-om. Njihovi nalazi pokazuju koliko je važno prepoznati poremećaje okusa kao relevantne kliničke značajke bolesti jetre, posebno s obzirom na njihove moguće implikacije na nutritivni status i napredovanje bolesti.

U poljskoj studiji (10) koja je obuhvatila 84 osobe s NAFLD-om i 120 zdravih kontrolnih osoba, istaknuto je da se najčešće promjene okusa odnose na slatki i umami okus. Uočen je značajno povećan prag prepoznavanja i smanjen intenzitet percepcije tih okusa. Pacijenti su izvijestili o smanjenom zadovoljstvu pri konzumiranju slatkih proizvoda i povećanom uživanju u hrani bogatoj umamijem (npr., riba, mliječni proizvodi). Te promjene bile su izraženije kod osoba s napredovalom fibrozom i steatozom. Uz to, autori studije otkrili su da poremećaji okusa mogu utjecati na preferencije pacijenata kad je riječ o hrani i pridonijeti prekomjernoj težini i metaboličkim poremećajima.

U pretraženim bazama podataka samo je jedno istraživanje u kojemu se istražuje disfunkcija okusa među pacijentima s Wilsonovom bolešću (WB) (51). WB je rijetka autosomno recesivna metabolička disfunkcija koja pridonosi abnormalnom nakupljanju bakra u organima među kojima su jetra, mozak i drugi. Patomehanizam uključuje oštećeno izlučivanje bakra u žuč, što se klinički manifestira kao jetreni, psihijatrijski i neurološki simptomi. Predominantna jetrena bolest može potaknuti blagu disfunkciju jetre, kronični hepatitis, cirozu, ili rijetko akutno zatajenje jetre. Pacijenti s WD-om liječe se kelatorima bakra trientinom i penicilaminom. Druga skupina lijekova je cink koji smanjuje apsorpciju bakra u crijevima (52).

U istraživanju Salmona i suradnika (51) pacijenti su stratificirani u dva podtipa simptoma: predominantni jetreni i neurološki WD. U rezultatima pacijenti s WD-om, bez obzira na podtip, nemaju smanjenje funkcije okusa, no uočeno je značajno smanjenje olfaktorne funkcije u usporedbi sa zdravim kontrolnim skupinama. Ipak, rezultati tvorničkih i gustatornih testova bili su slabo korelirani i za ispitanike s WD-om i za kontrolne ispitanike. Nije jasno utječe li WD na gustaciju, posebno težina jetrenih simptoma, nepoznati su patofiziološki mehanizmi odgovorni za poremećaje okusa i mirisa u toj skupini. Potrebna su daljnja istraživanja na većim kohortama.

Poremećaji okusa tijekom liječenja bolesti jetre

U studiji koju su proveli Klimacka-Nawrot i suradnici (26) procijenjena je korelacija između pegiliranoga interferona-alfa, terapije ribavirinom i oštrine okusa bolesnika s kroničnim hepatitisom tipa C. Nakon 12 tjedana terapije ty to salty and sweet was significantly decreased ($p < 0.05$), and sensitivity to bitter was described as being more unpleasant than before therapy ($p < 0.05$). The findings demonstrated that taste disturbances during therapy are multidirectional. No significant changes in food preferences were reported; however, a decrease in appetite was noted.

In order to evaluate the potential effects of adding boceprevir to the above-mentioned therapy, a double-blind study was conducted. The results showed that dysgeusia was reported more than twice as frequently in the boceprevir-treated groups compared to the control groups (24). Also in the study assessed by Bacon et al., dysgeusia was observed more frequently in the boceprevir groups than in the controls (25).

The literature also includes a comparison of treatment strategies for amebic liver abscess using metronidazole versus satranidazole. It has been demonstrated that a metallic taste occurred less frequently in patients treated with satranidazole. Furthermore, satranidazole was associated with significantly better tolerability compared to metronidazole, while maintaining similar therapeutic efficacy. Patients receiving satranidazole reported fewer adverse effects overall (27).

In a larger randomized clinical trial conducted in India (53), the efficacy and tolerability of metronidazole and tinidazole (derivatives of 5-nitroimidazole, like satranidazole) were compared in 150 patients with amoebic liver abscess. Patients were divided into two equal groups receiving either metronidazole or tinidazole. Taste disturbances in the form of a metallic taste were reported in 13.3% of patients in the metronidazole group and in 2.6% of patients in the tinidazole group ($p = 0.03$).

On the other hand, a meta-analysis conducted in 2021 (54) found that the incidence of metallic taste as an adverse effect was slightly lower with metronidazole compared to tinidazole. Although the difference was not statistically significant, switching from tinidazole to metronidazole could potentially reduce the incidence of metallic taste by 5.1%, while also offering broader antimicrobial coverage than tinidazole.

