Clinical Oral Investigations (2022) 26:4587–4592
https://doi.org/10.1007/s00784-022-04426-9

ORIGINAL ARTICLE

Nitrogenous compounds in the saliva and blood of cirrhotic patients: a cross-sectional study

Nathália Tuany Duarte[1] · Jefferson R. Tenório[2] · Natália Silva Andrade[3] · Fabiana Martins[4] · Marina Gallottini[1] · Karem L. Ortega[1]

Received: 20 October 2021 / Accepted: 19 February 2022 / Published online: 28 February 2022

Abstract

Objectives Serum increase of nitrogenous compounds (NC) in cirrhotic patients has been associated with the development of hepatic encephalopathy (HE). However, the relation between NC in saliva and HE is unclear. The objective of this study is to measure the levels of nitric oxide and urea in the blood and saliva in 38 cirrhotic patients and correlate them with clinical characteristics and presence and grades of HE.

Material and methods Automated enzymatic colourimetric assays were performed to determine the levels of NC. Diagnosis and severity of HE were determined based on the West Haven criteria and by using the inhibitory control test.

Results HE was diagnosed in 89.47% of the patients, with the majority (60.50%) presenting covert HE. With regard to the measurement of NC, although nitric oxide is moderately correlated with its amount in blood and saliva ($r=0.630$; $P<0.001$), only salivary levels were associated with the presence of ascites and ecchymosis ($P=0.013$ and $P=0.030$, respectively). In patients with HE, the serum levels of urea were higher ($P=0.013$) than those in patients without HE or minimal HE.

Conclusions Nitrogenous compounds in the saliva were correlated with neither the presence nor grades of HE, whereas in the blood, only urea was positively correlated with the severity and presence of HE.

Clinical relevance Saliva is an excellent fluid for diagnosing several diseases, but it does not seem to be able to collaborate with the identification of HE.

Keywords Cirrhosis · Saliva · Nitric oxide · Hepatic encephalopathy

Introduction

Cirrhotic patients have several complications and comorbidities, which can be systemic or local, interfering with the clinical management of these individuals at different degrees [1–5].

Hepatic encephalopathy (HE) is a complication resulting from acute or chronic liver failure or portosystemic shunt, which expresses itself through neurological and psychiatric alterations. This cognitive disorder is extremely common among cirrhotic patients, being graduated according to the severity of its neuropsychological manifestations and

✉ Karem L. Ortega
klortega@usp.br

Nathália Tuany Duarte
tuany8@hotmail.com

Jefferson R. Tenório
jeffersonrtenorio@odonto.ufrj.br

Natália Silva Andrade
natalia.andrade@academico.ufs.br

Fabiana Martins
fabmm@usp.br

Marina Gallottini
mhcgmaga@usp.br

[1] Department of Stomatology, School of Dentistry, University of São Paulo, Av. Prof. Lineu Prestes, 2227 – Cidade Universitária, São Paulo, São Paulo 05508-000, Brazil

[2] Department of Oral Pathology and Diagnosis, School of Dentistry, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil

[3] Department of Dentistry, Federal University of Sergipe, Lagarto, Sergipe, Brazil

[4] School of Dentistry, University of Santo Amaro, São Paulo, Brazil

eventually causing coma in the most severe cases [6]. HE is one of the clinical complications of liver cirrhosis being directly influenced by changes in the serum levels of nitrogenous compounds [7].

The severity of cognitive alterations in cirrhotic patients varies depending on the presence and severity of HE. It is important that the diagnosis of this complication should be made in the early stages, since patients may already have memory lapses and this may indicate a risk factor for more severe cases [8].

Different nitrogenous compounds participating in the process of HE are increased in cirrhotic patients. For example, ammonia (NH_3) is highly concentrated not only in the blood due to complications involving its detoxification [9, 10], but also in the brain, furthering cerebral oedema and astrocyte swelling [10–12]. On the other hand, the nitric oxide (NO), a potent vasodilator that acts on other cirrhosis complications (e.g. portal hypertension, ecchymosis, portosystemic collateral formation and gastrointestinal bleeding), also can act during HE by increasing the permeability of the blood–brain barrier in cases of cerebral oedema [7, 13, 14].

The relationship between serum NH_3 levels and the presence and severity of HE has been extensively studied [11]. On the other hand, although the increase in serum concentration of others nitrogenous compounds is correlated with the presence of HE, its relationship with different grades of complication is still controversial in the literature [15]. These nitrogenous compounds, which are well-known to be changed in the blood of HE patients, could be studied in the saliva as previous studies demonstrated that this fluid can be as adequate as blood for the detection and diagnosis of systemic alterations [16–18].

The objective of this study is to measure the levels of NO and urea in the blood and saliva of cirrhotic patients and correlate them with cirrhosis complications, particularly the presence and grades of HE by assessing whether saliva can be used as an indicator of such correlation.

Materials and methods

Study design and ethics

This cross-sectional study was approved by the Research Ethics Committee of the University of São Paulo School of Dentistry according to Declaration of Helsinki (protocol number 1730927) and conducted according to the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) recommendations for observational studies. All the participants read, understood, accepted and signed a written informed consent form prior to their inclusion in the study.

Case selection

Inclusion criteria

The study group consisted of consecutive cirrhotic adult patients who were in the liver transplant waiting list. All patients were recruited at the Special Care Dentistry Center of University of São Paulo Dental School, from August 2016 to August 2018.

Exclusion criteria

Patients to be submitted to re-transplantation or multiple transplantation as well as those presenting neurological or cognitive changes making it difficult to evaluate the HE were excluded.

Sample calculation

Only the levels of nitrogenous compounds in saliva and blood from patients with systemic impairment were considered for sample calculation [19], in which the average of compounds was determined to assess the minimum sample size for study. The Power and Sample Size software, version 3.1.2 [20], was used at a significance level of 5% and sample power of 90%, which was added by 20% in order to minimise possible data loss. The ideal sample size was 39 subjects for study.

Clinical and diagnostic data and classification of hepatic encephalopathy

HE was classified according to the severity and based on the criteria proposed by the International Society for Hepatic Encephalopathy and Nitrogen Metabolism (ISHEN), in which HE is considered as absent, covert and overt. Overt HE was diagnosed and classified according to the West Haven criteria [8], whereas covert HE (minimal or subclinical) was diagnosed by using the inhibitory control test (ICT), a computed test of attention and response inhibition. This test is available on the site https://chronicliverdisease.org/disease_focus/ICT/, being applied according to Gupta and collaborators (2015) [21].

In the case of the patient showing no positivity for the above-described diagnostic methods, then HE was considered absent.

Data on demographic characteristics and other complications of cirrhosis were extracted from the patients' clinical records.

Collection of saliva and blood samples

All patients were instructed to fast before the collection of saliva and blood samples.

For saliva collection, the patients were asked to perform no oral hygiene and ingest no food or beverage 60 min before the clinical examination. Patients rinse their mouth with distilled water for 30 s, and immediately after that, the whole saliva produced during 10 min was collected into a Falcon tube. At the end of the collection, the saliva was transferred into safe-lock Eppendorf tubes (Protein LoBind microcentrifuge tubes®, Hamburg, Germany) and frozen at − 80 °C until biochemical analysis.

The blood was collected by means of venous puncture, stored in a tube containing clot activator and being left at rest for 30 min at 4 °C. Immediately after resting, the centrifugation was done at 4 °C and 3000 rpm for 15 min, and the blood serum was stored in safe-lock Eppendorf Protein LoBind® microcentrifuge tubes, (Hamburg, Germany) and frozen at − 20 °C until biochemical analysis.

Determination of nitrogenous compound concentration in saliva and blood

The concentrations of NO and urea were determined by means of automated colourimetric enzymatic tests, respectively, EnzyChrom™ Nitric Oxide Synthase Assay and EnzyChrom™ Urea Assay Kit (BioAssay Systems, Hayward, CA, USA) according to their manufacturers' recommendations. The samples were read by using a Stat Fax reader, model 2100 (Awareness Technology). All samples were tested in duplicate for each assay.

Statistical analysis

The resulting data were analysed by using the BioEstat (version 5.3) and Statistical Package for the Social Science (SPSS® for Windows, version 22.0, SPSS Inc., Chicago, IL, USA). Non-parametric data distribution was verified by the Shapiro–Wilk test. Spearman's correlation test was used to assess the correlation between nitrogenous compounds in the saliva and those in the blood, including between them and independent variables. Bivariate analysis was performed by using Kruskal–Wallis and Mann–Whitney tests for comparison of independent variables with the concentrations of nitrogenous compounds in saliva and blood. The correlation of these variables with the presence and severity of HE was also assessed by determining the linear association. Values were considered statistically significant at $P \leq 0.05$.