A summary of literature data regarding taste disorders in selected liver diseases and administered drugs is presented in *Table 1.*

Nutrients deficiency in liver diseases

The liver plays a crucial role in nutrient metabolism. Therefore, cirrhosis significantly impairs metabolic pathways, negatively impacting patient prognosis (55). Malnutrition is a common complication in liver cirrhosis and is frequently accompanied by nutritional deficiencies, including zinc deficiency (22,56).

Zinc participates in protein structures formation, enzymes, transcription factors and homeostasis. It also has anti-inflammatory, anti-oxidant and anti- apoptotic properties, thus inhibiting cirrhosis-related fibrosis by modulating the function of hepatic stellate cells. Zinc deficiency may be responsible for the development or even intensification of malnutrition with hypoalbuminemia and hypogeusia. Clinically, zinc deficiency may present as worsening of appetite, hair loss, testicle atrophy, abnormal taste and smell, immunology

osjetljivost na slano i slatko značajno se smanjila ($p < 0,05$), a gorko je opisano kao neugodnije nego prije terapije ($p < 0,05$). Nalazi su pokazali da su poremećaji okusa tijekom terapije višesmjerni. Nisu zabilježene velike promjene u preferencijama hrane, ali zabilježeno je smanjenje teka.

Kako bi se procijenili potencijalni učinci dodavanja boceprevira gore spomenutoj terapiji, provedena je dvostruko slijepa studija. Rezultati su pokazali da je disgeuzija prijavljena više od dvostruko češće u skupinama liječenih boceprevirom u usporedbi s kontrolnim skupinama (24). Također u studiji koju su procijenili Bacon i suradnici, disgeuzija je češće uočena u skupinama liječenih boceprevirom nego u kontrolnima (25).

Literatura također uključuje usporedbu strategija liječenja amebnoga apscesa jetre korištenjem metronidazola u odnosu na satranidazol. Dokazano je da se metalni okus pojavljuje rjeđe pacijentima liječenima satranidazolom. Nadalje, satranidazol je bio povezan sa značajno boljom podnošljivošću u usporedbi s metronidazolom, uz održavanje slične terapijske učinkovitosti. Pacijenti koji su primali satranidazol prijavili su manje nuspojava ukupno (27).

U većem randomiziranom kliničkom ispitivanju provedenom u Indiji (53) uspoređena je učinkovitost i podnošljivost metronidazola i tinidazola (derivati 5-nitroimidazola, poput satranidazola), a sudjelovalo je 150 pacijenata s amebnim apscesom jetre. Bili su podijeljeni u dvije jednake skupine koje su primale ili metronidazol ili tinidazol. Poremećaji okusa poput metalnog okusa zabilježeni su kod 13,3 % pacijenata u skupini s metronidazolom i kod 2,6 % pacijenata u skupini s tinidazolom ($p = 0,03$).

S druge strane, metaanaliza provedena 2021. (54) otkrila je da je incidencija metalnog okusa kao nuspojave bila nešto niža kod metronidazola u usporedbi s tinidazolom. Iako razlika nije bila statistički značajna, prelazak s tinidazola na metronidazol potencijalno bi mogao smanjiti učestalost metalnog okusa za 5,1 %, a istodobno bi nudio širu antimikrobnu pokrivenost od tinidazola.

Sažetak podataka iz literature o poremećajima okusa kod odabranih bolesti jetre i primijenjenih lijekova nalazi se u tablici 1.

Nedostatak hranjivih tvari kod bolesti jetara

Jetra je ključna u metabolizmu hranjivih tvari. Stoga ciroza značajno narušava metaboličke putove, negativno utječući na prognozu pacijenta (55). Pothranjenost je česta komplikacija ciroze jetre i često je praćena nutritivnim nedostatcima, uključujući nedostatak cinka (22, 56). Cink sudjeluje u stvaranju proteinskih struktura, enzima, transkripcijskih faktora i homeostaze. Također ima protuupalna, antioksidacijska i antiapoptotička svojstva, inhibirajući fibrozu povezanu s cirozom modulirajući funkciju jetrenih zvjezdastih stanica. Nedostatak cinka može biti odgovoran za pojavu ili čak pogoršanje pothranjenosti s hipoalbuminemijom i hipogeuzijom. Klinički nedostatak toga kemijskog elementa može se manifestirati kao pogoršanje teka, gubitak kose, atrofija testisa, abnormalni okus i miris, imunosni ili čak neurološki defekti (57).

Table 1 Comparison between taste disorders in selected liver diseases and administered drugs
Tablica 1. Usporedba poremećaja okusa kod odabranih bolesti jetara i primijenjenih lijekova

Type of liver disease • Vrsta bolesti jetara	Type of study • Vrsta studije	Characteristics of groups • Karakteristike skupina	A type of taste disorder • Vrsta poremećaja okusa	N (%) of disorder • N (%) poremećaja	References • Referencija
Hepatitis C virus • Virus hepatitisa C	Double-blinded randomized controlled trial • Dvostruko zaslijepljeno randomizirano kontrolirano ispitivanje	Group 1 (control group = 363): • Skupina 1 (kontrolna skupina, N = 363): peginterferon alfa-2b ribavirin for 4 weeks next placebo plus peginterferon–ribavirin for 44 weeks • peginterferon alfa-2b ribavirin tijekom 4 tjedna, zatim placebo plus peginterferon-ribavirin tijekom 44 tjedna	Dysgeusia • Disgeuzija	64 (18%)	Poordad et al. 2011(24)
		Group 2 • Skupina 2 (N = 368): peginterferon alfa-2b–ribavirin for 4 weeks next boceprevir plus peginterferon–ribavirin for 24 weeks, and patients with a detectable HCV RNA level between weeks 8 and 24 administered placebo plus peginterferon-ribavirin for an extra 20 weeks • peginterferon alfa-2b-ribavirin tijekom 4 tjedna, zatim boceprevir plus peginterferon-ribavirin tijekom 24 tjedna, a pacijenti s detektabilnom razinom HCV RNA između 8. i 24. tjedna primali su placebo plus peginterferon-ribavirin tijekom dodatnih 20 tjedana	Dysgeusia • Disgeuzija	137 (37%)	
		Group 3 • Skupina 3 (N = 366): peginterferon alfa-2b–ribavirin for 4 weeks next boceprevir plus peginterferon–ribavirin for 44 weeks • peginterferon alfa-2b-ribavirin tijekom 4 tjedna, zatim boceprevir plus peginterferon-ribavirin tijekom 44 tjedna	Dysgeusia • Disgeuzija	156 (43%)	
	Single-blinded randomized controlled trial • Jednostruko zaslijepljeno randomizirano kontrolirano ispitivanje	Group 1 (control group, N = 80) • Skupina 1 (kontrolna skupina, N = 80) peginterferon alfa-2b ribavirin for 4 weeks next placebo plus peginterferon–ribavirin for 44 weeks • peginterferon alfa-2b ribavirin tijekom 4 tjedna, zatim placebo plus peginterferon-ribavirin tijekom 44 tjedna	Dysgeusia • Disgeuzija	9 (11%)	Bacon et al. 2011 (25)
		Group 2 • Skupina 2 (N = 162)): peginterferon alfa-2b–ribavirin for 4 weeks next boceprevir plus peginterferon–ribavirin for 32 weeks, and patients with a detectable HCV RNA level at week 8 administered placebo plus peginterferon–ribavirin for an extra 12 weeks • peginterferon alfa-2b-ribavirin tijekom 4 tjedna, zatim boceprevir plus peginterferon-ribavirin tijekom 32 tjedna, a pacijenti s detektabilnom razinom HCV RNA u 8. tjednu primali su placebo plus peginterferon-ribavirin tijekom dodatnih 12 tjedana	Dysgeusia • Disgeuzija	69 (43%)	
		Group 3 • Skupina 3 (N = 161): peginterferon alfa-2b–ribavirin for 4 weeks next boceprevir plus peginterferon–ribavirin for 44 weeks • peginterferon alfa-2b-ribavirin tijekom 4 tjedna, zatim boceprevir plus peginterferon-ribavirin tijekom 44 tjedna	Dysgeusia • Disgeuzija	72 (45%)	
Chronic hepatitis C • Kronični hepatitis C	Non-randomized controlled trial • Nerandomizirano kontrolirano ispitivanje	Group 1 • Skupina 1 (N=19) pegylated interferon-alpha 2b and ribavirin • pegilirani interferon-alfa 2b i ribavirin	Sensitivity to salty and sweet was decreased. • Osjetljivost na slano i slatko bila je smanjena. Bitter was more unpleasant than before the therapy. • Gorko je bilo neugodnije nego prije terapije.	19 (100%)	Klimacka-Nawrot et al. 2009 (26)
Amebic Liver Abscess • Amebni apsces jetara	Single-blinded randomized controlled trial with placebo • Jednostruko zaslijepljeno randomizirano kontrolirano ispitivanje s placebom	Group 1 • Skupina 1 (N=25) Metronidazole • Metronidazol	Metallic taste • Metalni okus	18 (72%)	Muzaffar et al. 2006 (27)
		Group 2 • Skupina 2 (placebo, N=24) Satranidazole • Satranidazol	Metallic taste • Metalni okus	3 (12.5%)	
	A randomized control trial • Randomizirano kontrolirano ispitivanje	Group M- Metronidazole (N=75) • Skupina M - Metronidazol (N=75)	Metallic taste • Metalni okus	10 (13.3%)	Sudhakar et al. 2018 (53)
		Group T- Tynidazole (N=75) • Skupina T - Tinidazol (N=75)	Metallic taste • Metalni okus	2 (2.6%)	

or even neurology defects (57).