Results

Thirty-nine patients were consecutively selected, but one lost the follow-up visit and was excluded, thus remaining 38. The sample consisted of a majority of males (68.4%), with mean age of 50.03 years (± 14.06/RANK 20–71) and mean MELD score of 18.08. Alcoholism, hepatitis C and cryptogenic cirrhosis were the most frequent aetiologies (31.6%, 21.1% and 15.8%, respectively).

The complications of cirrhosis in patients were portal hypertension (100%), hypersplenism (97.4%), portosystemic collaterals (92.1%), splenomegaly (84.2%), ascites (52.5%) and upper gastrointestinal bleeding (55.3%). Patients also presented fatigue (65.8%), oedema (63.2%), jaundice (57.9%) and ecchymosis (31.6%).

Based on the ISHEN classification, we found that the majority of the patients had covert HE (60.5%), followed by those with overt HE (29%), and only four patients (10.5%) had no clinical or psychometric sign of HE (Table 1).

Although more than half of the cirrhotic patients ($n = 21$; 55.26%) used some medication for HE (i.e. lactulose or L-ornithine-L-aspartate), almost all of them presented some degree of HE ($n = 20$; 95.23%) at the moment of clinical evaluation (Table 2).

The correlation between HE severity (i.e. absence of HE, minimal HE and West Haven HE) and other clinical complications resulting from cirrhosis showed that the more severe the HE, the higher the proportion of patients with portosystemic collaterals and ascites ($P = 0.017$ and $P = 0.040$, respectively). The mean MELD scores were statistically higher in patients with overt HE compared to those with covert HE ($P = 0.021$). The mean values for nitrogenous compounds in blood and saliva were assessed, including standard deviation and minimum and maximum values, all of which are shown in Table 3.

Spearman's correlation test comparing the blood and saliva indicated a moderate positive correlation only for

Table 1 Classification of hepatic encephalopathy according to ISHEN criteria

Severity of hepatic encephalopathy	*n* (%)
No encephalopathy	04 (10.5)
Covert hepatic encephalopathy	23 (60.5)
Minimal hepatic encephalopathy †	13 (34.2)
Grade 1 encephalopathy ‡	10 (26.3)
Overt hepatic encephalopathy	11 (29.0)
Grade 2 encephalopathy ‡	08 (21.1)
Grade 3 encephalopathy ‡	03 (7.9)

†Diagnosed with inhibitory control test. ‡Diagnosed according to West Haven criteria

Table 2 Use of medications for hepatic encephalopathy depending on severity

Variables	Use of medications for hepatic encephalopathy		*P*
	No ***n*** **(%)**	**Yes** ***n*** **(%)**	
Encephalopathy grades			0.266*
No encephalopathy	03 (75.0)	01 (25.0)	
Minimal encephalopathy	06 (46.2)	07 (53.8)	
Encephalopathy according to West Haven criteria			
Grade 1 encephalopathy	04 (40.0)	06 (60.0)	
Grade 2 encephalopathy	03 (37.5)	05 (62.5)	
Grade 3 encephalopathy	01 (33.3)	02 (66.7)	

*Linear association test

Table 3 Quantification of nitrogenous compounds in the blood and saliva ($n=38$)

Nitric oxide in saliva (U/L), μ (±)	20.06 ± 10.20/RANK 5.55–41.04
Nitric oxide in blood (U/L), μ (±)	6.44 ± 2.10/RANK 4.35–15.27
Urea in saliva (mg/dL), μ (±)	34.72 ± 13.02/RANK 16.12–85.15
Urea in blood (mg/dL), μ (±)	50.71 ± 12.93/RANK 30.93–99.09

μ, mean; ±, standard deviation. Reference values: urea 16–40 mg/dL; nitric oxide 10.3 to 66.8 μmol/L

NO ($r_s=0.630$, $P<0.001$), whereas urea had no correlations ($r_s=0.270$, $P=0.101$).

Nitrogenous compounds in blood and saliva were correlated with cirrhosis complications. It was observed that the mean values of salivary NO were statistically higher in patients who presented with ascites and ecchymosis compared to those who did not ($P=0.013$ and $P=0.030$, respectively). The mean value of urea concentration in the blood was statistically higher in patients with some degree of HE (West Haven) compared to those without HE or to those with minimal HE ($P=0.006$) and compared to only those with minimal HE ($P=0.024$) (Table 4).