It has been proven that lower zinc serum level occurs more often in patients with chronic liver disease and liver cirrhosis, responding with its severity and hepatic encephalopathy (56,58,59).

Patients with serum zinc concentrations under 60 µg/dL are at elevated risk for covert hepatic encephalopathy, independent of their ammonia levels, and are also more likely to progress to overt hepatic encephalopathy (60). One of the presented mechanisms of zinc deficiency in alcoholic liver disease is its increased excretion in the urine and reduced absorption in the intestine caused by chronic alcohol consumption (61). Similarly, in acute hepatitis, reduced serum zinc levels have been observed as a result of increased renal excretion (36).

A randomized clinical trial conducted by Juárez-Hernández et al. (62) evaluated the effects of a 6-month regimen of zinc supplementation (100 mg/day). The study demonstrated a 55% increase in the likelihood of improved taste perception for salty, sweet, sour, and umami flavors among patients receiving zinc. The recognition of umami taste improved specifically by 59%. However, no significant changes were observed in the perception of bitter taste.

Another deficiency found in patients with alcoholic liver disease was vitamin A deficiency. In line with prior research, the potential role of vitamin A in modulating taste perception was explored; however more recent literature on this topic remains scarce. There are only two studies in the searched databases regarding the influence of vitamin A on the perception of taste in liver cirrhosis patients (23,63). In the first study, Madden et al. (23) found no correlation between vitamin A and taste acuity. However, they did report a significant negative association between serum magnesium levels and both salt detection thresholds and overall gustatory scores. The second study conducted by Garrett-Laster (63) examined 37 patients with alcoholic liver cirrhosis and vitamin A deficiency, 11 of those had co-existing zinc deficiency. Patients were treated with oral vitamin A (10.000 µg/day) for 4 weeks. Comparing to 21 healthy controls, all study group presented a significant improvement ($P<0.01$) in detection and mean recognition level for salty and bitter taste, with no relation with zinc status. As a result of the improvement in the concentration of vitamin A in the serum, there was a better perception of taste. The mechanism of vitamin A on salty and bitter taste modalities remains unknown.

Nagao et al. (64) evaluated the effects of a supplement enriched with branched-chain amino acids (BCAA) on taste sensitivity and zinc levels in a small group of patients (9 subjects) with HCV-related liver disease. After 90 days of supplementation, improvements in sour and sweet taste sensitivity as well as increased zinc levels were observed, thus indicating the effectiveness of BCAA in treating taste disorders.

Numerous studies have described the individual effects of vitamins such as B3, B6, B12, C, D3, E and folic acid on the progression of liver diseases or taste disturbances (65,66). However, there is a lack of research specifically assessing the combined or interrelated impact of these factors.

Comparison available data from the literature correlating between nutrient and taste disorders among patients with liver diseases are presented in T*able 2*.

Dokazano je da se niža razina cinka u serumu češće pojavljuje ako pacijent boluje od kronične bolesti jetre i ciroze jetre, reagirajući svojom težinom i hepatičkom encefalopatijom (56, 58, 59).

Pacijenti s koncentracijom cinka u serumu manjom od 60 µg/dL imaju povećan rizik od prikrivene hepatičke encefalopatije, neovisno o razini amonijaka, a također se pretpostavlja da će češće napredovati do očite hepatičke encefalopatije (60). Jedan od predstavljenih mehanizama nedostatka cinka u slučaju alkoholne bolesti jetre jest njegovo povećano izlučivanje u urinu i smanjena apsorpcija u crijevima prouzročena kroničnom konzumacijom alkohola (61). Slično tomu, kod akutnog hepatitisa uočena je smanjena razina cinka u serumu kao rezultat povećanog izlučivanja putem bubrega (36).

U randomiziranom kliničkom ispitivanju koje su proveli Juárez-Hernández i suradnici (62) procijenjeni su učinci 6-mjesečnog režima suplementacije cinkom (100 mg/dan). Studija je pokazala 55-postotno povećanje vjerojatnosti da će se poboljšati percepcija okusa za slani, slatki i kiseli okus među pacijentima koji su primali cink. Prepoznavanje slanog okusa posebno se poboljšalo – za 59 %. No nisu uočene značajne promjene u percepciji gorkoga.

Još jedan nedostatak pronađen kod pacijenata s alkoholnom bolešću jetre bio je nedostatak vitamina A. U starijim studijama autori su istraživali potencijalnu ulogu toga vitamina u modulaciji percepcije okusa, no ta je tema u novijoj literaturi rijetka. U pretraženim bazama podataka samo su dvije studije o utjecaju vitamina A na percepciju okusa kod pacijenata s cirozom (23, 63). U prvoj studiji Madden i suradnici (23) nisu pronašli korelaciju između vitamina A i oštrine okusa. No izvijestili su o značajnoj negativnoj povezanosti između razine magnezija u serumu i pragova detekcije soli te ukupnih gustatornih rezultata. U drugoj studiji je njezin autor Garrett-Laster (63) pratio 37 pacijenata s alkoholnom cirozom i nedostatkom vitamina A, od kojih je 11 imalo istodobni nedostatak cinka. Pacijenti su liječeni oralnim vitaminom A (10 000 µg/dan) tijekom 4 tjedna. U usporedbi s 21 zdravom kontrolnom osobom, sve ispitivane skupine pokazale su značajno poboljšanje ($P < 0{,}01$) u detekciji i prosječnoj razini prepoznavanja slanoga i gorkog okusa, bez veze sa statusom cinka. Kao rezultat poboljšanja koncentracije vitamina A u serumu, poboljšala se percepcija okusa. Mehanizam djelovanja vitamina A na modalitete slanoga i gorkoga ostaje nepoznat.

Nagao i suradnici (64) procijenili su učinke dodatka prehrani obogaćenog aminokiselinama razgranatog lanca (BCAA) na osjetljivost okusa i razinu cinka u maloj skupini pacijenata (9 ispitanika) s bolešću jetre povezanom s HCV-om. Nakon 90 dana suplementacije uočena su poboljšanja u osjetljivosti na kiseli i slatki okus i povećana je razina cinka, što upućuje na učinkovitost BCAA u liječenju poremećaja okusa.

U mnogobrojnim studijama autori su opisali pojedinačne učinke vitamina poput B_3, B_6, B_{12}, C, D_3, E i folne kiseline na napredovanje bolesti jetre ili poremećaja okusa (65, 66). Međutim, nedostaje istraživanja u kojima se posebno procjenjuju kombinirani ili uzajamno povezani utjecaji tih čimbenika.

Usporedni dostupni podatci iz literature koji koreliraju između poremećaja hranjivih tvari i okusa kod pacijenata s jetrenim bolestima prikazani su u tablici 2.

Table 2 Correlation between nutrient deficiency and taste disorders among patients with liver diseases
Tablica 2. Korelacija između nedostatka hranjivih tvari i poremećaja okusa kod pacijenata s bolestima jetre

Nutrient deficiency • Nedostatak hranjivih tvari	Type of liver disease • Vrsta bolesti jetara	Connection with taste disorder • Povezanost s poremećajem okusa	References • Referencija
Zn	Cirrhosis • Ciroza	Yes • Da	Zalewski 2005 (57)
	Cirrhosis • Ciroza	No • Ne	Sturniolo 1992 (40)
	Cirrhosis • Ciroza	No • Ne	Madden 1997 (23)
	Cirrhosis • Ciroza	Yes • Da	Juárez-Hernández 2022 (34)
	Cirrhosis • Ciroza	Yes • Da	Juárez-Hernández 2024 (62)
	HCV infected liver disease • Bolest jetre, zaraza HCV-om	Yes • Da	Nago 2010 (64)
	Chronic/acute liver disease • Kronična/akutna bolest jetre	No • Ne	Smith 1976 (38)
	Chronic liver disease • Kronična bolest jetre	Yes • Da	Ozeki 2020 (67)
Vitamin A	Alcoholic liver cirrhosis • Alkoholna ciroza jetre	Yes • Da	Garrett-Laster 1984 (63)
	Cirrhosis • Ciroza	No • Ne	Madden 1997 (23)
Mg	Cirrhosis • Ciroza	Yes • Da	Madden 1997 (23)

Discussion

Taste disturbances represent a multifactorial and clinically relevant problem in patients with liver diseases. As outlined in the introduction, proper gustatory function is an important determinant of appetite regulation, dietary habits, and overall health. Findings reported in our review confirm the fact that alterations in taste perception occur both in acute and chronic liver conditions, and that their severity often typically follows the course of liver injury (31,33). These findings point out that taste disorders are not only a consequence of severe disease, but also may act as modifiers of nutritional status, thus creating a vicious cycle of malnutrition, sarcopenia, and reduced quality of life.

The repeated outcome of studies is a disruption of salty and umami taste modalities. These changes are particularly significant, because both taste qualities are involved in food preference, appetite stimulation, and protein intake. For example, patients with chronic hepatitis C exhibited increased umami recognition thresholds, as well as impaired perception of sweet taste. Similarly, a reduced sensitivity to salty taste was found in cirrhosis and it was often accompanied by aversion to sodium-containing foods (39). Findings suggest that gustatory dysfunction may directly influence food choices and contribute to nutrient imbalances commonly reported in chronic liver disease, including hypoalbuminemia and protein-energy malnutrition.