Discussion

HE is one of the major complications of cirrhosis, and the manifestations of this condition are unspecific, and the diagnosis is clinical and subjective. Identifying an exam that can help in the diagnosis, particularly in the early stages (e.g. minimal or covert), would be an important contribution. Although the prevalence of HE varies depending on its cause, severity and definition, it is assumed that the overall prevalences of overt and covert HE range, respectively, from 16 to 21% and from 20 to 80% [22, 23].

In the present study, 89.5% of the patients presented HE, and the great majority of them (60.5%) had covert HE. The severity of HE was found to be directly related to a major systemic impairment (i.e. presence of ascites and portosystemic collaterals) and higher risk of mortality within 3 months (MELD).

But the main objective of the study was to verify whether NC levels (particularly in saliva) can be correlated with grades of HE and whether saliva can be used as an indicator of such a correlation. Among the nitrogenous compounds, only serum levels of urea could be correlated with the severity of HE. Patients with overt HE had higher serum levels of urea than those who had covert HE or no HE. Maybe this is an important correlation. Cirrhosis deeply affects the urea cycle in the body, firstly by making the transformation of NH_3 into urea unfeasible, which causes high accumulation of the former in the body [24].

Table 4 Correlation between mean value of laboratory tests and hepatic encephalopathy

Variables	Nitric oxide in saliva (U/L)	Nitric oxide in blood (U/L)	Urea in saliva (mg/dL)	Urea in blood (mg/dL)
No encephalopathy and minimal encephalopathy	19.24 ± 8.84	6.13 ± 1.08	32.69 ± 7.17	44.44 ± 8.35
West Haven	20.72 ± 11.36	6.69 ± 2.66	36.36 ± 16.31	55.69 ± 13.97
*P**	0.954	0.931	0.639	0.006
Minimal encephalopathy	20.40 ± 9.82	6.08 ± 1.04	30.77 ± 5.47	46.14 ± 7.57
West Haven	20.72 ± 11.36	6.69 ± 2.66	36.36 ± 16.31	55.69 ± 13.97
*P**	0.972	0.986	0.362	0.024
Covert hepatic encephalopathy	20.88 ± 9.31	6.81 ± 2.50	33.62 ± 12.42	48.90 ± 8.26
Overt hepatic encephalopathy	20.00 ± 13.51	5.72 ± 1.03	35.49 ± 15.84	58.60 ± 17.67
*P**	0.496	0.122	0.854	0.146

*Mann–Whitney test

Urea begins to accumulate in the patient's body because the renal perfusion may be compromised as a result of systemic and splanchnic arterial vasodilation and consecutive reduction in the effective circulating blood volume [25]. The serum levels of urea in our patients ranged from 30.93 to 99.09 mg/dL, with a mean value of 50.71 mg/dL (reference values, 16–40 mg/dL). It is possible that the high levels of urea in patients who already had high levels of NH_3 accounted for the cognitive changes observed in our study, thus suggesting a correlation between serum levels of urea and HE. However, the current study design does not allow us to draw this conclusion, and further studies should be carried out to test this hypothesis.

On the other hand, there were 21 patients taking medications for HE treatment, and one of the medications used by them was L-ornithine-L-aspartate, which increases blood urea levels [26]. Thus, the use of LOLA can contribute to the association between HE severity and blood urea.

Another unexpected finding was the lack of correlation between serum and salivary urea concentrations; just NO shows some correlations between these two fluids. This is probably due to the transport of NO from the blood to the saliva. However, salivary NO is also locally produced by bacteria, and this increases its concentration up to 10 times than that in the blood, which explains the threefold higher levels in the saliva of our patients [27, 28].

We believe that the present study has some limitations. The cross-sectional design is one of them. Maybe a longitudinal study might allow us to understand how the excretion of these compounds work in the saliva and thus to suggest the best time for collection. Other possible reasons for not finding positive results were the sample characteristics. Almost all patients had some degree of HE, and any correlation would be more evident if there were a higher number of non-HE patients in the study. However, we calculated the ideal sample size, and perhaps one could find some statistical difference by increasing the sample number.

The nitrogenous compounds in the saliva were not found to be correlated with the presence or grades of HE in the present study. Only urea in the blood was positively correlated with presence and severity of HE.

Author contribution Conceptualisation, Nathália Tuany Duarte and Karem López Ortega; methodology, Jefferson Rocha Tenório, Nathália Tuany Duarte and Natália Silva Andrade; formal analysis and investigation, Nathália Tuany Duarte, Jefferson Rocha Tenório and Natália Andrade; writing — original draft preparation, Nathália Tuany Duarte, Fabiana Martins and Marina Gallottini; writing — review and editing, Jefferson Rocha Tenório, Marina Gallottini, Fabiana Martins and Karem López Ortega; funding acquisition, Karem López Ortega; supervision, Karem López Ortega.

Funding This research has been supported by the Fundação de Amparo à Pesquisa do Estado de São Paulo – FAPESP (grant # 2017/18938–6).

Declarations

Ethics approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Consent to participate Informed consent was obtained from all individual participants included in the study.

Conflict of interest The authors declare no competing interests.

References

1. de Oliveira Rech B, Rocha Tenório J, Bertoldi Franco J, Medina JB, Gallottini M, Pérez-Sayáns M, Ortega KL (2021) Risk of bleeding during oral surgery in patients with liver cirrhosis: a systematic review. J Am Dent Assoc (1939) 152(1):46-54.e2. https://doi.org/10.1016/j.adaj.2020.09.018
2. Marinho GB, Tenório JR, Munhoz L, Andrade NS, Arita ES, Ortega KL (2021) Detection of calcified atheromas on panoramic radiographs of cirrhotic patients. Special care in dentistry : official publication of the American Association of Hospital Dentists, the Academy of Dentistry for the Handicapped, and the American Society for Geriatric Dentistry 41(2):164–169. https://doi.org/10.1111/scd.12551
3. Di Profio B, Inoue G, Marui VC, de França BN, Romito GA, Ortega KL, Holzhausen M, Pannuti CM (2018) Periodontal status of liver transplant candidates and healthy controls. J Periodontol 89(12):1383–1389. https://doi.org/10.1002/JPER.17-0710
4. Medina JB, Andrade NS, de Paula Eduardo F, Bezinelli L, Franco JB, Gallottini M, Braz-Silva PH, Ortega KL (2018) Bleeding during and after dental extractions in patients with liver cirrhosis. Int J Oral Maxillofac Surg 47(12):1543–1549. https://doi.org/10.1016/j.ijom.2018.04.007
5. Di Profio B, Villar CC, Saraiva L, Ortega KL, Pannuti CM (2017) Is periodontitis a risk factor for infections in cirrhotic patients? Med Hypotheses 106:19–22. https://doi.org/10.1016/j.mehy.2017.06.022
6. Yu H, Chen Y, Jiang P (2019) Prognostic value of hepatic encephalopathy for survival of patients with liver failure: a systematic review and meta-analysis. Ann Hepatol 18(4):607–612. https://doi.org/10.1016/j.aohep.2019.01.006
7. Iwakiri Y, Groszmann RJ (2007) Vascular endothelial dysfunction in cirrhosis. J Hepatol 46(5):927–934. https://doi.org/10.1016/j.jhep.2007.02.006
8. Vilstrup H, Amodio P, Bajaj J, Cordoba J, Ferenci P, Mullen KD, Weissenborn K, Wong P (2014) Hepatic encephalopathy in chronic liver disease: 2014 Practice Guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver. Hepatology (Baltimore, Md.) 60(2):715–735. https://doi.org/10.1002/hep.27210
9. Quero Guillén JC, Herrerías Gutiérrez JM (2006) Diagnostic methods in hepatic encephalopathy. Clinica chimica acta international journal of clinical chemistry 365(1–2):1–8. https://doi.org/10.1016/j.cca.2005.08.003
10. Rahimi RS, Rockey DC (2014) Hepatic encephalopathy: how to test and treat. Curr Opin Gastroenterol 30(3):265–271. https://doi.org/10.1097/MOG.0000000000000066
11. Cichoż-Lach H, Michalak A (2013) Current pathogenetic aspects of hepatic encephalopathy and noncirrhotic hyperammonemic encephalopathy. World J Gastroenterol 19(1):26–34. https://doi.org/10.3748/wjg.v19.i1.26