Several pathophysiological mechanisms are likely responsible for these taste disorder alterations. Zinc deficiency remains the most consistently reported factor, with evidence of reduced serum zinc concentrations in cirrhosis and hepatitis, often related to impaired absorption, altered transport, or increased urinary loss. Zinc plays an essential role in the structure and function of taste buds, and supplementation trials have demonstrated improved sensitivity for salty, sweet, and umami tastes (36,56,58,59,62). Similarly, vitamin A deficiency, particularly in alcoholic liver disease, has been associated with changes in bitter and salty taste perception, although available data remain limited, and studies are outdated (63). Recent studies also point to vitamin D deficiency as an indirect contributor, through its role in oral pathology

Rasprava

Poremećaj okusa je multifaktorijalan i klinički relevantan problem kad je riječ o pacijentima s bolestima jetre. Kao što je navedeno u uvodu, pravilna funkcija okusa važna je odrednica u regulaciji teka, prehrambenih navika i općeg zdravlja. Nalazi izneseni u našem pregledu potvrđuju da se promjene u percepciji okusa pojavljuju i kod akutnih i kod kroničnih stanja jetre te da njihova težina često prati tijek oštećenja toga organa (31, 33). U tim nalazima ističe se da poremećaji okusa nisu samo posljedica teške bolesti, nego mogu djelovati i kao modifikatori nutritivnog statusa, stvarajući začarani krug pothranjenosti, sarkopenije i smanjene kvalitete života.

Ponovljeni ishod studija jest poremećaj modaliteta slanog okusa. Te promjene posebno su značajne jer su obje kvalitete okusa uključene u preferencije hrane, stimulaciju apetita i unos proteina. Na primjer, pacijenti s kroničnim hepatitisom C pokazali su povećane pragove u prepoznavanju slanog okusa i oštećenu percepciju slatkoga. Slično tomu, smanjena osjetljivost za slani okus pronađena je kod oboljelih od ciroze i često je bila praćena odbojnošću prema hrani koja sadržava natrij (39). Nalazi upućuju na to da poremećaj okusa može izravno utjecati na izbor jela i pridonijeti neravnoteži hranjivih tvari koja se često prijavljuje kad je riječ o kroničnim bolestima jetre, uključujući hipoalbuminemiju i proteinsko-energijsku pothranjenost.

Nekoliko patofizioloških mehanizama vjerojatno je odgovorno za te promjene u poremećaju okusa. Nedostatak cinka ostaje najčešće prijavljeni čimbenik, s dokazima o smanjenim koncentracijama toga kemijskog elementa u serumu u slučaju ciroze i hepatitisa, često povezanima s oštećenom apsorpcijom, promijenjenim transportom ili povećanim gubitkom urina. Cink je itekako važan u strukturi i funkciji okusnih pupoljaka, a ispitivanja suplementacije pokazala su poboljšanu osjetljivost na slani i slatki okus (36, 56, 58, 59, 62). Slično tomu, nedostatak vitamina A, posebno u slučaju alkoholne bolesti jetre, povezan je s promjenama u percepciji gorkoga i slanog okusa, iako su dostupni podatci i dalje ograničeni, a studije zastarjele (63). U nedavnim studijama autori također upozoravaju na nedostatak vitamina D kao na neizravni doprinos, na temelju njegove uloge u oralnoj patosuch as oral lichen planus, which may exacerbate gustatory dysfunction (19,20). Our analysis suggests that micronutrient deficiencies as a cause of taste disturbances should be considered in the context of overall nutritional disorders and their clinical consequences in patients with liver diseases, including an increased risk of oral pathologies that may themselves exacerbate gustatory dysfunction. However, it should be emphasized that this hypothesis requires confirmation by further studies specifically targeting this patient population. Oral health itself emerges as a key factor. Periodontitis and halitosis, as noted in epidemiological studies, may influence taste perception through local inflammatory mechanisms and altered saliva composition (32). The bidirectional association between periodontal disease and liver dysfunction provides further support for the role of oral health in modulating gustation in this population. In our review, most recent studies on MASLD and NAFLD highlighted the frequent coexistence of taste disturbances with oral dryness and mucosal inflammation, indicating that oral pathology is not only a comorbidity but also a potential mediator of altered taste perception, thereby reinforcing the hypothesis proposed earlier (15,30).

Another dimension of taste impairment in liver disease relates to pharmacological treatment. Interferon-based regimens, as well as antiviral therapies with boceprevir, have consistently been associated with dysgeusia, often described as metallic or bitter sensations (24–26). These alterations, although usually reversible, may significantly impact appetite and adherence to therapy. Likewise, antimicrobial treatments such as metronidazole frequently induce metallic taste, whereas newer agents like satranidazole or tinidazole appear to have a more favorable profile (53,54). Beyond these adverse effects, recent data have suggested a more complex role of pharmacotherapy, particularly with GLP-1 receptor agonists. Originally developed for diabetes and now increasingly used in MASLD, these drugs not only improve metabolic outcomes, but also interact with gustatory nerve pathway receptors, enhancing sweet sensitivity. This newly recognized mechanism of action requires further investigation; however, it offers promising potential in the treatment of taste disturbances that may contribute to the development of MASLD.