12. Savlan I, Liakina V, Valantinas J (2014) Concise review of current concepts on nomenclature and pathophysiology of hepatic encephalopathy. Medicina (Kaunas) 50(2):75–81. https://doi.org/10.1016/j.medici.2014.06.008
13. Mohammed NA, Abd El-Aleem S, Appleton I, Maklouf MM, Said M, McMahon RF (2003) Expression of nitric oxide synthase isoforms in human liver cirrhosis. J Pathol 200(5):647–655. https://doi.org/10.1002/path.1377
14. González-Abraldes J, García-Pagán JC, Bosch J (2002) Nitric oxide and portal hypertension. Metab Brain Dis 17(4):311–324. https://doi.org/10.1023/a:1021957818240
15. Papadopoulos N, Soultati A, Goritsas C, Lazaropoulou C, Achimastos A, Adamopoulos A, Dourakis SP (2010) Nitric oxide, ammonia, and CRP levels in cirrhotic patients with hepatic encephalopathy: is there a connection? J Clin Gastroenterol 44(10):713–719. https://doi.org/10.1097/MCG.0b013e3181d47f71
16. Bezinelli LM, Eduardo FP, de Carvalho D, Dos Santos Ferreira CE, de Almeida EV, Sanches LR, Esteves I, Campregher PV, Hamerschlak N, Corrêa L (2017) Therapeutic salivary monitoring of IV busulfan in patients undergoing hematopoietic stem cell transplantation: a pilot study. Bone Marrow Transplant 52(10):1384–1389. https://doi.org/10.1038/bmt.2017.142
17. Castro T, Fink M, Figueiredo M, Braz-Silva PH, Pannuti CM, Ortega KL, Gallottini M (2017) Polyomavirus BK and JC in individuals with chronic kidney failure, kidney transplantation, and healthy controls. Journal of clinical virology: the official publication of the Pan American Society for Clinical Virology 89:5–9. https://doi.org/10.1016/j.jcv.2017.02.003
18. Figueiredo MA, Domingues Fink MC, Castro T, Braz-Silva PH, Steffens JC, Eduardo FP, Gallottini M, Ortega KL (2017) Detection of human polyomaviruses JC and BK in liver pretransplant patients. Oral Dis 23(8):1127–1133. https://doi.org/10.1111/odi.12707
19. Lasisi TJ, Raji YR, Salako BL (2016) Salivary creatinine and urea analysis in patients with chronic kidney disease: a case control study. BMC Nephrol 17:10. https://doi.org/10.1186/s12882-016-0222-x
20. Dupont WD, Plummer WD (1990) Power and sample size calculations: a review and computer program. Control Clin Trials 11:116–128
21. Gupta D, Ingle M, Shah K, Phadke A, Sawant P (2015) Prospective comparative study of inhibitory control test and psychometric hepatic encephalopathy score for diagnosis and prognosis of minimal hepatic encephalopathy in cirrhotic patients in the Indian subcontinent. J Dig Dis 16(7):400–407. https://doi.org/10.1111/1751-2980.12248
22. Elsaid MI, Rustgi VK (2020) Epidemiology of hepatic encephalopathy. Clin Liver Dis 24(2):157–174. https://doi.org/10.1016/j.cld.2020.01.001
23 FerreAracil C, Núñez Gómez L, TéllezVillajos L, Albillos Martínez A (2019) Epistaxis in the cirrhotic patient: a complication to be considered. Epistaxis en el paciente cirrótico: una complicación a tener en cuenta. Gastroenterologia y hepatologia 42(1):11–15. https://doi.org/10.1016/j.gastrohep.2018.08.003
24. Bigot A, Tchan MC, Thoreau B, Blasco H, Maillot F (2017) Liver involvement in urea cycle disorders: a review of the literature. J Inherit Metab Dis 40(6):757–769. https://doi.org/10.1007/s10545-017-0088-5
25. Bucsics T, Krones E (2017) Renal dysfunction in cirrhosis: acute kidney injury and the hepatorenal syndrome. Gastroenterology report 5(2):127–137. https://doi.org/10.1093/gastro/gox009
26. Kircheis G, Lüth S (2019) Pharmacokinetic and pharmacodynamic properties of L-ornithine L-aspartate (LOLA) in hepatic encephalopathy. Drugs 79(Suppl 1):23–29. https://doi.org/10.1007/s40265-018-1023-2
27. Allaker RP, Silva Mendez LS, Hardie JM, Benjamin N (2001) Antimicrobial effect of acidified nitrite on periodontal bacteria. Oral Microbiol Immunol 16(4):253–256. https://doi.org/10.1034/j.1399-302x.2001.160410.x
28. Qu XM, Wu ZF, Pang BX, Jin LY, Qin LZ, Wang SL (2016) From nitrate to nitric oxide: the role of salivary glands and oral bacteria. J Dent Res 95(13):1452–1456. https://doi.org/10.1177/0022034516673019