Importantly, our synthesis reveals that the majority of studies investigating taste disturbances in liver disease are outdated, limited in sample size, and often restricted to viral hepatitis or alcoholic liver disease. Only a few recent observational studies have assessed dysgeusia in MASLD, despite it being the most common chronic liver disease worldwide. The reported prevalence of dysgeusia in MASLD ranged from 7% in compensated to nearly 60% in decompensated stages, underlining the strong relationship between disease severity and gustatory dysfunction(15). However, heterogeneity in testing methods and the lack of standardized taste assessment protocols remain major obstacles to drawing firm conclusions.

The interpretation of our findings is limited by several important factors. Firstly, a considerable proportion of the cited literature was published decades ago and focused primarily on viral liver diseases. This restricts the applicability

logiji poput oralnoga lihen planusa koji može pogoršati poremećaj okusa (19, 20). Naša analiza sugerira da bi nedostatke mikronutrijenata, kao uzroka za poremećaje okusa, trebalo razmotriti u kontekstu ukupnih prehrambenih poremećaja i njihovih kliničkih posljedica kod pacijenata s bolestima jetre, uključujući povećani rizik od oralnih patologija koje same po sebi mogu pogoršati disfunkciju okusa. No treba istaknuti da ta hipoteza zahtijeva potvrdu u budućim studijama posebno usmjerenim na tu populaciju pacijenata. Samo oralno zdravlje pojavljuje se kao ključni čimbenik. Parodontitis i halitoza, kako je navedeno u epidemiološkim studijama, mogu utjecati na percepciju okusa putem lokalnih upalnih mehanizama i promijenjenog sastava sline (32). Dvosmjerna povezanost između parodontne bolesti i disfunkcije jetre pruža daljnju potporu ulozi oralnoga zdravlja u modulaciji okusa u toj populaciji. U našem pregledu, u novim studijama o MASLD-u i NAFLD-u istaknuta je česta koegzistencija poremećaja okusa sa suhoćom usne šupljine i upalom sluznice, što upućuje na to da oralna patologija nije samo komorbiditet, nego i potencijalni posrednik promijenjene percepcije okusa, čime se pojačava ranije predložena hipoteza (15, 30).

Druga dimenzija oštećenja okusa kod bolesti jetre odnosi se na farmakološko liječenje. Režimi liječenja na bazi interferona, te antivirusne terapije boceprevirom, dosljedno su povezani s disgeuzijom, često opisanom kao metalni ili gorki okus (24 – 26). Te promjene, iako obično reverzibilne, mogu znatno utjecati na apetit i terapiju. Slično tomu, antimikrobni tretmani poput metronidazola često izazivaju metalni okus, a noviji agensi poput satranidazola ili tinidazola imaju povoljniji profil (53,54). Osim tih nuspojava, nedavni podatci sugeriraju složeniju ulogu farmakoterapije, posebno s agonistima receptora GLP-1. Izvorno razvijeni za dijabetes, a sada se sve više koriste u slučaju MASLD-a, ti lijekovi ne samo da poboljšavaju metaboličke ishode, nego i interagiraju s receptorima gustatornoga živčanog puta, povećavajući osjetljivost na slatko. Taj tek prepoznati mehanizam djelovanja zahtijeva daljnja istraživanja, no nudi obećavajući potencijal u liječenju poremećaja okusa koji mogu pridonijeti pojavi MASLD-a.

S obzirom na visoku prevalenciju MASLD-a i ciroze diljem svijeta te dokazanu povezanost između promjena okusa, nutritivnog statusa i ishoda bolesti, uključujući oralno zdravlje, hitno je potrebno daljnje istraživanje. Buduća istraživanja trebala bi koristiti standardizirane i validirane metode za procjenu poremećaja okusa, uključivati veće kohorte s duljim praćenjem i pokrivati različite stadije bolesti jetre. Također je potrebno dubinsko istraživanje molekularnih mehanizama koji leže u osnovi promjena okusa, uključujući ulogu GLP-1 receptora i drugih metaboličkih medijatora. Konačno, treba sustavno procijeniti sveobuhvatan utjecaj nedostataka hranjivih tvari i lijekova koji se primjenjuju u liječenju bolesti jetara na percepciju okusa.

of conclusions to the current epidemiology of MASLD and modern therapeutic strategies. Secondly, numerous studies relied on small patient cohorts or single-case descriptions, which increases the risk of bias and limits generalizability. Thirdly, methodological heterogeneity – including variability in tools and protocols used to assess taste perception – complicates reliable comparisons across studies and synthesis of evidence. In addition, there is a lack of long-term prospective and interventional data, particularly the data regarding the impact of supplementation or emerging treatments, such as GLP-1 receptor agonists on gustatory function in liver disease.

Given the high prevalence of MASLD and cirrhosis worldwide, and the demonstrated connection between gustatory alterations, nutritional status, and disease outcomes including oral health, there is an urgent need for further research. Future studies should employ standardized and validated methods for assessing taste disturbances, include larger cohorts with longer follow-up, and cover different stages of liver disease. In-depth investigation of molecular mechanisms underlying taste alterations, including the role of GLP-1 receptors and other metabolic mediators, is also warranted. Finally, the comprehensive impact of nutrient deficiencies and medications used in liver disease therapy on taste perception should be systematically evaluated.

Conclusions

Taste disturbances are under-recognized in hepatology. Taste perception modulated by pharmacological treatments, oral health and nutritional status, plays a crucial role in appetite regulation and is significantly altered in patients with liver diseases. Zinc deficiency is the most studied nutritional factor contributing to altered taste perception. Taste modulators, including GLP-1 receptor agonists, by altering eating habits leading to weight loss, may prove beneficial in the treatment of MASLD. Addressing taste disorders may help combat malnutrition or obesity; improve the quality of life and prognosis in patients with liver diseases. Further research is needed.

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Zaključak

Poremećaji okusa nisu dovoljno prepoznati u hepatologiji. Percepcija okusa modulirana farmakološkim tretmanima, oralnim zdravljem i nutritivnim statusom ključna je u regulaciji teka i značajno je promijenjena kod pacijenata s bolestima jetre. Nedostatak cinka najproučavaniji je nutritivni faktor koji pridonosi promijenjenoj percepciji okusa. Modulatori okusa, uključujući agoniste receptora GLP-1, promjenom prehrambenih navika što rezultira gubitkom težine, mogu se pokazati korisnima u liječenju MASLD-a. Rješavanje poremećaja okusa može pomoći u borbi protiv pothranjenosti ili pretilosti, poboljšati kvalitetu života i prognozu pacijenata s bolestima jetre. Potrebna su daljnja istraživanja.

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Doprinos autora: A. K-C, K. C, R. C. – konceptualizacija; **A. K-C, K. C** – metodologija i prikupljanje podataka ,priprema i uređivanje izvornog nacrta; **R. C.** – pregled i nadzor rukopisa; Svi autori pročitali su tekst i složili se s objavljenom verzijom.

Sažetak

Svrha rada: Steatotična bolest jetre povezana s metaboličkom disfunkcijom (MASLD) jedna je od najbrže rastućih bolesti toga organa u svijetu, a prouzročena je pretilošću i dijabetesom tip 2. Percepcija okusa ključna je u regulaciji apetita i prehrani, a utječe i na napredovanje drugih bolesti jetre. U ovom pregledu sažeti su nekadašnji i aktualni dokazi o poremećajima okusa tijekom bolesti jetre i njihovim kliničkim implikacijama. **Materijali i metode:** Proveden je, korištenjem odabranih MeSH termina, narativni pregled baza podataka PubMed, Web of Science, Google Scholar i ResearchGate. **Rezultati:** Poremećaji okusa zabilježeni su u slučaju virusnog hepatitisa, ciroze, Wilsonove bolesti, amebnih apscesa jetre i NAFLD/MASLD-a, te nutritivnih nedostataka (cink, magnezij, vitamin A, aminokiseline razgranatog lanca). Disgeuzija je bila povezana sa smanjenim tekom, sarkopenijom, pothranjenošću, promijenjenim prehrambenim preferencijama i rizikom od pretilosti kod MASLD-a. Poremećaji okusa pogoršavaju se s progresijom disfunkcije jetre. Nekoliko lijekova (npr., interferon, metronidazol) pridonosi disgeuziji. Nedostatak cinka bio je najdosljedniji faktor. Modulatori receptora glukagonu sličnoga peptida-1 (GLP-1), koji utječu na apetit i percepciju slatkoga/umamija, čine se kao da obećavaju u terapiji MASLD-a. **Zaključci:** Poremećaji okusa raširena su pojava i još uvijek nedovoljno prepoznata u populacijama s bolestima jetre. Uzrok ostaje nejasan. Većina dostupnih studija koje utječu na nedostatke hranjivih tvari zastarjela je. Potrebna su nova istraživanja usmjerena na molekularne putove modulacije okusa (npr., receptori GLP-1) te određivanje prevalencije i kliničkih posljedica disgeuzije u specifičnim stadijima bolesti jetre kako bi se bolje razumjelo na koji način nedostatci mikronutrijenata i lijekovi utječu na poremećaj okusa.

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